Medication Safety in Neonatal and Children's Intensive Care

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

2021

Anwar Ali M Alghamdi

Division of Pharmacy and Optometry

School of Health Sciences

Table of contents

Total word count: 43,655

List of Tables

List of Figures

List of Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ASHP	American Society of Health-System Pharmacists
BNF-C	British National Formulary for Children
CDS	Clinical Decision Support
CI	Confidence Intervals
CINAHL	Cumulative Index to Nursing and Allied Health Literature
FDA	Food and Drug Administration
ISMP	Institute for Safe Medication Practices
ICU	Intensive Care Unit
IPA	International Pharmaceutical Abstracts
IQRs	Interquartile Ranges
IV	Intravenous
MIDIRS	Maternity & Infant Care Database
MAE	Medication Administration Error
ME	Medication Error
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning System
NICU	Neonatal Intensive Care Unit
OBD	Observed Occupied Bed Day
OR	Odds Ratio
OE	Opportunities for Error
PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
PISA	PatIent SAfety classification
PINCER	Pharmacist-led Information Technology Complex Intervention
PE	Prescribing Error
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Abstract

Aims: This thesis aimed to understand the frequency, nature and underlying contributory factors of medication errors (MEs) and preventable adverse drug events (ADEs) in children admitted to paediatric and neonatal intensive care units (PICUs and NICUs) in order to generate recommendations for strategies that promote the safe use of medications in this vulnerable patient group.

Methods: A systematic review was first conducted to identify and critically evaluate the published peer reviewed evidence on the prevalence and nature of MEs and preventable ADEs in PICUs and NICUs in hospitals worldwide. A subsequent prospective observational cohort study was conducted across three English PICUs to assess the incidence, nature, preventability and severity of ADEs. A mixed methods analysis was then carried out to understand the nature and contributory factors of medication-related safety incidents reported from children's intensive care settings in England and Wales to the National Reporting and Learning System (NRLS) during 2010-2018. This included a descriptive analysis of reported incidents and content analysis of harmful incidents.

Results: Thirty-five studies were identified for inclusion in the systematic review. In PICUs, the median rate of MEs was 14.6 per 100 medication orders (interquartile range 5.7–48.8%, n=3 studies) and between 6.4 and 9.1 per 1000 patient-days (n=2). In NICUs, ME rates ranged from 4 to 35.1 per 1000 patient-days (n=2) and from 5.5 to 77.9 per 100 medication orders (n=2). In both settings, prescribing and medication administration errors were found to be the most common MEs. Preventable ADE rates were reported in three PICU studies as 2.3 per 100 patients (n=1) and 21–29 per 1000 patient-days (n=2). In NICUs, preventable ADE rates from three studies were 0.86 per 1000 doses (n=1) and 0.47–14.38 per 1000 patient-days (n=2). Anti-infective medications were commonly involved with MEs/preventable ADEs in both settings. The systematic review identified a lack of evidence concerning the burden of ADEs in these settings from the United Kingdom. Of 302 patients included in the subsequent observational cohort study involving three PICUs in England, one or more ADEs was detected in 47 (15.6%) patients. A total of 62 ADEs were identified, with an estimated incident rate of 20.5 per 100 patients (95% CI, 15.3-27.5) and 16.7 per 1000 patient-days (95% CI, 9.3-29.9). The majority of ADEs were considered preventable (36/62, 58.1%). Most ADEs caused temporary harm and were associated with problems with prescribing medicines. Medications for the central nervous system, infections and cardiovascular system were commonly implicated with ADEs. Patients with a PICU stay of seven or more days (OR 6.29, 95% CI, 2.42-16.32) were more likely to experience an ADE compared to patients with a stay of one to six days. Following examination of a total of 25,567 medication-related incidents reported to the NRLS, incidents were commonly reported to occur during medicines administration and prescribing stages. Anti-infectives were the medications most commonly associated with reported incidents and incidents that were reported to have caused patient harm accounted for 12.2% (3,129/25,567) of the total. Neonates were involved in 47.9% of all incidents, half (50.2%) of harmful incidents and 64.1% of anti-infective incidents. Common contributing factors to harmful incidents comprised staff-related factors such as failure to follow protocols or errors in documentation, which were associated often with challenging working conditions, inadequate guidelines, and design of systems and protocols.

Conclusions: This programme of research has found that MEs and related ADEs are common in children's intensive care settings and may lead to serious harm in critically ill children. Based on the in-depth understanding of these events that was generated by this research programme, a number of informed recommendations have been identified including improvements in staffing and workload, system design and processes, the use of anti-infective medications as well as decreasing the length of stay in intensive care units that may help reduce the risk of these preventable events in clinical practice and make care safer for PICU and NICU patients.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other learning institute.

Copyright Statement

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and he has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made only in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://documents.manchester.ac.uk/DocuInfo.aspx?DocID=24420), in any relevant Thesis restriction declarations deposited in the University Library, The University Library's regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in The University's policy on Presentation of Theses.

Dedication

This thesis is dedicated to my father, Ali Al-Souliman Alghamdi, who died in Saudi Arabia on 23rd May 2019 whilst I was completing this PhD programme in the United Kingdom. I also dedicate this thesis to the memory of my uncle, Ali Mohammad Al-Lafi, who I lost on 10th September 2020. Our target was completing this PhD programme and my dream was having them in the audience when I receive my doctorate degree.

Acknowledgments

First and foremost, I thank God Almighty for sustaining me throughout this PhD programme and helping me through the hard times over the past four years.

I offer my sincerest gratitude to my supervisors Professor Darren M. Ashcroft and Dr Richard N. Keers whose sincerity and encouragement I will never forget. Both Professor Ashcroft and Dr Keers helped me immensely and have been my inspiration as I hurdle all the obstacles in the completion of this research work.

A big thank you goes to Adam Sutherland, who always had helped whenever necessary in relation to undertaking my research studies. I also would like to thank Andrew Carson-Stevens, Afia Manaf, Jennifer Gray, Rhian E. Isaac, Graham Mason and Mark Hann for their involvement, help and support in the studies that I carried out for this research programme.

I would also like to convey thanks to the King Abdul Aziz University (my sponsor) and the Cultural Bureau of Royal Embassy of Saudi Arabia for supporting and providing the financial means.

Last but not least, my mother, wife and two children, Azzam and Bassam, have given me their infinite love and support throughout everything, as always, for which my mere expression of thanks likewise does not suffice.

About the Author

Anwar Ali Alghamdi graduated with a Bachelor of Pharmaceutical Science degree (5.06 out 7 GPA) from the College of Pharmacy, Griffith University, Australia, in 2010. Anwar then started pursuing a master's degree in Pharmacy at Griffith University after he was awarded a scholarship for this degree from the King Abdul Aziz University in Saudi Arabia. He graduated with a Master of Medical Research in Pharmacy degree in 2012 (6.75 out of 7 GPA) and received the Award for Academic Excellence for the academic year 2012 from Griffith University. Afterwards, Anwar worked as a lecturer at the Health Information Technology department in the King Abdul Aziz University for four years (2013 – 2016) before he was awarded another scholarship by the King Abdul Aziz University to pursue a PhD degree in Pharmacy at the University of Manchester in 2017. During this journey, Anwar has worked on many research projects and won several prizes such as the Distinguished Bachelor (in 2010) and Master (in 2012) Student Awards from the Saudi Cultural Mission in Australia and the Distinguished Instructor Award for the academic year 2015-2016 from the King Abdul Aziz University in Saudi Arabia.

Dissemination of the Research

Publications

- Alghamdi, A. A., Keers, R. N., Sutherland, A., Ashcroft, D. M. (2019). Prevalence and Nature of Medication Errors and Preventable Adverse Drug Events in Paediatric and Neonatal Intensive Care Settings: A Systematic Review. Drug safety, 42(12), 1423–1436. https://doi.org/10.1007/s40264-019-00856-9. **(Chapter 4)**
- Anwar A. Alghamdi, Richard N. Keers, Adam Sutherland, Andrew Carson-Stevens, Darren M. Ashcroft. A Mixed-Methods Analysis of Medication Safety Incidents Reported in Children's Intensive Care. Pediatric Drugs. DOI 10.1007/s40272-021-00442-6. **(Chapter 6)**

Conference Abstracts

- Anwar A. Alghamdi, Richard N. Keers, Adam Sutherland, Darren M. Ashcroft. The Burden of Medication Errors and Preventable Adverse Drug Events in Critically Ill Children: A Systematic Review. The Prescribing and Research in Medicines Management (UK & Ireland) 30th Annual Conference. London; December 2018 (Oral presentation). The abstract has been published in the Pharmacoepidemiology and Drug safety Journal in February 2019 (https://onlinelibrary.wiley.com/toc/10991557/2019/28/S1). **(Chapter 4)**

- Anwar A. Alghamdi, Richard N. Keers, Adam Sutherland, Afia Manaf, Jennifer Gray, Rhian E. Isaac, Graham Mason, Mark Hann, Darren M. Ashcroft. Incidence and Nature of Adverse Drug Events in Paediatric Intensive Care Units: A Prospective Multicentre Study. The World Federation of Pediatric Intensive and

Critical Care Societies (WFPICCS) 10th conference. Mexico (virtual); December 2020. (Poster presentation). The abstract has been published in the Pediatric Critical Care Medicine Journal. **(Chapter 5)**

- Anwar A. Alghamdi, Richard N. Keers, Adam Sutherland, Andrew Carson-Stevens, Darren M. Ashcroft. A Mixed-Methods Analysis of Medication Safety Incidents Reported in Children's Intensive Care Settings Across England and Wales. The World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS) 10th conference. Mexico (virtual); December 2020. (Poster presentation). The abstract has been published in the Pediatric Critical Care Medicine Journal. **(Chapter 6)**

- Anwar A. Alghamdi, Richard N. Keers, Adam Sutherland, Andrew Carson-Stevens, Darren M. Ashcroft. An Analysis of Medication Safety Incidents in Children's Intensive Care Settings Reported to The National Reporting and Learning System. The Prescribing and Research in Medicines Management (UK & Ireland) 32nd Annual Conference. Manchester (virtual); January 2021 – postponed due to the COVID-19 pandemic (date not specified). (Poster presentation). The abstract has been accepted for publication in the Pharmacoepidemiology and Drug safety Journal. **(Chapter 6)**

- Anwar A. Alghamdi, Richard N. Keers, Adam Sutherland, Andrew Carson-Stevens, Darren M. Ashcroft. An Analysis of Medication Safety Incidents Reported in Children's Intensive Care Settings Across England and Wales between 2010-2018. The International Society for Quality in Health Care (ISQua) 37th International Conference. Italy; September 2020 – postponed due to the COVID-19 pandemic to July 2021. (Poster presentation). The abstract has been accepted for

publication in the International Journal for Quality in Health Care (IJQHC).

(Chapter 6)

Achievement

Winner of the Top Viewed Poster Presentation Award at the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS) 10th Virtual World Congress that was held on 1 – 4 December 2020.

Chapter 1. Introduction and overview of the thesis

1.1 Introduction

Children represent a large group of the general population. During their different stages of growth and development starting from the neonatal stage to late adolescence, children go through health-related challenges that may necessitate medical intervention.[1] This may include risk of diseases (e.g. infectious or inherited diseases) and accidents. With regard to health care, children are different from adults in many ways.[2,3] For example, children have different physiological responses to diseases from adults (e.g. each population have different normal values of vital signs or laboratory test results).[4] Additionally, medication use can be more complicated in children than adults. For example, medication doses are often calculated according to weight and age of children whilst doses in adults are normally prescribed per day in separated doses.[5] As a result, children need health care that is designed specifically for their unique needs. This includes environments designed for children and specialised health care professionals who are trained to deliver children's health care effectively.[6]

Children receive health care services commonly in hospital environments.[7] For example, it has been estimated that one in 10 paediatric patients visiting general practitioners in the United Kingdom (UK) will be admitted to hospital.[8] In the United States of America (USA), 8.3 million children hospital admissions occurred between 2010 and 2016 and the number of children with complex chronic diseases increased from 16.6% in 2010 to 20.2% in 2016.[9] Children are also at risk of severe injuries and critical illnesses (e.g. acute traumatic injuries and single or multiple organ failure) that require admission to hospital intensive care units (ICUs).[10-12] Paediatric and neonatal intensive care units (PICUs and NICUs) are usually the dedicated areas in hospitals for critically ill children and neonates, respectively.[13] These units provide focused and continuous care by specialised medical and other healthcare staff for children with life-threatening medical and surgical conditions.[14,15]

The demand for intensive care services for children is increasing, particularly in the past decade due to increased numbers of children with complex care needs.[16,17]

Despite the intention of health care services and staff being to care for patients safely [18], medical errors during health care (e.g. surgical and diagnosis errors) are common and may result in patient harm (adverse events), which is considered a worldwide leading cause of morbidity and mortality.[19] An adverse event is defined as "an injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalisation, produced a disability at the time of discharge, or both".[20] Adverse events due to medical errors are defined as "adverse events or near misses that are preventable with the current state of medical knowledge".[21] The World Health Organization (WHO) estimated that around 42.7 million adverse events occur globally every year in hospitalised patients.[22,23] Therefore, safety of patients during medical care, which is defined as "the prevention of harm to patients", is a global health concern.[24,25]

The use of medication is a principal component of patients' care. However, medication use is associated with risks such as medication errors (MEs), which are among the most common causes of patient harm in health care systems worldwide.[24] All MEs are considered preventable and can occur at all stages of medication use process including prescribing, dispensing, administration and monitoring.[26] There are variable definitions of MEs in the published literature.[27] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) developed a standard definition for MEs. The NCC MERP defined a ME 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 healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order

communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use".[26]

MEs can lead to adverse drug events (ADEs), which are considered preventable and defined as "harm caused by the use of a drug as a result of error".[28] MEs and related ADEs affect all patient populations ranging from new-born children to older adults.[29] In a recent large meta-analysis (2020), it was estimated that one in 30 patients experience preventable medication-related harm across all medical care settings and over a quarter (26%) of all these preventable events are classified severe or life-threatening.[30]

In addition, preventable ADEs have also been found to be a cause of patients' admission to hospitals, life-threatening patient injuries and deaths as well as increased economic burden. In the USA, it has been estimated that 350,000 hospital admissions are caused by ADEs each year.[31] The financial impact of these ADEs was estimated to cost the health care system an additional 3.5 billion USA Dollars per year. Within the National Health Service (NHS) in England, it is estimated that 237 million MEs occur every year across all health care settings and related preventable ADEs contribute to 1,708 hospital admissions and cause 712 hospitalised patient deaths.[29] These ADEs were found to cost the health care system around £98.5 million annually. More broadly, the WHO estimated that the cost associated with MEs globally is 42 billion USA Dollars per year.[24]

Patients admitted to hospital ICUs may be more likely to be affected by MEs and preventable ADEs than those admitted to other clinical wards.[32] This may be due to factors related to the ICU environment (e.g. differences in staff workload and pharmacological interventions) and the nature of patients admitted to ICUs (e.g. rapidly changing physiological functions and deranged drug metabolism).[33] MEs in PICUs have been reported to occur seven times more frequently than other paediatric inpatient units in one

UK study (1998), which examined 441 MEs in 682 hospitalised children over two years.[34] Elsewhere, infants in NICUs were found to be at higher risk of preventable ADEs than children in other wards using data from two hospitals in the USA.[35]

Possible contributory factors behind these events may include: frequent use of unlicensed (not authorised for use in children) or off-label (prescribed outside the conditions of the license) medicines in NICUs and PICUs. These medicines may be associated with one third of preventable ADEs in hospitalised children.[36,37] Other related factors may include a lack of adequate dosing information for children [38-41] and that children in ICUs are also often sedated or may be pre-verbal and therefore unable to prevent errors themselves.[42,43] There is also often a need for the use of 'high-risk' medicines (that may cause serious patient harm when they are used in error) [44] and/or those with narrow therapeutic indices in these settings (including opioids, benzodiazepines and anticoagulants).[45]

In 2017, the WHO has made reducing patient harm due to MEs its third global patient safety challenge with the aim of reducing severe avoidable harm associated with MEs by 50% within five years.[24] Specifically, young children were identified in this global patient safety challenge as being at high-risk of medication-related preventable harm. To support this global campaign and subsequent national plans to improve medication safety [46,47], it is essential to examine and understand the burden, nature and risk factors of MEs and associated ADEs as well as their underlying contributory factors.[46,48,49] This is particularly important in patient populations at high risk of these preventable events such as critically ill children admitted to settings such as PICUs and NICUs.[24] This provides an opportunity to inform the development and optimisation of safety policies and practices to prevent patient harm in these settings and reduce the substantial impact MEs and preventable ADEs can have on patients and health care systems.[29,46,48,49]

Therefore, this research programme sought to understand the frequency, nature and underlying contributory factors of MEs and preventable ADEs in children admitted to PICUs and NICUs in order to help inform the development of theory-driven remedial interventions in the future to improve medication safety in this specialist setting. Hence, this thesis aimed to identify and critically evaluate the published peer reviewed evidence on the prevalence and nature of MEs and preventable ADEs in PICUs and NICUs in hospitals worldwide. It has, subsequently, established incidence rates, assessed the nature of preventable ADEs, and examined their underlying contributory factors in children's intensive care settings in the UK. This programme of work has identified areas of risk to critically ill children and generated important recommendations for changes to improve medication safety in this vulnerable patient population. It has also explored areas for further research that can guide future remedial interventions to reduce MEs and associated harm in PICUs and NICUs.

1.2 Thesis structure

This thesis is structured as outlined below:

- **Chapter 1** presents an introduction to this thesis to highlight the focus of this research programme and to describe the structure of this PhD thesis.
- **Chapter 2** presents an overview on children as a special patient population. This chapter then provides an overview on medical errors and MEs. It then outlines the hospital environment and the risk it may present to patient safety, before providing an overview of intensive care in hospitals. It then presents the background to the burden of MEs and related ADEs in children and their commonly associated contributory factors. Following this, a rationale for examining medication safety and the risk of MEs and related harm in intensive care to patients, specifically in

critically ill children is outlined. The reminder of this chapter describes the distinction between ADEs and adverse drug reactions (ADRs) and MEs. It also discusses MEs in terms of variations in definitions, classifications and reported rates drawn from published studies.

- **Chapter 3** summarises the case for exploring MEs and related ADEs in children admitted to intensive care settings and how this aligns to the current national and international efforts to improve the safe use of medicines and reduce preventable patient harm in these settings. Consequently, this chapter outlines the aim and objectives of this PhD programme with a rationale provided for each objective of this research programme.

- **Chapter 4** presents a systematic review of the literature examining the prevalence and nature of MEs and preventable ADEs in critically ill children worldwide. This chapter describes the methods and findings of the systematic review and recommendations for future research needed to improve medication safety in children's intensive care settings.

- **Chapter 5** presents a cohort study (informed from the findings of the systematic review presented in Chapter 4) that was carried out to determine the incidence, nature, severity, preventability and predictors of ADEs across three PICUs in England. This chapter describes the methods that have been utilised, findings from the study as well as discussing potential targets for remedial interventions.

- **Chapter 6** presents a mixed-methods analysis of medication safety incidents reported from children's intensive care settings in the NHS hospitals across England and Wales over a nine-year period (January 2010 – December 2018) in order to examine more in-depth the nature and underlying contributory factors of

these incidents. This chapter describes the methods that involved descriptive statistics of reported data as well as content analysis of textual descriptions of harmful incidents in order to explore the underlying contributory factors associated with their occurrence.

- **Chapter 7** first evaluates the achievements of the PhD thesis in meeting its overall aim and objectives in relation to policy agendas and existing literature to improve medication safety, which includes presenting a summary of the key findings from this research programme. It then outlines the strengths and limitation of the overall thesis before discussing the implications of the findings of this research programme for policy and clinical practice, and presenting recommendations for future research.

Chapter 2. Background

2.1 Children: Special population

Children are a large group of the population and their numbers have been increasing in recent years. In the UK, number of children aged less than 16 years increased by 8% between 2009 and 2019 to 12.7 million persons representing 19% of the total population.[50] This number continues to increase (e.g. 464,437 live births occurred in England and Wales between January and September 2020).[51] In 2019, children accounted for more than 72 million persons in the USA and it is estimated that they make up one in four people of the population.[52,53] Children are categorised by the WHO into different age groups including:[54]

- Preterm new-born: less than 38 weeks gestational age
- Neonates: birth – 30 days of age
- Infants: 1 month – 2 years of age
- Young child: 2 – 6 years of age
- Child: 6 – 12 years of age
- Adolescent: 12 – 18 years of age

However, age grouping for children is not reported consistently in the academic literature.[55] For example, clinical trials examining efficacy and safety of medicinal interventions in children often define children's age groups differently.[56,57] The National Institute of Child Health recommends age stage classification for children to be used consistently in clinical trials that provide important information for paediatricians, health care providers and policy makers about medicines use in children.[58] This classification includes neonate (aged 0 – 27 days), infant (aged 28 days – 12 months), toddler (aged 13 months – 2 years), early childhood (aged 2 – 5 years), middle childhood (aged 6 – 11 years), early adolescence (aged 12 – 18 years) and late adolescence (aged 19 – 21 years).

However, children's age groups are defined differently by other organisations such as the USA Food and Drug Administration (FDA) and the British National Formulary for Children (BNF-C). Both the FDA and BNF-C divide children's age groups similarly including neonate (aged 0 – 28 days), infant (aged 28 days – 24 months), child (aged 2 – 12 years) and adolescent (aged 12 – 18 years).[59,60] Rapid changes over time in children's physical, cognitive and psychosocial processes are not well understood, which may contribute to this variation in defining their stages of development.[58]

Improving quality of life for children is an important policy target across countries worldwide, which includes identifying and treating their health conditions.[1] This relies mainly on health care systems, which require continuous improvement in providing care safely for children.[61,62] Developmental changes in children are associated with variable challenges (e.g. chronic or infectious diseases with relatively immature immune systems to protect them), that sometimes make children need medical intervention during this period of their lives.[63] For example, it is estimated that one in five children aged less than 19 years in the UK is diagnosed with asthma, which is considered a chronic disease that requires continuous medical care.[8] In addition, there are also possible risks of accidents in children's normal lives leading to injuries that may need medical intervention. For example, for every 1000 children in England, 425 children needed emergency hospital care in 2015/16.[64]

Within health care systems, medical interventions are often provided for children in the hospital environment, which may frequently involve the need for intensive care due to critical illnesses or injuries.[16,65,66] For example, 2.5 million hospital consultation episodes (12.2% of all episodes) in NHS England involved children (0 – 18 years old) during 2018-19.[67] In a study that followed up more than one million children within NHS hospitals in England from birth to age 10 between 2005 and 2015, 1,315,338 admissions occurred

during this period and 63% of these were emergency admissions.[7] Treatment for infection-related illness was the main cause of these admissions to the NHS hospitals. Additionally, there has been increasing demand for children's intensive care within the NHS. For example, the number of PICU admissions increased in the NHS by 15% between 2004 (13,982 admissions) and 2013 (16,100 admissions).[68] These numbers have further increased in recent years (e.g. around 20,000 PICU admissions occurred annually in the NHS during 2016 and 2018).[65]

However, paediatric patients are also at risk of experiencing incidents caused by avoidable errors (e.g. delayed diagnosis errors and MEs) while they are in contact with the health care system. Paediatric patients are vulnerable to such incidents which could be serious or life-threatening. Awareness about paediatric patient safety has grown in recent years at both national and international levels. In the UK, paediatric patients were highlighted in many national research studies, reports and plans to improve patient safety.[25,29,46,48,69-78]

2.2 Patient safety: A global concern

Patient safety is a worldwide public concern in health care organisations.[49] The WHO estimated that one in four patients experience harm during the care they receive across different heath care settings.[24] Awareness about potential risks to the safety of patients in healthcare grew substantially after the publication of the landmark Harvard Medical Practice Study in 1991.[79,80] The study was conducted in the USA and assessed the safety of health care practice in 51 randomly selected acute care settings in the state of New York. The study reported that 3.7% of hospitalised patients experienced an adverse event caused by medical intervention. These events were due to errors (e.g. wrong diagnosis and errors of omission) in the medical practices or techniques used and 13.6% of those events led to

death. Complications due to medication use (19.4%) were the most common type of preventable adverse event.[20]

Despite the importance of the Harvard study findings regarding patient safety, the focus on this issue did not intensify until later in 1999, when the Institute of Medicine published a report entitled "To Err is Human: Building a Safer Health System".[49] This report described medical errors in health systems and estimated that nearly 98,000 patients may die annually in the USA due to MEs or suffer from their consequences. The report attracted attention from the media as well as health care organisations and government agencies globally, and prompted them to examine the safety of medical care in their systems.[81,82] For instance, the Department of Health in the UK released a report called "An Organisation With a Memory" in 2000, which enhanced the awareness about patient safety issues and highlighted the need for national reporting systems.[48] It was estimated that, due to failures in the UK health care, around 10,000 people in the UK have experienced serious adverse reactions to medications every year. Following this report, the National Patient Safety Agency (NPSA) was set up in 2001 to promote and monitor patient safety nationwide, including the safe use of medications. As part of NPSA work programme, the National Reporting and Learning System (NRLS) was implemented. The NRLS was established with a goal to collect incident data regarding patients' safety from NHS organisations across England and Wales, which could be analysed and used to improve health care systems.[83]

Even though the level of awareness concerning patient safety problems started to increase many years ago, the current literature continues to demonstrate that MEs compromise patient safety and represent the largest subset of medical errors in healthcare settings.[29,84-86] Whilst MEs may occur at any stage of the medication use processes (e.g. prescribing, dispensing and administering medications) [87], most MEs occur at the prescribing and

administrations stages.[30,88-91] Approximately 1-2% of hospitalised adult patients in the UK and USA may suffer from the consequences of MEs.[92] MEs may lead to preventable ADEs, which could be associated with significant patient harm.[93] In USA hospitals, it is estimated that 1.5 million patients experience preventable ADEs annually.[94]

Whilst medication safety issues pose a challenge to all patient groups, children are likely to be an especially vulnerable patient population and require particular attention.[42] Medication use is the most common intervention in providing medical care for children, which is associated with challenges such as limited availability of scientific dosing guidelines.[95-97] For instance, there is diversity in the age groups and physiological development of children extending from premature neonates to adolescents. Each age group often have different health care requirements.[98] This includes the complexity of medication use (e.g. complicated dosing calculations).[38,45,98]

2.3 Risk of the hospital environment on patient safety

Hospitals are expected to be safe places for patients. However, medical errors (e.g. surgical errors, delayed diagnosis or treatment, patient misidentification or MEs) in hospitals occur frequently and have been associated with patient harm and, in some instances, death. This may be associated with several factors such as the complexity of processes and systems and high-stress environment of hospital that may increase the likelihood of human errors when providing health care for patients.[22] In the USA, for example, these errors have been classified as the third leading cause of patient death. In the latest update (2016) on the death rate in the USA hospitals, deaths caused by medical errors were estimated to be 251,454 patients per year.[99]

Children are at risk of medical errors in hospitals.[100] In a large UK study across 25 NHS

children's hospitals, data from 3,992 randomly selected patient admission records were reviewed and 14.2% of patients (567 children) were reported to experience at least one adverse event during their hospital stay. This study identified 1001 adverse events (preventable and non-preventable) and their severity ranged from temporary harm to patient death.[101] Internationally, it is estimated that medical errors occur in one third of children admitted to hospitals and most of these are related to medication use.[102-104]

Furthermore, despite differences in reporting the rate and nature of MEs and ADEs [92], it has been estimated that 10% of hospital admissions are associated with ADEs and that they extend the patient's hospitalisation by 4.6 days on average.[105,106] It has been reported that all MEs are preventable and with between 28% and 56% of ADEs considered preventable.[33,105,107]

These rates of errors and related events that pose threats to patient safety in hospitals have led to increased awareness about the need to understand and improve patient safety in hospitals to reduce avoidable patient harm.[18,108] Hence, research has started to identify ways to make hospitals safer environments. For example, the transfer of patient care between hospital settings or health care professionals increases risk of errors that may lead to serious patient harm.[24] Interventions to reduce communication errors during this critical stage may minimise this risk. For example, a significant decrease in medical errors (from 33.8 to 18.3 per 100 admissions) was found in one children's hospital after implementing a handover bundle that include educational and system redesign components.[109]

2.4 Intensive care

2.4.1 Overview

Intensive care, also called critical care, is defined as "a multidisciplinary and interprofessional specialty dedicated to the comprehensive management of patients having, or at risk of developing, acute, life-threatening organ dysfunction".[14] However, there are variations in the definitions and capacities of providing critical care across countries.[110] Critical care services were established during the World War II (shock units for severely injured patients) and the 1952 poliomyelitis epidemic in Denmark.[111,112] Over time, critical care became an essential part of the health care services provided in hospitals, particularly, with high numbers of acutely ill patients requiring this level of care. For example, it was recently estimated that more than 175,000 adult patients were admitted to ICUs in England, Wales and Northern Ireland during one year (April 2018 – March 2019).[113]

In the UK, a framework to deliver critical care for acutely ill patients was established by the Department of Health in April 1999.[114] This framework included a division of critical care in hospitals into high dependency and intensive care beds. An updated framework was published by the Department of Health in May 2000 that established new approach in dividing the critical care in NHS organisation.[114] This updated framework has modernised critical care services in NHS hospitals and divided critical care according to the severity of patient illness regardless of their locations. This replaced the previous critical care bed types and included the following critical care levels:

- Level 0: Patient care can be met in general ward in an acute hospital,
- Level 1: Patients who need close monitoring by the critical care team due to risk of their health condition deteriorating, including those transferred from higher level of

critical care and their needs (e.g. face mask oxygen support) can be met in an acute ward,

- Level 2: Patients requiring support for a single organ system (without need for mechanical ventilation) including post-operative patients and those transferred from higher critical care levels,
- Level 3: Patients requiring support for two or more organ systems with advanced respiratory support (e.g. mechanical ventilation). This level includes all patients with complex critical illnesses with several organ failures.

Paediatric critical care services have been organised in the NHS since 1997 following the publication of the Paediatric Intensive Care Framework [13] and PICU became the dedicated area in hospitals to provide life-saving care for children. There has been increasing demand for paediatric critical care services in the recent years in the UK. According to the Paediatric Intensive Care Audit Network (PICANet) annual report (2019), rates of PICU bed occupancy was considered high (exceeding the 85% maximum recommended operational capacity)[115] across England, Republic of Ireland, and Scotland.[65] For example, PICU bed occupancy rates in NHS England, Northern Ireland and the Republic of Ireland exceeded 80% and 96% in Scotland. PICANet's report also highlighted high rates of high dependency bed occupancy in the NHS in England, Wales and Republic of Ireland.

Levels of paediatric critical care vary widely in the UK hospitals due to factors related to specialist care provided (e.g. congenital heart diseases services), different facilities, and staffing levels.[65] Quality of care in these units is usually examined through mortality prediction models (e.g. the Pediatric Index of Mortality) that measures survival rates among critically ill paediatric patients.[116] Death rates in the UK PICUs are low as reported by PICANet for the period 2016 – 2018.[65] Children that were discharged alive during this

period accounted for 96.5% and this indicates the success of these services in the UK health care system.

There are several activities involved in providing care for patients in NHS PICUs with increases in the amount of these activities during recent years (2010 – 2018).[65] For example, the most common critical activities across NHS PICU, high dependency units, paediatric hospital wards in 2018 – 2019 were:

- Monitoring of pulse oximetry
- Monitoring of electrocardiogram
- Oxygen support treatment
- Invasive mechanical ventilation
- Monitoring of arterial line

The NHS reports that more than half (54%) of the total activities across these settings related to PICU, which shows the frequent need for paediatric critical care services within NHS hospitals.[67]

2.4.2 Risk of medication errors and preventable adverse drug events in intensive care

In a high-acuity environment such as ICU, patients are particularly prone to MEs and related ADEs more than hospitalised patients in other wards.[30,32,117] High levels of fatigue among ICU staff, heavy workload, inadequate staffing levels and frequent distractions and interruptions are common factors that make ICU a stressful environment.[118,119] Such factors may adversely affect the performance of ICU staff and contribute to errors in providing care for patients, commonly in using medications.[120,121] For example, data from adult ICUs indicates that about 78% of medical errors in ICU setting are caused by MEs.

In addition, about 19% of MEs were found to cause life-threatening harm to ICU patients.[85]

In a study that aimed to compare the rates of ADEs between ICU and non-ICU patients, 4,031 hospitalised adults in ICUs and other hospital wards of two hospitals were followed up prospectively for 6 months.[122] The study concluded that the ADE rate in ICU setting was double the rate of the other hospital wards examined. Another study observed 1200 doses administered to patients in ICUs prospectively and errors were found in more than half (51.8% error rate) of the doses.[123]

Therefore, ICU patients may be at higher risk for MEs and associated ADEs.[124] In a recent meta-analysis (2020) that examined the prevalence of preventable medication-related harm across all health care settings worldwide, ICU was found to be a highly problematic setting that had the second highest prevalence rate (7%, 95% confidence intervals (CI), 4 – 12%) following elderly patient settings.[30]

2.5 Medication safety in children

Medications that are developed specifically for paediatric use are limited. It is estimated that the safety of more than 70% of medications used in children have not been examined scientifically.[125] Clinical trials that examine safety and efficacy of medications to be approved for medical use usually do not include children.[126] This is due to several reasons such as ethical concerns (e.g. exposing children to potential risks) and the small market of children's medications that makes it an economically unattractive investment.[57,127] Therefore, there is insufficient evidence on the safety and efficacy of many medications for children use. This, subsequently, made the development of optimal medicines prescribing guidelines for children challenging, which increases the risk of MEs and ADEs in this patient population.[42,96,97]

Due to lack of scientific evidence, many medications used for paediatrics are either unlicensed or off-label and they may be associated commonly with ADEs occurrence in hospitalised children.[38,39] Unlicensed drugs are those that did not go through regulatory procedures to ensure the quality, safety and efficacy. They also include changes made to licensed medications such as compounding liquid form doses by crushing tablets. Oral medications for children are usually provided in liquid form.[128] It is commonly thought that tablets are not suitable for young children as they cannot swallow them.[129] However, studies have shown that younger children from the age of three were able to swallow tablets following appropriate training to switch them from liquid form to tablets.[129,130] Due to health care professionals' lack of knowledge about the feasibility of switching children to tablets, they usually manipulate dosage forms (e.g. crushing tablets) to make suitable doses for children in liquid form.[130] It is estimated that 19% of medications administered to paediatric patients are manipulated.[131] This, consequently, increases the risk of MEs and ADEs due to the possibility of inaccurate dosing and lack of drug stability and bio-availability data.[131,132]

Off-label medications are licensed drugs but prescribed out of the terms of their market approval, and they are used more often than unlicensed drugs in both children and adults.[133-135] In neonates, it is estimated that 90% of medications used are unlicensed or off-label.[36] Off-label medication use in children is permitted for FDA licensed medications, but it is not an approved or regulated practice by the FDA.[136] Rules for children's medications were implemented in 2007 by the European Union regulatory authorities that included regulations such as providing appropriate formulations and safety and efficacy data for new paediatric medications.[137] However, due to limited approved medications for children use, clinicians continue to prescribe off-label medications for paediatric patients.[95,138] It is also believed that widespread of off-label medication use is

causing delays in needed research to provide safety and efficacy data for medication use in children.[139]

Doses for paediatrics usually need to be adjusted separately according to the child's weight, age, health condition and/or body surface area. There might also be changing pharmacokinetic and pharmacodynamic (e.g. nephrotoxicity due to high dose of vancomycin) characteristics as children grow, which if not considered could increase the possibility of ADE occurrence.[140,141] Dosing errors, particularly overdosing, may be a frequently reported ME in paediatrics.[142-146] Weights of neonates and children are variable (can range from 0.5 kg preterm neonates to >100 kg obese older children), which make dosing calculations based on weight (mg/kg) or body surface area (mg/M^2) complicated and a potential source of dosing errors.

Furthermore, medications available in different concentrations with their strengths expressed in ratios on their labels may add to the confusion and contribute to MEs in children. For example, adrenaline/epinephrine is available in several concentrations (e.g. 100 micrograms/1 mL, 150 micrograms/0.3 mL and 1 mg/10 mL) with variable strengths presented in ratios on labels (e.g. 1:10,000 and 1:2,000).[59] This was found commonly involved with 10-fold errors in critically children during emergency situations.[147] The FDA has recently asked pharmaceutical companies to change ratios on labels of medications used in critical care and use amount per unit of volume (mg/mL) instead to prevent dosing errors.[148] In addition, to reduce errors associated with dosing calculation, readily accessible pre-calculated doses to be used during stressful situations (e.g. emergency life-saving procedures) in critically ill children helped in reducing MEs.[147]

Additionally, good communication is essential between patients and health care providers, and it is thought that it could reduce MEs.[149,150] This is not a developed skill in some

young children and, therefore, may affect their response about errors or preventable ADEs. Even in older children who can communicate well, they may prefer simply not to make decisions about their health care and rely largely on their parents or physicians.[151]

Therefore, children may be at higher risk from MEs and the harm caused by medications than adults.[152,153] A comparison between two hospital based studies utilising the same error detection method, one in a paediatric hospital and the other in adults, found that the occurrence of ADEs was three times more frequent in paediatrics.[35] In addition, in a study that examined medication prescribing errors in adults and children admitted to general hospital wards, dosing errors were the most common error type, which were found to occur more frequently in children (5.89 per 1000 medication orders) than adults (4.12 per 1000 medication orders).[154]

Furthermore, incident rates of these MEs and preventable ADEs were compared in two large Japanese studies; one conducted across three adult hospital and one in two paediatric hospitals.[155,156] Incidence of preventable ADEs was higher in children (37.8 per 1000 patient-days) than adults (17 per 1000 patient-days). The incidence rates of MEs in these studies was found to be nearly eight times higher in children (65.1 per 1000 patient-days) than adults (8.7 per 1000 patient-days). Additionally, in a study that examined 200 prescribing errors that occurred in a large teaching hospital in the USA (caring for both adult and paediatric patients), nearly 70% of errors involved children and 30.9% of these were considered serious MEs that could cause patient harm.[157]

2.5.1 Medication errors and adverse drug events in hospitalised children

Rates of between 5.1% and 40.4% were found in studies (published between 1983 – 2010) investigating MEs in paediatric patients admitted to general hospital wards.[158] In a study

that was conducted in the UK across multiple children's hospitals in 2009, incident rates of medication prescribing errors were 13.2 per 100 medication orders and for administration errors 19.1 per 100 administered doses.[159]

In addition, it was reported that out of 60,000 national medication-related incident (ME and ADE) reports in the UK, 10.1% involved paediatrics aged from 0 to 4 years, while only 5.6% of all bed-days in UK hospitals were occupied by this age group.[160] In the USA, nearly 30% of more than 200,000 medication incident reports submitted annually from hospitals to the poison-control centres involve children under six years old.[161] However, there is still little focus on children in the published literature designed to explore the safety and quality of medication use when compared with those aimed for adults.[134,162,163]

2.5.2 Risk of medication errors and preventable adverse drug events in children's intensive care

PICUs in hospitals are designed for critically ill or injured new-borns, infants, children and adolescents. Data from several studies suggest that MEs and preventable ADEs may be much more frequent in PICUs patients than other paediatric settings.[35,55,164-169] In these settings, patients are exposed more frequently to medications than other clinical paediatric settings, which may threaten medication safety. For example, it is estimated that an average of 8.6 medications are prescribed for critically ill infants during their ICU stay [170] whilst three medications were reported as the average number of medications prescribed for children admitted to general hospital wards.[171] Accordingly, the likelihood of ADEs increases by 1.7% for each additional drug prescribed for paediatric patients.[40]

The use of high-risk medications such as opioids and anticoagulants may be associated with risk of preventable ADEs in children's ICU.[172,173] These medications may be used in children's intensive care setting more frequently than general wards and errors in using

them in children and could lead to harm. Prescribing errors associated with using high-risk medications, particularly due to incorrect weight-based dosing, were found to occur more frequently in children than adults.[174] For example, aminoglycoside antibiotics were previously classified as high-risk medications in PICU due to the risk of serious harm (e.g. acute kidney injury) associated with using them erroneously.[45] These medications are used widely in children's ICU and require accurate dosing adjustments and close monitoring of their serum levels in order to avoid toxicity. This may increase the risk of MEs and related ADEs associated with using these medications frequently in ICU environment.[175]

Furthermore, intravenous (IV) medications, which have instant bioavailability, are employed more frequently in critically ill patients. More severe ADEs can result from errors in preparing or administrating IV medications.[176] Moreover, medication administration errors were found higher (48% of total opportunities for error) with the IV route of administration than other administration routes (8.2% of total opportunities for error excluding wrong time errors) in a systematic review examining medication administration errors in health care settings.[177]

IV medications are used widely in critically ill children as they are commonly sedated during their ICU stay as well as due to their developmental differences (e.g. unable to swallow tablets).[178] In a study that examined 100 critically ill children for 851 ICU days, 86% (3,017/4,419) of all prescribed medications were administered intravenously.[179] IV medications were found to be associated with 61% of all MEs observed in a multicentre study that examined paediatric inpatients including those admitted to the ICU.[35] These medications are commonly involved with issues such as drug compatibility in concurrent IV medication administration that frequently occur in critically ill children and may lead to preventable ADEs (e.g. extravasation injuries).[180] In addition, 10- to 100-fold overdose errors in neonates have been reported to be associated with using IV medications more

commonly than other drug formulations.[181] This is mainly due to the lack of IV medications vials that are suitable for use in this patients' age group. IV medications used in neonates and children are usually provided by manufacturers with high drug concentrations that are appropriate for adult use, which increases the risk of dosing errors.[182]

Children's ICUs commonly admit preterm new-borns and neonates with undeveloped body organs and impairment in their body systems (e.g. hepatic or renal dysfunction). This could alter the absorption and clearance of medication in their bodies and, consequently, doses need to be recalculated regularly. These frequent calculations as well as lack of data on the pharmacokinetics and pharmacodynamics of the medicines for the different age groups increase the risk of MEs and related harm.[38] For example, due to their undeveloped hepatic and renal function, new-born and neonate patients may be at risk of experiencing harm associated with using some medications that adults are not at risk of. For instance, the use of antibiotics such as chloramphenicol may cause 'Grey baby' syndrome and sulfonamides could lead to brain damage (kernicterus disorder) in neonates, but not in adult patients.[183,184]

New-born children with severe illnesses are in some countries admitted to PICUs [185-187], but usually NICUs are the dedicated areas in hospitals for this group of patients.[38] In a study conducted to determine the incidence and types of medical errors in a NICU, 73 patient medical charts were reviewed of patients aged less than seven days. The most common type of errors in this study was MEs (84.2% of 95 adverse events detected).[86] In addition, MEs and potential ADEs (MEs that are likely to cause harm) were found to occur more frequently in neonates admitted to NICU than those in other clinical areas. Kaushal et al. (2001) compared rates of these events in 54 NICU patients and 129 neonates in other hospital wards. The reported rates in Kaushal's study were higher in NICU (91 MEs and

46 potential ADEs per 100 patients) than neonates in other hospital areas (50 MEs and 9 potential ADEs per 100 patient).[35]

2.5.2.1 Reducing medication errors and preventable adverse drug events in children's intensive care

There are existing medication safety interventions designed to reduce MEs and preventable ADEs in children's intensive care settings (e.g. computerised physician order and clinical pharmacy services), which have shown some positive impact in reducing MEs.[187,188] These interventions have been examined by previous systematic reviews, which have found that the number of studies that have assessed them, particularly in the UK, and their effectiveness in reducing patient harm are still limited.[189-191] It has been recommended that these interventions should be based on theory-driven knowledge of causation and need robust approaches to be used in evaluating their effectiveness (e.g. controlled randomised studies).[192] Therefore, providing theoretical understanding on the scale, nature and contributory factors of MEs and ADEs in children's intensive care is essential to inform the implementation of existing or new evidence-based interventions.

National organisations that aim to improve health care safety need a clear understanding about the failures in the systems that could harm patients.[193] An example of this is the UK organisation PICANet. It conducts an audit that collects clinical data on all children admitted to PICUs in the UK and Republic of Ireland. For example, in the 2015 report of PICANet, an excess mortality rate (8.4% of admissions compared to 3.7% in 2013) was reported in a PICU located in the North West England.[194] However, this relied solely on Standardized Mortality Ratio, which was 2.23 (95% CI 1.7 – 2.85), as the only available clinical indicator in this setting. Following further investigation by PICANet, it was recommended that other essential indicators such as MEs and related harm are also

required. A better understanding of these errors and related harm that occur in this population are important components for targeted safety interventions to prevent such events in the future.[152,195]

The safety of patients in children's intensive care settings was specifically highlighted in the recently announced NHS Patient Safety Strategy.[25] This NHS strategy included an early warning system, which is being developed collaboratively by NHS England and NHS Improvement, the Royal College of Paediatrics and Child Health and the Royal College of Nursing to identify and respond to risks in children's intensive care settings.

Despite awareness about the importance of medication safety in paediatrics, and particularly in those admitted to ICUs (due to the risks of MEs and related harm as described in the previous section of this chapter) [196], little is known about how common these preventable events are in critically ill children and where gaps remain in the current knowledge base. To prevent MEs, which could harm patients, it is essential to detect, analyse and understand the problem as highlighted by the current national and international medication safety policy initiatives.[24,25,48,49] This includes a detailed understanding of rates, nature and risk factors of MEs and ADEs as well as their underlying contributory factors. Accordingly, this would help in developing theory-driven interventions with better chances of success. Limited understanding of the underlying contributory factors associated with MEs/ADEs could lead to the design of ineffective prevention strategies limiting opportunities for improvement in patient safety.[48,186]

Systematic literature reviews are a valuable methodology that could be used in providing evidence on the scale and nature of MEs and ADEs in health care.[197,198] Systematic reviews provide accessible health-related research evidence with reduced risk of biases by identifying, critically appraising and summarising published peer reviewed evidence to

inform decisions of clinicians, policymakers and future research as observed in other health care settings.[198-201]

The current burden of MEs and preventable ADEs in children's intensive care settings are not well understood. There is lack of systematic reviews in the literature that examine MEs and preventable ADEs in children's critical care settings. Earlier systematic reviews focused on a specific country in examining the scale and nature of MEs in children [160], explored ADEs that were not associated with MEs (non-preventable ADRs) in children [40,202,203] or were conducted more than ten years ago and new information is available.[33,91,144,145,185,204] Other more recent systematic reviews did not involve all age groups of critically ill children (examined specific age group or medication classes) [38,196,205,206], did not focus broadly on both preventable ADEs and MEs occurring in all stages of medication use process [196,207,208] or examined medicines prescribing or administration errors only.[209-211]

In addition to the lack of systematic reviews concerning the global evidence of the burden of MEs and related harm in children's ICU, this chapter also found a lack of understanding of the contributory factors associated with these events in the UK. Based on examining the recent published literature, a limited number of studies originating from the UK were found. For example, UK based studies that have been published recently examined MEs, particularly focussed on prescribing in PICU and NICU.[212,213] This may indicate a knowledge gap and highlight the need for further research that will be guided by searching the literature systematically and identify areas that need to be examined.

In addition, exploring contributory factors associated with the occurrence of MEs and related ADEs, ideally at a national level, is important to generate learning from these preventable events that may help improvement efforts to reduce their recurrence.[214,215]

Contributory factors to the occurrence of patient safety incidents are defined by the WHO as "the circumstances, actions or influences which are thought to have played a part in the origin or development of an incident or to increase the risk of an incident".[216] These factors affect the performance of health care professionals in delivering the care to patients safely and may cause avoidable incidents.[215] This makes understanding them an essential step in developing preventive strategies. This is part of the knowledge generating process (following understanding the scale and nature of MEs and related ADEs), which is needed to inform actions that should be taken to prevent the occurrence of these events in the future.[46,48,49]

In the current literature, contributory factors of MEs and ADEs in children's intensive care have been reported in the form of description of these events (e.g. inappropriate drug formulations, off-label medications or weight-based dosing calculations) by epidemiological studies in paediatrics without focusing on the ICU envionment.[121,158,162,163,217,218] This did not consider other factors such as contextual and cognitive factors that may also contribute to errors or focused specifically on factors associated with errors at one stage of the medication use process (e.g. medicine prescribing).[121,219-222] An important source of this information is the medication-related safety incidents (MEs and ADEs) reported to national safety systems, which provide the opportunity to explore such factors at a national level and provide system-wide learning.[24,223] The national view of understanding these factors may also provide the opportunities to obtain generalisable samples and generate recommendations that can inform medication safety practice across centres to reduce MEs and ADEs.[214,224-226] Analysing these incidents could generate important insights about the human (e.g. knowledge deficit) and system (e.g. working conditions) factors associated with medication-related incidents that may help inform remedial interventions.[172,227]

There is, therefore, a need to examine the evidence on the rates, nature of both MEs and related ADEs in children's intensive care settings more broadly (including all stages of medication use process, both children's ICU types (NICU and PICU) and all children's age groups). To support these investigations, it is important to understand the underlying contributory factors associated with these preventable events, which is currently not well understood in children's intensive care settings.[121,162] This will provide a broader understanding of the safety of medication use in these settings at a national level and identify areas of risk to patients in order to generate recommendations for improvement in clinical practice and an action agenda for future research.

2.6 Research methods for studying medication errors and adverse drug events in hospitals

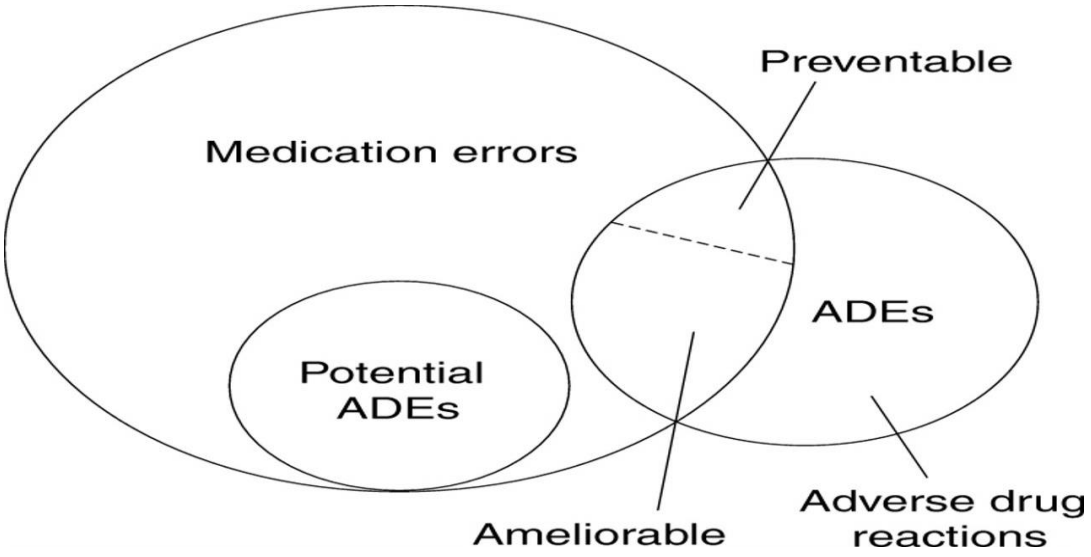
This section critically assesses the definitions and detection methods used in conducting research to explore MEs and ADEs in hospitals, in order to inform direction of this research programme and the appraisal of data gathered to examine these events in children's intensive care settings.

2.6.1 Terms and definitions

The intention of medication utilisation is to achieve therapeutic benefits, however medicines may also produce side effects. These effects may lead to consequences ranging from very minor effects to extremely serious and sometimes fatal effects.[228] This type of harm that a patient may experience is a non-preventable ADE and commonly called an ADR, which is not associated with ME.[206] The WHO defines an 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".[229] Current literature frequently reports such reactions according to this

definition.[230]

The overlap between ME, ADE and ADR is illustrated in Figure 2.1, which was developed by Morimoto et al.[93] All intercepted and corrected MEs, which have the ability to cause patient harm, are considered potential ADEs and may also called near misses.[226] Morimoto defined ADEs as "an injury due to a medication", which are divided into three categories: preventable ADEs, ADR and ameliorable ADEs. The term "ameliorable" was used to describe types of events related to the severity and duration of ADEs. Ameliorable ADEs are associated with MEs and defined as "injuries of which the severity or duration could have been significantly reduced if different actions had been taken".[93] While non-ameliorable ADEs are "injuries in which there is no current sensible way to reduce the severity or duration", hence not related to MEs.



Abbreviations: ADE: adverse drug event

Figure 2.1 Relationship between ME, ADE and ADR.
(Source: Morimoto (2004))[93]

There is a wide variation in how MEs have been defined in the published literature.[27,231] For instance, the American Society of Health-System Pharmacists (ASHP) developed a

definition of MEs as "episodes in drug mis-adventuring that should be preventable through effective systems controls involving pharmacists, physicians and other prescribers, nurses, risk management personnel, legal counsel, administrators, patients, and others in the organisational setting, as well as regulatory agencies and the pharmaceutical industry".[232]

The NCC MERP definition of MEs (presented in Chapter 1) was developed to be utilised internationally as standard definition and has now been adopted by ASHP.[26] However, MEs definition is still inconsistent across studies investigating MEs even with the development of international definitions.[27,231] A systematic review conducted to describe ME definitions in studies examining the prevalence of MEs in hospitals found 45 definitions and 26 of them use different terminologies. This inconsistency in MEs definitions has an impact on the reported prevalence of MEs in the included studies in this review, which ranged from 2 to 75%.[27] The majority of studies used the NCC MERP definition, but only one valid rate of MEs found in these studies as most of them relied on reporting systems in collecting their data with no denominators for the MEs rate.

2.6.2 Classification of medication errors

Human error theory provides insight into the antecedents of MEs.[233] Errors have been described to result from 'active' and 'latent' failures. This is a psychological analysis theory that was developed by James Reason to distinguish human (active) from system (latent) errors.[234] In health care settings, active errors involve unsafe actions of professionals who are in contact with patient directly. They may occur in three forms, which are slips, lapses, and mistakes. Slips are actions that were performed differently from the given plan (e.g. dispensing diltiazem instead of diazepam). Lapses are unsafe acts that are related to failures in memory (e.g. forgetting to write a dose frequency or route of administration on a prescription).[234-236] Both slips and lapses are skill-based errors occur at

carrying out the action. They are labelled as unintentional acts and were found to be frequently associated with MEs occurring in hospitals.[88]

Intentional acts are divided into mistakes and violations. Mistakes are errors in planning or knowledge (e.g. prescribing heparin in a patient diagnosed with heparin-induced thrombocytopenia). Violations result from non-compliance with standardised procedures (e.g. prescribed guidelines for drug administration) applied to enhance medication safety.[237,238]

Latent errors, by contrast, may ultimately cause harm due to flaws in designing the health care systems. This type of failure is more likely to lead to patient harm than active failures and violations due to the weaknesses in the defence mechanisms to prevent ADEs.[239] An example of these mechanisms is the use of clinical pharmacist on the units/wards, which showed a substantial impact in intercepting MEs that could result in patient's harm.[187,240] Latent failures occur as the result of decisions made at the higher levels of an organisation and their negative effects may lie inactive for a long time in the system. They become apparent when they interact with local contributing factors that break the system's defenses.[241] Reason's theory (as illustrated in Figure 2.2) can be used to show how gaps in the health care organisation system (latent failures) may allow actions that might be carried out by individuals incorrectly (active failures) to cause undesirable effects.[239]

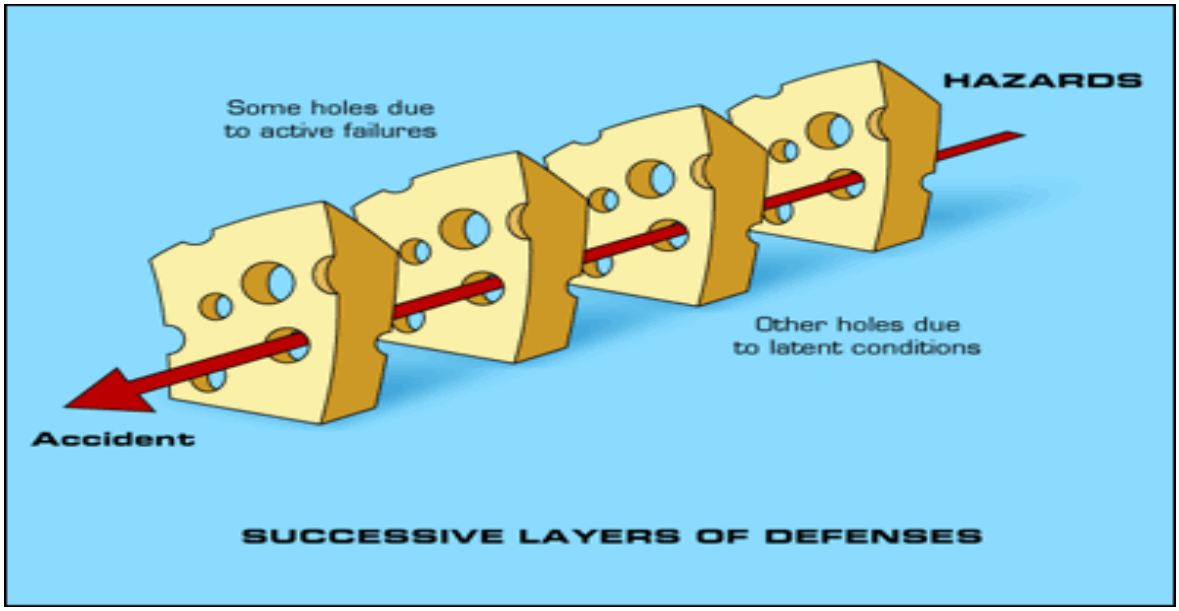


Figure 2.2 Reason's "Swiss Cheese" error causation model.
(Source: Reason (2000))[242]

Furthermore, 'omission' error or 'commission' error are alternative terms used to describe MEs.[85] Errors of omission are described as a failure to execute a suitable action. This includes failure to deliver the optimal care to the patient (e.g. failure of administering medication at the right time as prescribed). Errors of commission represent actions that are performed incorrectly, which could lead to patient harm (e.g. administering an overdose).[243] The majority of studies on medication safety investigate errors of commission and errors attributed to omission are rarely studied.[231,236,243]

Classification of MEs is a practical approach to understand how they occur and how to prevent them.[244] There have been numerous attempts made to classify detected MEs and ADEs in the literature.[245-248] For example, one of the commonly used criteria is the nine categories of Medication Errors Index proposed by the NCC MERP.[249] It classifies ME according to the injury it produced with key definitions of terms used in some categories as shown in Figure 2.3. Categories 'A' through 'D' are MEs that did not cause harm and categories 'E' through 'I' are injuries associated with MEs.

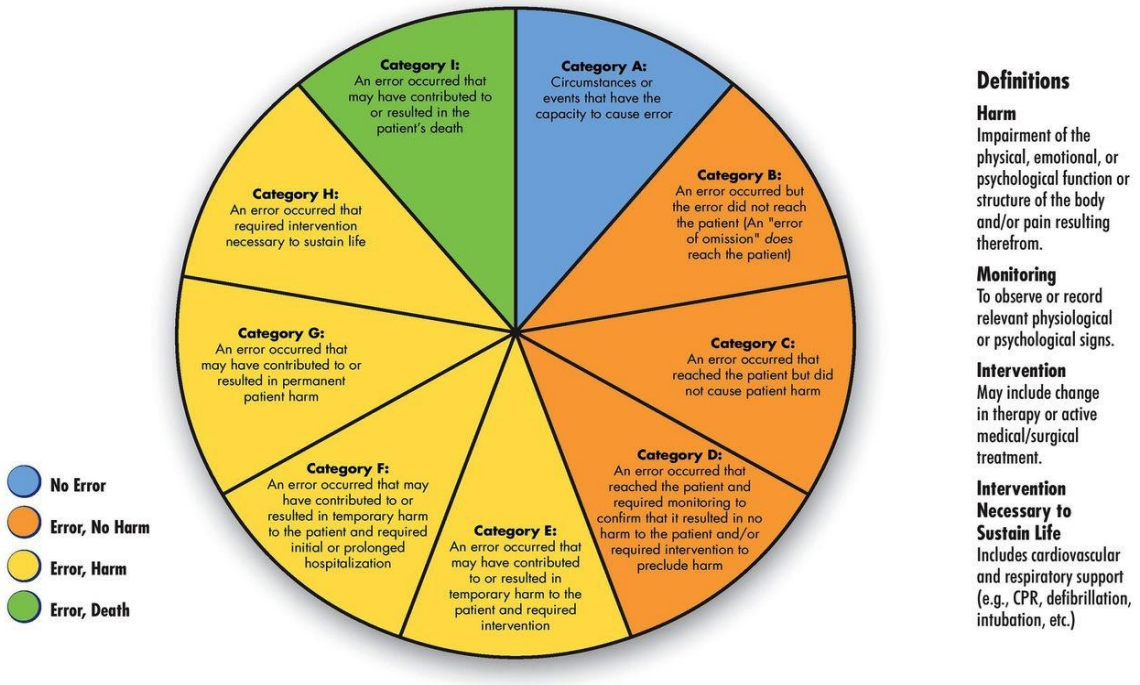


Figure 2.3 NCC MERP Medication Error Index for MEs classification according to the severity of the outcome.

(Source: NCC MERP)[249]

Classification of MEs that could inform prevention strategies should be based on a psychological theory. Therefore, Ferner and Aronson developed a classification index, which is based on Reason's model of active failure types and has the benefit of explaining events and not only describing them (Figure 2.4). Hence, this approach has the potential to identify factors that have an impact on errors occurring and help to design defence mechanisms to prevent them. This approach has a disadvantage, which is highlighting flaws in the individual more than problems in the system.[250] However, a structured and systematic way to explore such factors (e.g. using available frameworks such as the London Protocol) as a process for investigation and analysis of events may identify multiple events and variable factors (e.g. active and latent failures) that may interact with each other and contribute to the final event.[251] Hence, this may change the culture of blaming individuals and instead identify the contributory factors that have the greatest impact on the events.[252]

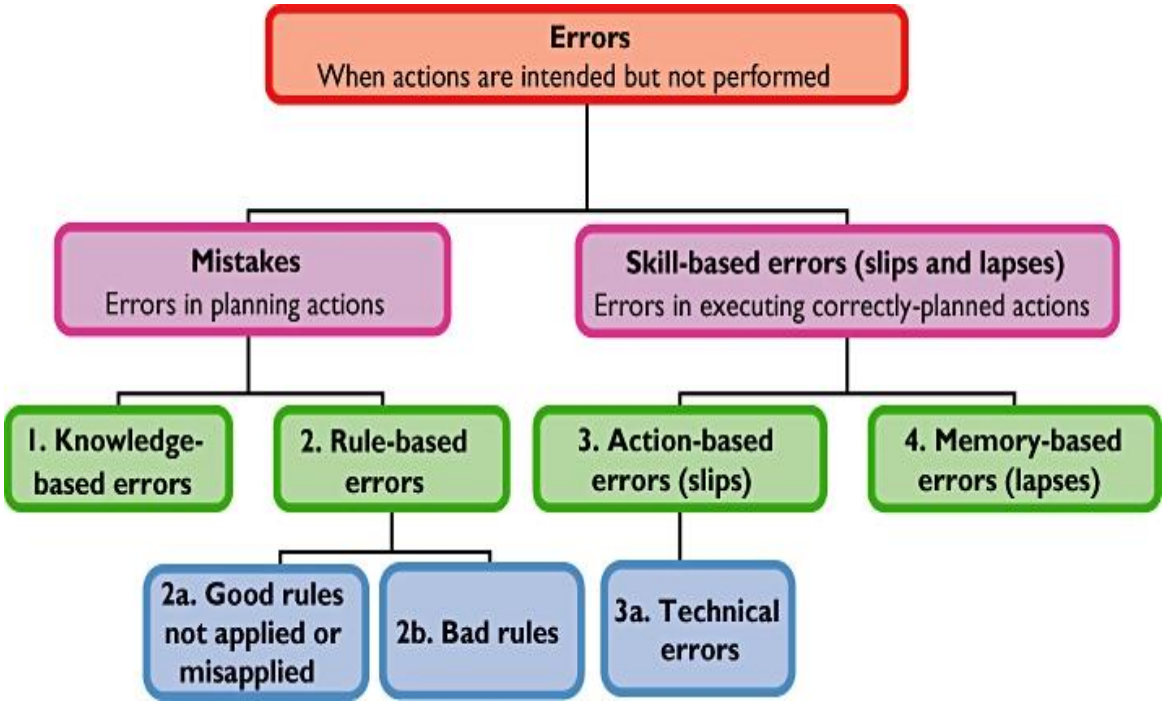


Figure 2.4 The classification of MEs based on a psychological approach.
(Source: Ferner (1999))[250]

2.6.3 Variation in identifying and reporting medication errors and adverse drug events

There is marked variation in the frequency of MEs reported in the literature.[30,177] NCC MERP stated four factors that contribute to this variation, namely: differences in ME definitions (as described earlier in this chapter), patient populations examined, type of detection systems and culture of health organisations (non-punitive versus punitive systems).[253]

There are several methods that have been used in epidemiological studies quantifying MEs and related harm.[254] Methods commonly used in these studies include review of patients' medical charts (e.g. medical records or medication orders), review of voluntary safety incident reports, direct observations of medication use processes and application of "trigger tools" to detect ADEs.[255] These methods differ in their ability to detect MEs/ADEs and no gold standard is presented as a best method. However, these methods may be better

suited to finding particular outcome/data (e.g. analysing incident safety reports to explore their underlying contributory factors).

2.6.3.1 Analysis of patient safety incident reports

Examining patient safety incidents may help in identifying high risk areas and trends/patterns to help direct improvement efforts. Understanding the contents of incident reports is also important to explore the contributory factors associated with incident occurrence.[214] This could be carried out using one of the several frameworks (e.g. PatIent SAfety classification' (PISA) and the London protocol) that have been established to classify factors that contributed to incidents in health care settings.[216,251,256,257] Such investigations using patient incident reports could highlight targets to improve practices and health care systems to reduce patient harm at both organisational and national levels.[24,258]

Patient safety incident reporting relies entirely on health care professionals reporting ME/ADE data and many incidents might be missed and not reported due to factors such as punitive systems or the pressure of workload.[259] This may underestimate the level of MEs/ADEs and has led to underutilisation of incident reports data in studies measuring the frequency and nature of MEs and related harm events.[260,261] However, analysis of incident reports can still provide learning and help identify ways to reduce their occurrence in the future.[226]

Several countries have established national incident reporting systems including the UK, Netherlands, Denmark, and Australia,[262] with the NRLS in England and Wales being the largest worldwide.[263] NRLS reports are used nationally in a non-punitive way to promote incident reporting. It is also a good example of a reporting system based on the WHO

"Draft Guidelines for Adverse Event Reporting and Learning Systems" [226], which gather necessary information about incidents that enables system-wide analysis and dissemination of recommendations for safety improvement in healthcare systems. In addition, since 2010 it has been mandatory to report all harmful incidents occurring in the NHS hospitals to the NRLS, which makes it an important database to identify and address areas where patients could be harmed. Incident reports submitted to the NRLS have been the source of information in creating national patient safety alerts, rapid response reports and medication safety guidance and research that aimed to reduce MEs and related ADEs across different health care settings.[214,264-267]

2.6.3.2 Medical chart review

Reviewing medical records (chart review) is a popular and widely used method and has been found to capture more ME/ADEs than incident report review.[255] This has common pitfalls that should be handled by the researcher to maintain the quality of the study. For instance, the data collector should be trained to understand the complexity of medical records data. Monitoring data collector is also required to check accuracy of data collected in a timely manner. The low quality of data documentation of the medical charts is another issue found when using this method and may affect the accuracy of data collected.[268]

2.6.3.3 Direct observation

Observing the medication process has been reported to detect MEs more frequently than chart review and incident reports.[269] This method needs a trained observer and obtaining consent from health care staff being observed. However, this method may rely too heavily on subjective judgment and a potential source of bias, which can result in systematic distortions of study results.[270] Another drawback of this method is the presence of the

observer. This may affect the performance of the participant, but a disguised observation may overcome such a negative effect.[271]

2.6.3.4 Trigger tool

Chart review and direct observation are conventional methods in examining MEs/ADEs and can be linked to the trigger tool method.[255] The trigger tool is a different approach designed to detect events that are linked directly to the actual harm more accurately than the traditional chart review and direct observations approaches.[272] The detection strategy of this method is through using triggers that may help identify MEs/ADEs. For example, the use of specific medications (e.g. antidotes, antiemetics, antidiarrheal or laxative or stool softener drugs), abrupt stop of medication, abnormal laboratory results (e.g. rising serum creatinine or unusual serum glucose level) or symptoms such as rash could be used as triggers to identify MEs/ADEs. This method requires trained medical staff to collect data and panel of medication safety experts to evaluate collected data.[273] In addition, trigger tool should be designed specifically for the examined target (e.g. specific patient population) to achieve the desired objective (detecting more events). For example, a trigger tool designed for adult patients may be not applicable for children due to several factors such as variable potential harm types and frequently used medications in the two patient populations.[274]

ADEs harm patients and the purpose of measuring them is to provide understanding about their occurrence (e.g. rate and nature) and find ways to reduce it in the future.[275] Conventional methods identify MEs with the belief that stopping MEs will reduce ADEs, but this was found less effective in preventing these events when compared with the use of trigger tool.[276] When trigger tool is designed broadly to involve a wide range of clinical consequences due to medication use, it was shown to be powerful approach to detect,

quantify and track ADEs. Data provided by the trigger tool methodology provide the basis for consistent methods to identify the significant risk for ADEs.[272,276-279] Any health organisation can establish a trigger tool method (initially a manual version and preferably to move to an automated version) and analysed data could be used directly at the stage where the harm is occurring to solve the problem and prevent the harm. Using this promising method, some health organisations have successfully reduced ADEs by half within a 6-month period.[277]

In summary, multifaceted approaches, which combined several of the aforementioned methods, seem to be a rigorous technique in detecting more MEs and related harm than using a single method.[33,280] Moreover, consistent methods and parameters such as definitions and settings may minimise the wide variation of reported rates in studies examining their frequency.[174]

Chapter 3. Research aims and objectives

3.1 Introduction

MEs are common across health care settings and among the most common causes of adverse events in hospital settings.[24,29,281] Based on examining the published literature concerning the safety of medication use in paediatrics, it is apparent that both early studies (1987 – 1998) [34,282-284] and more recent ones (2010 – 2017) [143,145,155,159,186,285] report some similar findings about the burden of MEs and associated harm which indicate that they may be an enduring risk to critically ill children admitted to ICUs. These preventable events were found to occur more frequently in critically ill children than other children or adults hospital wards.[35,186,285-288] However, understanding the scale, nature and contributory factors of these events remains limited in children's intensive care settings.

There is, therefore, a pressing need to examine this area in greater depth. This includes following international and national agendas to reduce preventable medication-related harm, which highlight that understanding the scale and nature of MEs and related harm is an important first step toward reducing these events.[24,46] This then needs to be supported by further knowledge about the risk factors and underlying contributory factors of medication related harm.[46,48,49] Generating this understanding is needed for the development, targeting and implementation of theory informed medication safety interventions with improved chance of success.[289-292]

As described in the previous chapters of this thesis, factors such as the frequent use of medications with a narrow therapeutic range and disturbed drug handling associated with pressurised working environment of ICU, complicated weight-base dosing, communication barriers with children and severe and unstable illness may increase the risk of MEs and related ADEs in critically ill neonates and children. Changes in blood parameters and

organ function due to critical illness which may lead to significant changed pharmacokinetics for medications administered in ICU children may also be contributing factors.[40,288,293-296] Additionally, there is insufficient pharmacokinetic data for many medications to treat children due to a lack of widespread clinical trials involving this population.[297] Consequently, prescribers usually use off-label and unlicensed medications in children, which could increase the risk of ADEs due to lack of scientific information about the optimal dosing for these medications.[38]

3.2 Research aim

This PhD aimed to assess the frequency, nature and contributory factors associated with MEs and ADEs occurring in critically ill children in order to identify targets and generate actionable recommendations to improve medication safety in this vulnerable patient population.

3.3 Research objectives

As highlighted in the previous chapter, there is lack of systematic literature reviews that summarise the available evidence concerning the scale and nature of MEs and related ADEs in children's intensive care settings.

Therefore, the objectives of this programme of research were:

- To systematically review the literature worldwide on the prevalence rates and nature of MEs at the different stages of the medication use process (prescribing, dispensing, transcription and administration) as well as ADEs occurring in critically ill children admitted to PICU and NICU.

This systematic review identified knowledge gaps across medication safety topics in PICU

and NICU and informed the next study of this research programme.

The methods and findings of the systematic review that was carried out to meet the first aim of this research programme are presented in chapter 4.

- To carry out a prospective observational study to determine the incidence, nature, severity, preventability and risk factors of ADEs occurring in patients admitted to PICUs within three NHS hospitals in England.

A gap in the literature (identified by the systematic review) was that only a limited number of studies have examined the epidemiology of ADEs in critically ill children worldwide and none of these studies were carried out in the UK. Studies identifying and reporting drug related harm in children would help highlight priority areas to improve medication safety and enhance awareness of the actual occurrence of patient harm due to deficiencies in the process of ensuring safe medication use.[297,298] In addition, preventable ADEs are the most amenable events to remedial actions and priority targets for improvement initiatives as highlighted by national and international policies.[24,46,299]

The methods and findings of the study that was carried out to meet the second aim of this research programme are presented in Chapter 5.

- To describe and understand the nature and contributory factors associated with medication-related safety incidents (MEs and preventable ADEs) reported in children's intensive care settings across England and Wales,

Detailed analysis of medication safety incidents from a national reporting system is important in guiding improvement strategies by understanding their underlying antecedents and prioritising high-risk areas.[214,223,300] As highlighted in Chapter 2, there is lack of understanding in the current literature about the underlying contributory factors associated

with MEs and ADEs in children's intensive care settings. Such understanding is essential to inform the planning of medication safety interventions. Hence, the objective of this research programme would be to support efforts to reduce preventable medication-related harm, as highlighted in the WHO Third Global Patient Safety Challenge. The strategic framework of the WHO's global challenge includes incident reporting and learning as a key component.[24]

The methods and findings of the study that was carried out to meet the third objective of this research programme are presented in Chapter 6.

- To make recommendations arising from studies originated from this research programme to inform clinical practice, policy makers and future research in designing safety measures to reduce MEs and ADEs in critically ill children.

The insights generated from this research programme (Chapters 4, 5 and 6) were assessed collectively to meet the fourth objective of this thesis as described in Chapter 7.

Chapter 4. Prevalence and nature of medication errors and preventable adverse drug events in paediatric and neonatal intensive care settings: A systematic review

4.1 Introduction

As discussed in Chapters 2 and 3, there is lack of understanding about the scale and nature of MEs and preventable ADEs in neonatal and children's intensive care settings. This broad understanding is needed to provide reliable estimates of these events and identify priority areas for medication safety improvement in these settings as well as knowledge gaps that should be addressed by further research. Earlier systematic reviews have examined the nature and burden of MEs in a specific country [160], investigated non-preventable ADEs (ADRs) in paedatrics [40,202,203] or involved database searches that are now more than ten years old and are in need of updating.[33,91,144,145,185,204,301-303] Other more recent systematic reviews were not designed for all age groups of critically ill children [38,196,205,206], did not focus on both MEs (including different stages of the medication use process) and preventable ADEs [196,207] or assessed errors at the drug administration or prescribing stage only.[209-211]

4.2 Aims and objectives

This chapter aimed to systematically identify and critically evaluate the available evidence on the global prevalence and nature of both MEs and preventable ADEs in PICUs and NICUs.

The objectives of this systematic review were:

- To search relevant electronic literature databases to locate eligible studies reporting on the rate and nature of MEs and preventable ADEs in NICU and PICUs,
- To assess the quality of the included studies,

- To determine the frequency of MEs and preventable ADEs for the different phases of the medication use process including prescribing, dispensing, transcribing and administering medications,
- To further examine the nature of these events including medications involved and perceived severity,
- To explore the variation of definitions and data collection methods used to evaluate MEs/ADEs in PICUs/ NICUs and how this might influence reported rates,
- To examine and compare ME rates associated with using electronic and paper-based prescribing systems in PICUs and NICUs,
- To provide key recommendations for future research in this field.

4.3 Method

4.3.1 Search strategy

The search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[304] As the patient safety literature has grown substantially since November 1999 after publication of "To Err is Human: Building a Safer Health System" by the Institute Of Medicine [49] and to include more contemporary studies, this systematic review retrieved studies published between January 2000 through March 2019.

Seven electronic databases were searched without language restrictions including: Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, International Pharmaceutical Abstracts, Web of Science, Maternity & Infant Care Database and Scopus. The first databases search was conducted between January 2000 and July 2017. The search was subsequently updated to cover the period between July 2017 and March 2019.

The search terms used fell into four groups to describe related terms to ME/preventable ADE, target population, setting and study design. To cover the main concepts of this review, several combinations of keywords, Medical Subject Headings terms and truncations were employed. Appendix 1 shows the details of the search strategy applied on the selected databases. Non-English literature databases were not searched and the different terms that were used in the review's search strategy were only in English and may not have covered terms in other languages.

In order to identify relevant studies, EndNote™ X8 was utilised as a reference manager to import citations and also to identify and exclude duplicate citations. One author of the review (AAA) screened titles followed by abstracts against the study inclusion criteria.[305] Subsequently, full texts papers were assessed by AAA to identify potentially relevant studies. During screening, uncertain cases were discussed amongst the research team (involving AAA, RNK, DMA and AS) and agreed by consensus. A hand search was performed on the reference lists of all identified studies and relevant review articles to identify any additional eligible studies. Grey literature (e.g. Google™ and Google scholar™) was also examined to identify any eligible studies for inclusion. Abstracts from conferences were also included where they provided rates of MEs or preventable ADEs in PICUs/NICUs. When additional data were required in relation to study methods and/or results, the authors of the study were contacted by email to provide more detailed information.

4.3.2 Inclusion and exclusion criteria

To reflect the population of interest, included studies focused on children from birth to 18 years and reported data that was attributable specifically to ICU settings.

The review considered all empirical studies that assessed the prevalence of ME/preventable ADE at any phase of the medication use process, or contained sufficient information to calculate the prevalence rate. Studies examining the impact of interventions on ME/preventable ADE rates were also included if data on the baseline prevalence rates before implementation of the intervention for this systematic review could be extracted.

This systematic review excluded studies only focussing on subtypes of prescribing, dispensing or administration errors, for instance, focussing only on 'wrong dose'. The review also excluded studies that used an estimated denominator to calculate the prevalence of MEs/preventable ADEs or reporting MEs/preventable ADEs rates for a single or specific class of medication, or specific treatment or patient group with a particular illness. Studies which relied on spontaneous error reporting systems for data collection were also excluded as these are widely known to underestimate the rate of MEs/preventable ADEs.[159,269,303,306-308] However, studies that collected incident report data alongside other methods (e.g. chart review) were included. The review also excluded studies reporting data only on irrational/potentially inappropriate prescribing or non-preventable ADEs/ADRs.

4.3.3 Data extraction

Relevant data was extracted from each included study independently by two of the research authors (AAA and RNK, DMA or AS) using a standardised form (Appendix 2). Any disagreements were resolved within the team by consensus. Data were collected on year of publication, country of origin, study type, setting, detection method, definitions of ME/preventable ADE, severity assessment criteria and any methods used for validation of the detected events. Data extraction also included rates of MEs/preventable ADEs and their types, severity and medication classes involved. Data regarding the type of prescribing

system (paper-based or electronic medication chart) were collected from each of included studies to compare error rates between the two systems.

4.3.4 Quality assessment

Assessment criteria established by Allan and Barker [309], which has been used frequently in previous systematic reviews examining MEs [92,197,310,311], were adapted to evaluate the quality of each study that met the inclusion criteria of this systematic review. The quality appraisal included the following 10 criteria:

1. Aims/objectives of the study clearly stated.
2. Definition of what constitutes a ME/preventable ADE.
3. ME/preventable ADE categories specified.
4. ME/preventable ADE categories defined.
5. Presence of a clearly defined denominator.
6. Data collection method described clearly.
7. Setting in which study conducted described.
8. Validity measure in place to confirm the occurrence of ME/preventable ADE.
9. Reliability measures (e.g. assessing inter-rater reliability).
10. Limitations of study listed.

Two of the review authors (AAA and RNK, DMA or AS) calculated the quality of each included study independently and consensus was achieved through discussion for any inconsistencies in scoring items.

4.3.5 Data analysis

Data were summarised descriptively in tables, including prevalence rates for overall ME/preventable ADEs as well as prevalence rates of ME types including prescribing

errors, dispensing, transcription and administration errors. Where appropriate, studies were grouped using common denominators (e.g. medication orders or patient days) and rates presented using medians with Interquartile Ranges (IQRs).

Rates of events were calculated where sufficient information was provided by dividing the total number of MEs/preventable ADEs that occurred by the relevant denominator such as patients, medication orders or administrations and then multiplying by 100.

The most commonly observed drug classes involved with MEs/preventable ADEs in PICUs or NICUs were extracted. Common drugs presented in this systematic review were the frequently reported top three drug classes across studies. The most common ME subtype(s) (e.g. common subtypes of prescribing errors) reported in this systematic review were the most commonly reported error categories reported in each of included study. The median rates with IQRs of prescribing errors in PICU and NICU were calculated based on the type of prescribing system (electronic or paper-based) in each ICU type where possible.

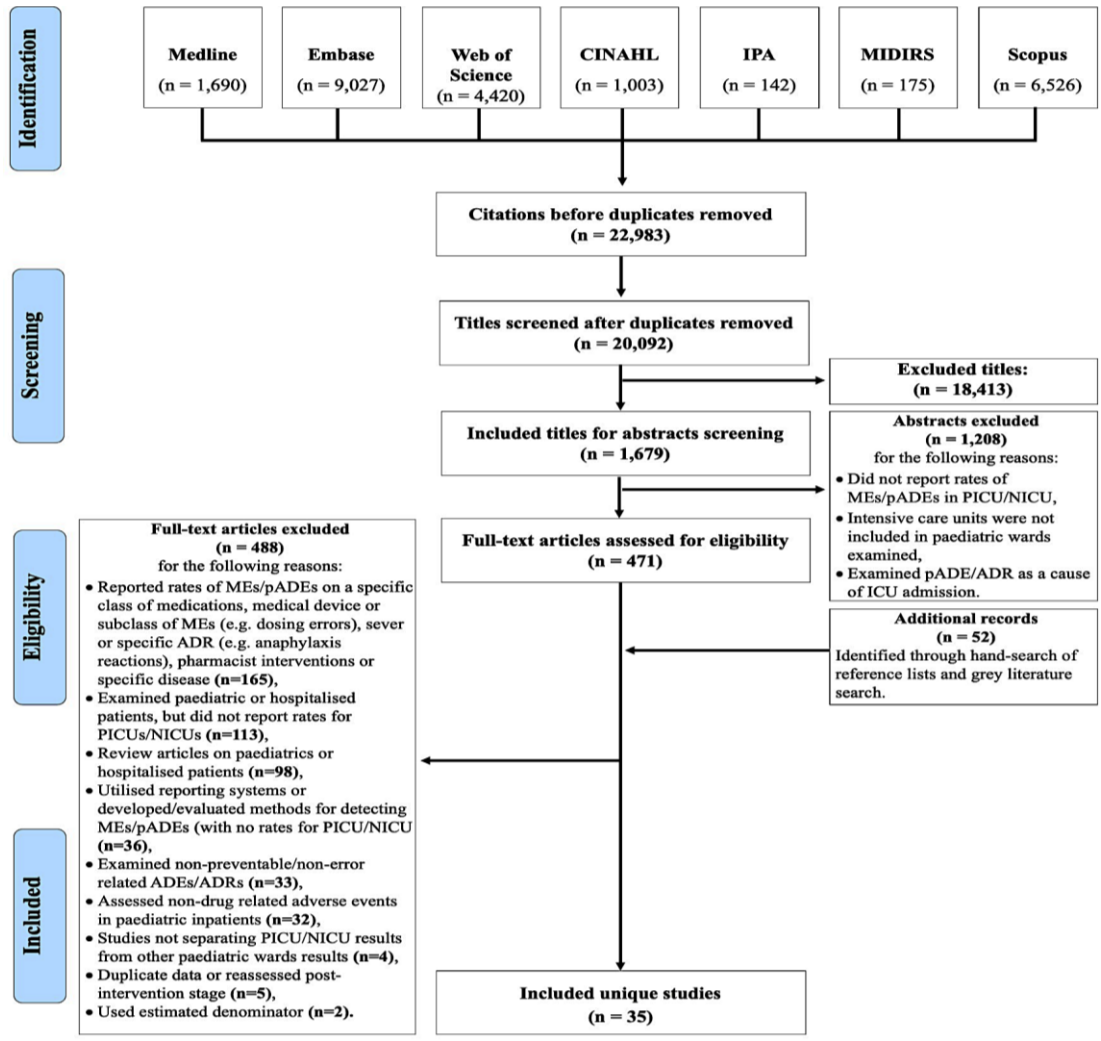
4.4 Results

4.4.1 Literature search results

The literature search yielded 22,983 records. As shown in Figure 4.1, 20,092 titles were screened after removing duplicate citations. There were 18,413 non-relevant titles that were then excluded and the abstracts of the remaining 1,679 citations were inspected. Full texts of 471 studies were subsequently examined and 37 publications were eligible for inclusion in this systematic review including seven conference abstracts. All eligible studies were published in English. Two of the included studies which focused on NICUs [312,313] and two others which included data for both units [35,314] reported on the same

population of patients and were considered as single studies (using the reports that included the more detailed information for this systematic review), resulting in a total of 35 unique studies being included.

The updated literature search that was conducted to identify studies published between July 2017 and March 2019 yielded four studies that were not eligible for inclusion in this systematic review as described in Appendix 3.



Abbreviations: ADEs: adverse drug events, ADRs: adverse drug reactions; CINAHL: Cumulative Index to Nursing and Allied Health Literature; ICU: intensive care unit; IPA: International Pharmaceutical Abstracts; MEs: medication errors; NICU: neonatal intensive care unit; pADE: preventable ADE; PICU: paediatric intensive care unit; MIDIRS: Maternity & Infant Care Database.

Figure 4.1 Flow diagram of articles included/excluded for the systematic literature review.

As the included studies were heterogeneous in setting and design, meta-analysis could not be performed. For instance, sources of heterogeneity were in event measures such as error type and subtype (e.g. including/excluding dosing error in assessing prescribing errors) examined and denominators used in reporting event rates (e.g. per 100 patients, per 100 medication orders, per 100 or 1000 patient days, or per 1000 occupied bed day). Clinical heterogeneity was also noted in included studies in specifying different age ranges (neonates/children) for patients admitted to these ICU types or not reporting this basic demographic data.

4.4.2 Summary of study characteristics

More than half of the included studies (20/35, 57.1%) were published from January 2010 onwards and the remaining 15 studies (15/35, 42.9%) between January 2000 and December 2009. Seventeen studies (17/35, 48.6%) were conducted in PICUs, and 13 studies (13/35, 37.1%) were conducted in NICUs. Five studies (5/35, 14.3%) were conducted across both ICU types.[35,155,286,301,315] The included PICU studies are summarised in Appendix 4, NICU studies in Appendix 5, and studies in both ICU types in Appendix 6. These tables present extracted data from each study regarding country of origin, publication date, study design, detection method(s), setting(s), patients age, rates of MEs and preventable ADEs and severity data.

Six (6/17, 35.3%) PICU studies were conducted in the USA [164,186,187,307,316,317], and five studies (5/17, 29.4%) were undertaken in the UK.[143,212,318-320] The remainder included one study each from the Netherlands [321] Switzerland [185], Egypt [322], Israel [188], Iran [91] and Hong Kong [145]. The NICU studies included three studies (3/13, 23.1%) from the USA [323-325] and two studies from India (2/13, 15.4%).[302,306] The remainder included one study each from the UK [213], Spain [146], the Netherlands [326], New Zealand [312], Malaysia [327], Switzerland [303],

Brazil [144] and South Africa [204]. The five studies involving both ICU settings were from the USA [35], Japan [155], Morocco [286], Argentina [301] and Malaysia [315].

The majority of studies which focused on one type of ICU were single-center studies (15/17 (88.2%) PICU, 13/13 (100%) NICU) while the combined PICU and NICU studies were almost all multi-center (4/5, 80%). Many of the included studies were interventional (8/17 (47.1%) PICU, 7/13 (54%) NICU), however there was only one interventional study across both units.[301] There was variation in study design, with 11/18 (61.1%) PICU studies, 8/13 (61.5%) NICU and 3/5 (60%) combined settings collecting data prospectively, with the remainder being retrospective or cross-sectional studies.

Medication chart review was the most common method used for ME/preventable ADE detection in PICUs (15/17, 88.2%), in NICUs (10/13, 76.9%) and across both units (4/5, 80%). Pharmacists were the only data collectors in 12/35 (34.3%) studies, with a mixture of healthcare professionals used across the remaining studies. A total of 5 studies (5/35, 14.3%) did not provide any details on those involved in data collection.[164,204,212,318,321]

The definition of ME/preventable ADE varied across studies. Almost half of included studies (17/35, 48.6%) used locally developed definitions of ME/preventable ADE, while the remainder used a range of other definitions used previously (e.g. three studies [144,301,327] used the standard definition of MEs developed by the ASHP [232]). Nine studies (9/35, 25.7%) did not provide any operational ME/ADE definitions.[146,212,213,302,307,318,319,321,325] Variable definitions, subtypes and rates of MEs in studies examining NICUs and PICUs are summarised in Appendix 7.

There was variation in the methods used for ensuring the validity (confirming causation) of identified MEs/preventable ADEs. For PICU studies, 11/17 (64.7%) reported a method for reassessment of some or all of the identified cases along with 3/5 (60%) joint studies,

while only 4/13 (30.8%) NICU studies reported some mechanism to assure validity. The most common method to validate data across all studies involved a panel of health care professionals reassessing some or all detected outcome events (18/35 studies reporting validation method, 51.4%).

Some element of severity or impact assessment was described in 8/17 (47.1%) of PICU studies [91,145,164,185,186,188,317,322], 4/5 (80%) of the joint studies [35,155,286,315] and 4/13 (30.8%) of NICU studies.[306,312,323,326] Severity assessment methods were variable, with some reporting expert panels convened to assign severity using a scale the researchers either developed internally, adapted from existing definitions used internally (n=10) or from existing definitions (NCC MERP (n=5) [249], ASHP criteria (n=1) [248]) being reported.

4.4.3 Quality assessment

After applying the quality assessment criteria as shown in Appendix 8, only six studies of the 35 included studies (17.1%) fulfilled all 10 criteria and were considered as high-quality studies.[164,186,187,212,286,316] Six studies met nine criteria, 10 met eight criteria [35,155,312,315,317,326], four met seven criteria [145,320,322,327], two met six criteria [146,319], and three met five criteria.[213,318,321] The remaining studies met less than five criteria.[212,302,307,325]

The data collection method and denominator used were described in all included studies. Nine of the 35 included studies (25.7%) did not provided any definition for MEs/preventable ADEs. Six studies did not specify categories of MEs/preventable ADEs and more than half of studies (18/35, 51.4%) did not define MEs categories. Many of the included studies did not describe any validity measures to confirm the occurrence of ME/preventable ADE (18/35, 51.4%) and did not assess inter-rater reliability (25/35, 71.4%).

4.4.4 Prevalence and nature of medication errors and preventable adverse drug events in PICUs

Data regarding rates and common types of MEs/preventable ADE rates in PICUs were provided in 21 (21/35, 60%) of the included studies (Table 4.1). The overall ME rate in PICUs was reported in five studies (5/21, 23.8%); three used medication orders as a denominator with a median prevalence of 14.6 per 100 medication orders (IQR 5.7 – 48.8) [35,91,317] and the remaining two studies, one which was rated as high-quality [286], used patient-days as a denominator with the ME rate ranging from 6.4 – 9.1 per 1000 patient days.[155,286] Errors in prescribing and drug administration were the most commonly reported types of MEs in PICUs across all five studies.

Prescribing errors were the most common ME type examined in PICUs. Sixteen studies (15/21, 71.4%) presented rates of prescribing errors; three used different denominators and further analysis could not be performed [143,319,322] with the remaining 12 studies (two of which were rated as high-quality) [164,316] using medication orders as the denominator yielding a median rate of 13.25 (IQR 9.5 – 29.35) per 100 medication orders. Six studies out of these 12 studies were conducted in PICUs that utilised paper-based medication chart systems with a median rate of prescribing errors calculated as 13 per 100 medication orders (IQR 10.9 – 37.4).[145,185,301,316,318,320] Two studies (2/12) assessed prescribing errors in PICUs using electronic prescribing systems and the rate of error ranged from 8.3 – 27.1 per 100 medication orders.[164,315] The remaining four studies did not describe how their prescribing systems functioned.[91,188,212,321] Dosing and documentation errors were the most frequently reported prescribing error subtypes.

One study presented rates of dispensing and transcription errors (0.78 and 4.88 per 100 orders, respectively).[91] Two studies reported rates of medication administration errors

using two different denominators [91,301]; these rates were 28.9 per 100 orders and 8.2 per 100 drug administrations, with wrong time or wrong route errors being commonly reported medication administration errors.

A total of 10 out of the 21 studies reported ME severity data in PICUs using different scales [91,145,155,164,185,188,315,317,318,322], which could not be grouped into main categories to allow comparison between studies. Therefore, severity data of each study were summarised in Appendices 4, 5 and 6.

Three studies originating from the USA presented overall preventable ADE rates.[186,187,307] In two of these studies, which were rated to be of high-quality, preventable ADEs ranged from 21 – 29 per 1000 patient-days.[186,187] One of these studies reported a 4% increase in the risk of preventable ADE for each additional one-year increase in age.[186] The rate of preventable ADEs in the remaining study was 2.3 per 100 patients.[307]

The severity of harm from preventable ADEs was assessed in two studies.[186,307] The majority of events in one study by Agarwal et al. were assigned a low level of severity using the NCC MERP scale.[249] Larsen et al. in the other study categorised all detected harms as minor, but did not describe the assessment scale used.

Table 4.1 Rates and common types of MEs and preventable ADEs in PICUs.

Event	Rate		Common types ***
	Same denominator *	Different denominators **	
Medication errors	Median: 14.6 (IQR 5.7 – 48.8) (n=3) [35,91,317] (Denominator: per 100 medication orders)		• PEs (n=3) • MAEs (n=2)
	Range: 6.4 – 9.1 per 1000 patient-days (n=2) [155,286]		
Prescribing errors	• Overall median: 13.25 (IQR 9.5 – 29.35) (n=12) [91,145,164,185,188,212,301,315,316,318,320,321] (Denominator: per 100 medication orders)	78.1% of total OEs § [322]	• Dosing errors (n=9) • Documentation errors (n=5)
		892 errors per 1,000 PICU OBDs § [143]	
	○ PICUs using paper medication charts Median: 13 (IQR 10.9 – 37.4) per 100 medication orders (n=6) [145,185,301,316,318,320]	12.4 errors per patient [a] § [319]	
	○ PICUs using electronic medication charts Range: 8.3 – 27.1 per 100 medication orders (n=2) [164,315]		
Dispensing errors	0.78 per 100 medication orders § [91]		
Transcription errors	4.88 per 100 medication orders § [91]		
Medication administration errors		28.9 per 100 medication orders § [91]	• Wrong time or route of administration (n=3)
		8.2 per 100 administrations § [301]	
Preventable adverse drug events	21 – 29 preventable adverse drug events per 1000 patient-days [a] (n=2) [186,187]	2.3 preventable adverse drug events per 100 patient [a] § [307]	

* Range of rates or median of MEs/preventable ADEs rates and IQRs were calculated.
** Range of rates or median rates of MEs/preventable ADEs and IQRs could not be calculated due to different denominators used and each rate was reported by only one study.
*** Frequently reported most common types across all included PICU studies.
[a] Self-calculated.
§ Only one study provided event rate.
Abbreviations: PICU(s): paediatric intensive care unit(s); OBD(s): observed occupied bed day(s) OE(s): opportunities for error(s); PE(s): prescribing error(s); MAE(s): medication administration error(s); IQR(s): interquartile range(s).

The most common drug classes associated with MEs/preventable ADEs in PICUs were reported in four studies (4/21, 19.04%) (Table 4.2) and involved anti-infectives (n=4), cardiovascular agents (n=3), nervous system agents such as sedatives (n=2), IV fluids (n=1), respiratory agents (n=1), and diuretics (n=1).[145,315,317,322]

Table 4.2 Common drug classes associated with MEs and preventable ADEs in NICUs and PICUs.

Setting	Author (year)	Common drug classes
PICU	Ewig et al. (2017) [145]	Anti-infectives
		Cardiovascular agents
		Intravenous fluids
	Khoo et al. (2017) [315]	Anti-infectives
		Nervous system agents
		Diuretics
	Alagha et al. (2011) [322]	Anti-infectives
		Respiratory agents
		Cardiovascular agents
	Buckley et al. (2007) [317]	Anti-infectives
		Nervous system agents
		Cardiovascular agents
NICU	Khoo et al. (2017) [315]	Anti-infectives
		Folates
		Multivitamins
	Palmero et al. (2015) [303]	Anti-infectives
		Intravenous fluids
		Respiratory agents
	Machado et al. (2015) [144]	Anti-infectives
		Nervous system agents
		Cardiovascular agents

Abbreviations: PICU: paediatric intensive care unit; NICU: neonatal intensive care unit.

4.4.5 Prevalence and nature of medication errors and preventable adverse drug events in NICUs

Seventeen studies (17/35, 48.6%) provided data from NICUs to calculate the rates of MEs and preventable ADEs. Table 4.3 shows rates and frequently occurring ME types as well as the rates of preventable ADEs.

The overall rates of MEs in NICUs ranged from 4 – 35.1 per 1000 patient-days (two studies [155,286], one was rated as high-quality [286]) and 5.5 – 77.9 per 100 medication orders (two studies).[35,204] A further two studies, one was rated to be of high-quality [323], reported ME rates using different denominators; namely, 69.5 MEs per 1000 doses [323] and 26.4 per 100 case records.[302] Prescribing errors and medication administration errors were the most commonly reported ME types in NICUs. The severity of detected MEs in these studies was either not addressed [204,286,302] or addressed through preventable/potential ADEs; two preventable ADEs out of 148 MEs [155], 46 potential ADEs per 100 admissions [35] and 0.86 preventable ADEs per1000 doses.[323]

Six out of eight studies reporting prescribing error rates provided rates per medication orders with a median of 14.9% (IQR 4.25 – 29.9). Three of these six studies examined NICUs using paper-based prescribing systems and the median error rate was calculated as 28.9 per 100 medication orders (IQR 22.5 – 32.8).[146,301,303] NICUs with electronic medication chart systems were examined only in one study where the prescribing error rate was 7.3 per 100 medication orders.[315] The remaining two studies (2/6) did not describe their NICU prescribing systems.[213,325] Dosing errors were the prevalent prescribing errors subtype.[146,213,301,303,315,325] Only one of these studies reported prescribing error severity data finding that most errors were not significant. One study reported a combined rate of

prescribing errors and dispensing errors, which was 0.7 per patient with no significant harm and dosing errors representing 48.1% of errors.[306]

The median prevalence of medication administration errors was 31.4 per 100 administrations (IQR 8.2 – 84.8) across three studies; with severity addressed in only one study, which found that most observed errors were of moderate severity.[301,326,327] Commonly reported medication administration errors were dosing errors, omitted doses, wrong time and wrong administration rate errors.

Three studies (3/17, 17.6%) reported rates of preventable ADEs in NICUs across different countries.[155,312,323] Two of these studies used the same denominator (per 1000 patient-days) and preventable ADE rates ranged from 0.47 – 14.38.[155,312] These studies classified preventable ADE severity using different scales. One study [155] categorised all preventable ADEs as serious and another [312] found 14.3% of preventable ADEs resulted in persistent disability. The third study reported a preventable ADE rate of 0.86 per 1000 administered doses and no data were provided regarding the severity of these events.[323]

Only three studies (3/17, 17.6%) reported the commonly observed drug classes associated with MEs/preventable ADEs in NICUs (Table 4.2) including anti-infectives (n=3), nervous system agents (n=1), IV fluids (n=1), cardiovascular agents (n=1), respiratory agents (n=1), folates (n=1) and multivitamins (n=1).[144,303,315]

Table 4.3 Rates and common types of MEs and preventable ADEs in NICUs.

Event	Rate		Common types ***
	Same denominator *	Different denominators **	
Medication errors	Range: 5.5 – 77.9 per 100 medication orders (n=2) [35,204]	69.5 per 1000 doses § [323]	• PEs (n=6) • MAEs (n=5)
	Range: 4 – 35.1 per 1000 patient-days (n=2) [155,286]	26.4 per 100 case records [a] § [302]	
Prescribing errors	• Overall median: 14.9 (IQR 4.25 – 29.9) (n=6) [146,213,301,303,315,325] (Denominator: per 100 medication orders) ○ NICUs using paper medication charts Median: 28.9 per 100 medication orders (IQR 22.5 – 32.8) (n=3) [146,301,303] ○ NICUs using electronic medication charts 7.3 per 100 medication orders (n=1) [315]	43.5% of total prescribed drugs § [144] 8.5% of total OEs § [324]	• Dosing errors (n=10) • Absence of administration route or wrong diluent (n=6)
Prescribing & dispensing errors	0.7 per patient § [306]		• Dosing errors (n=1)
Medication administration errors	Median: 31.4 (IQR 8.2 – 84.8) (n=3) [301,326,327] (Denominator: per 100 administrations)		• Dosing errors or omissions (n=3) • Wrong time (n=2) • Wrong rate (n=2)
Preventable adverse drug events	Range: 0.47 – 14.38 per 1000 patient-days (n=2) [155,312]	0.86 preventable adverse drug events per1000 doses § [323]	

* Range of rates or median of MEs/preventable ADEs rates and IQRs were calculated.
** Range of rates or median rates of MEs/preventable ADEs and IQRs could not be calculated due to different denominators used and each rate was reported by only one study.
*** Frequently reported most common types across all included NICU studies.
[a] Self-calculated.
§ Only one study provided event rate.
Abbreviations: NICU(s): neonatal intensive care unit(s); OE(s): opportunities for error(s); PE(s): prescribing error(s); IQR(s): interquartile range(s); MAE(s): medication administration error(s).

4.5 Discussion

This chapter presented a systematic review which examined the frequency and nature of both MEs and preventable ADEs in critically ill neonates and children admitted to NICUs and PICUs. This comprehensive systematic review has included 35 unique studies and found that MEs are a common problem in PICUs (14.6 per 100 medication orders and 6.4 – 9.1 per 1000 patient days) and NICUs (ranging from 4 – 35.1 per 1000 patient-days and 5.5 – 77.9 per 100 medication orders). In PICUs, rates of preventable ADEs were 2.3 per 100 patients (one study) and 21 – 29 per 1000 patient -days (two studies). In NICUs, preventable ADE rates were reported in three studies (0.86 per 1000 doses (one study) and 0.47 – 14.38 per 1000 patient-days (two studies)). Across both ICU types, errors in prescribing and drug administration were found to be frequent types of MEs. Dosing errors were a frequently reported error subtype across both NICU and PICU in most of the studies included in this review.

Data regarding medications commonly associated with MEs/preventable ADEs was reported in four PICU and three NICU studies. The commonly reported prevalent drugs implicated in MEs/preventable ADEs in both settings were medicines used to treat infections followed by agents targeting the cardiovascular and nervous system as less frequently reported drug classes.

Few studies included a robust assessment of severity of identified MEs and preventable ADEs in PICU and NICU settings. In the small number of studies that considered severity, the variation in scales used (e.g. using a panel of medical experts [322], criteria set out by the NCC MERP [323] or the ASHP criteria [306]) made comparison across these studies impractical. Differences were also observed in definition, data collection method and study design of included studies in this systematic review which may have contributed to

variations in reported rates of MEs and ADEs. For example, studies that were designed to collect data prospectively reported higher rates of MEs [145,146,164,303,316,321] than retrospectively designed studies.[188,212,306,319,324,325] Prospective study designs may be more sensitive in detecting MEs and ADEs than retrospective.[33,174,328]

This systematic review identified limited data examining the safety of medicine dispensing and administration across both PICU and NICU compared to other stages of the medication use process (e.g. prescribing stage). This systematic literature review also found limited published data concerning the frequency and nature of harms due to MEs (preventable ADEs) in PICUs and NICUs and the studies available were restricted mostly to one country.[186,307,317,323] This constitutes an important area for further research to guide efforts to reduce avoidable patient harm. Describing the epidemiology of preventable ADEs (examining outcome as opposed to only process) is valuable to identify areas that are commonly involved with risk of MEs that lead to actual patient harm, which will help inform an action agenda for improvement.[46] In addition, high rates of MEs were found in a number of studies conducted across both ICU settings, with little change between recent studies and those 10 years past.[145,146,164,303] This highlights the need to understand the underlying contributory factors associated with MEs to inform preventive strategies.[298]

The key strength of this review is the inclusion of both MEs and related preventable ADEs together providing a more complete overview of the risks associated with medication use in children's intensive care settings. This will help to better target attention towards interventions that might reduce preventable events and associated harm. The limitations of this systematic review included marked levels of observed heterogeneity amongst included studies which precluded meta-analysis. Some of the included studies in this review may have featured preventive policies/interventions already implemented to reduce MEs [329,330], which may have influenced the rates of MEs. Unfortunately, detailed data on such

policies/interventions was not routinely reported. In addition, this systematic review did not assess quantitatively the impact of differences in MEs definitions, error detection methods, and hospital context (differences in units examined) on the error rates across included studies. Furthermore, assessing the quality of several studies (e.g. conference abstracts) was not feasible due to lack of sufficient information. High quality research in the future is needed to acquire a better estimate of the prevalence and nature of MEs and preventable ADEs in children's intensive care settings. Only English language publications were included in this systematic review and studies published in other languages may have been missed.

In conclusion, this systematic review identified 35 unique studies and found that preventable medication-related events are an enduring threat to the safety of children in intensive care. This systematic review has also identified potentially important targets such as dosing errors and anti-infective medications that could help set an improvement agenda for clinicians, health care leaders and researchers. This systematic review also acknowledges the pressing need for standardisation of study design and definitions due to high levels of observed heterogeneity and recognises a need for future research to explore issues such as medication administration errors and preventable ADEs in more detail as there is little attention to these in the current body of evidence.

The next chapter will present the findings of a prospective observational cohort study that was conducted to determine the incidence, nature, preventability, severity and risk factors of ADEs occurring in critically ill children at UK hospitals.

Chapter 5. Incidence and nature of adverse drug events in paediatric intensive care units: A prospective multicentre study

5.1 Introduction

As described in chapter 4, the systematic review findings showed that preventable ADEs might be common in critically ill children based on four studies conducted across three different countries. Rates of these outcomes in PICUs ranged from 21 to 29 preventable ADEs per 1000 patient-days (two studies)[186,187] and from 0.47 to 14.38 per 1000 patient-days (two studies)[155,312] in NICUs. However, it was observed that medication safety research in this high-risk patient population generally focuses on MEs with limited available data regarding ADEs. None of the studies that were identified examining the burden and nature of preventable ADEs in critically ill children were conducted in UK hospitals, which represents a knowledge gap and barrier to improvement efforts given also differences in care and medicines management processes between PICUs.[110,331,332]

5.2 Aim and objectives

This study aimed to determine the incidence, nature, preventability, severity and risk factors of ADEs across three NHS PICUs in England.

The objectives of this chapter were:

- To assess the rate of ADEs occurring in PICU including both preventable (due to ME) and non-preventable (due to ADRs),
- To assess the nature of detected ADEs in terms of causality, preventability, severity and commonly involved stages of medication use process and medication classes,
- To assess the association between the presence of ADEs and independent variables (age, follow up period, number of medications and participated PICU site),
- To highlight targets for remedial interventions to reduce the risk of avoidable patient harm in PICUs.

5.3 Method

5.3.1 Study design and setting

The study utilised a prospective cohort design and was carried out over a three-month period (90 days) during 2019 across three PICUs (17 (PICU-C), 18 (PICU-B) and 31 (PICU-A) bedded units) that provide regional acute care specialities for new-born babies and children up to 18 years of age in the North West, West Midlands, South West of England and South Wales.

5.3.2 Eligible patients

All patients admitted to any one of the three PICUs and who stayed for a minimum of 24-hours (including those already admitted to PICUs when the study started) during the study period were eligible for inclusion. In order to include similar patient populations in terms of severity and complexity of health condition, high dependency unit (level 1 PICU) patients were excluded. Normally, those patients are not receiving care for critical illnesses and admitted to PICU to facilitate close monitoring only.[333]

The study's endpoint for each included patient related to the earliest of the following events: transfer to another inpatient ward/unit/hospital, discharged into the community, died or remained an inpatient on the PICU at the end of the study data collection period.

5.3.3 Study sampling

This study aimed to screen a sample of 300 patients across three NHS PICUs. This number was calculated to be sufficient to estimate the percentage of participants experiencing an ADE across these PICUs to within ±15% with 95% confidence, assuming an intra-hospital

correlation coefficient of 0.05 and that the number of participants recruited will differ between centres (coefficient of variation = 0.4).

5.3.4 Classification of adverse drug events and main outcomes

ADEs were defined as "injuries that result from the use of a drug".[35] ADE is a broad term that encompasses injury that is a result of both MEs or unavoidable side effects. Harm associated with a ME was considered preventable. Both preventable and non-preventable ADEs were collected for this study. However, this study is based on the findings of the earlier systematic review (Chapter 4) [334], hence an important focus was on ADEs that were preventable.

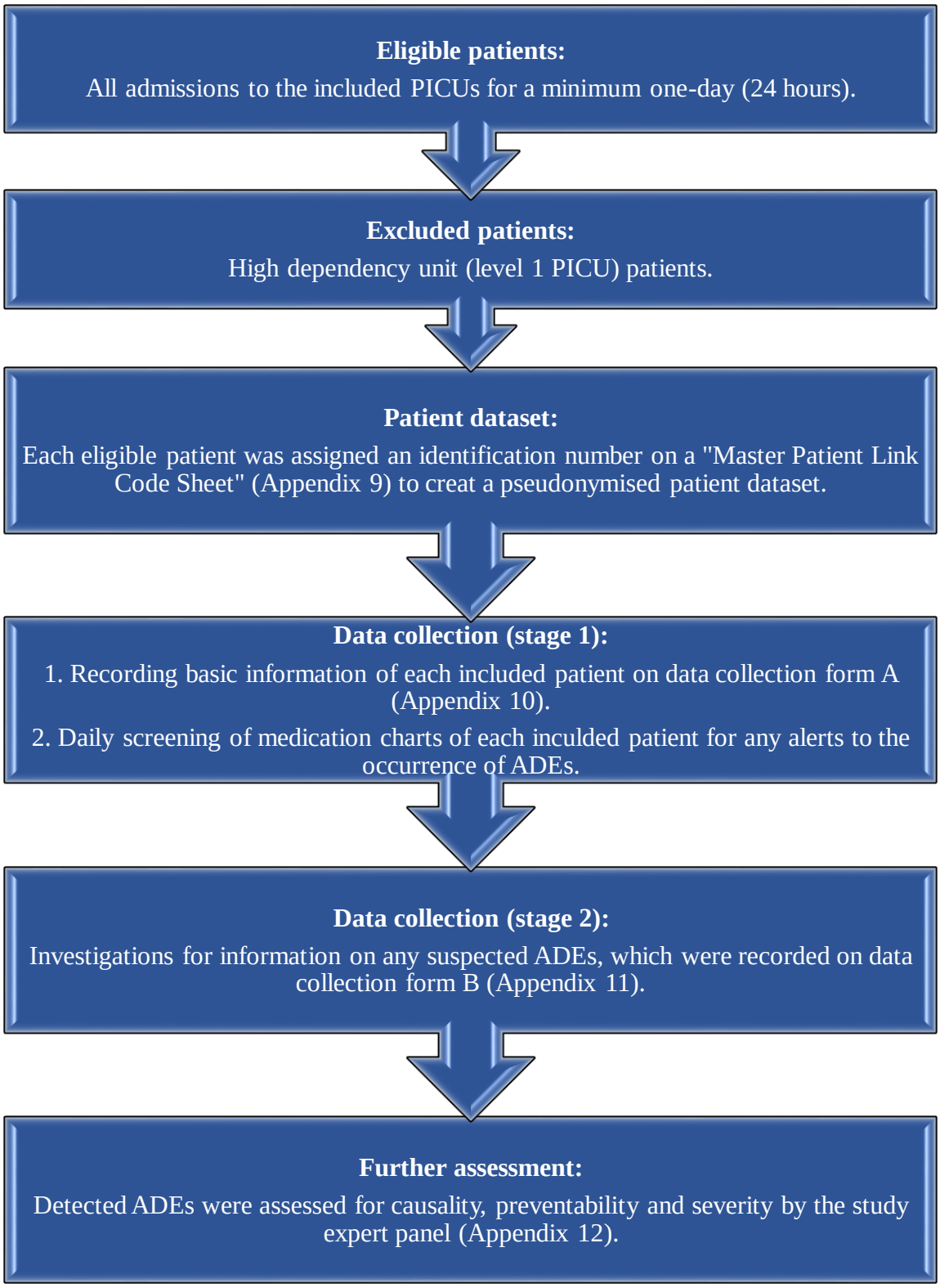
The primary outcome measure was to determine the frequency of ADEs and preventable ADEs per 100 patients and 1000 patient-days. The secondary outcome measures were to determine measures of causality, preventability, severity, involved medications and stage of medication use process with ADEs as well as examining risk factors associated with ADEs and preventable ADEs in PICUs. Risk factors were identified by assessing the association between ADEs occurrence and characteristics of patients including age, number of medications on admission, duration of follow up and PICU site.

5.3.5 Data collection

Intensive surveillance of included patients for all suspected ADEs occurring in PICUs was performed by PICU clinical pharmacists employed by the host NHS trusts as shown in Figure 5.1. Pharmacists each received a face-to-face training session delivered by two of the research team members (AAA and AS) on the data collection process and were given supporting resources to help them identify potential ADEs as described in Appendix 9.

These resources included a guide that could help detect and track ADEs adapted from the literature and tailored by an experienced PICU clinical pharmacist to UK paediatric critical care [335,336], which contains useful triggers to identify ADEs. However, the detection of suspected ADEs relied mainly on the clinical judgement of the PICU clinical pharmacists, which they performed by virtue of their routine clinical roles. During the training session, ADE case scenarios were provided to the pharmacists in order to establish and clarify their understanding of the data collection process and the study objectives (Appendix 9). These case scenarios were developed by one of the research authors (AAA) and reviewed by one PICU clinical pharmacist (AS) and one consultant paediatric intensivist (GM).

The data collection process was piloted (including the data collection forms developed for this study) and necessary amendments were made according to feedback from involved clinical pharmacists. The pilot work was carried out over two weeks in PICU-C. The research objectives were described to the lead pharmacist in this PICU who was participating in this study as a data collector. The pharmacist was provided with the supporting resources and the study's data collection forms (Appendices 9, 10 and 11). Based on the findings of the pilot work, amendments were made on the data collection forms, which involved changing the structure (order of the form sections) so that it flowed better and the forms took less time to complete.



Abbreviations: ADEs: adverse drug events; PICUs: paediatric intensive care units.

Figure 5.1 Flow chart of the data collection process for ADEs identification.

Demographic information for each eligible patient was collected including age at admission, date of admission to the PICU, history of drug allergies and number of medications on the admission date after the medication reconciliation has been completed (Appendix 10).

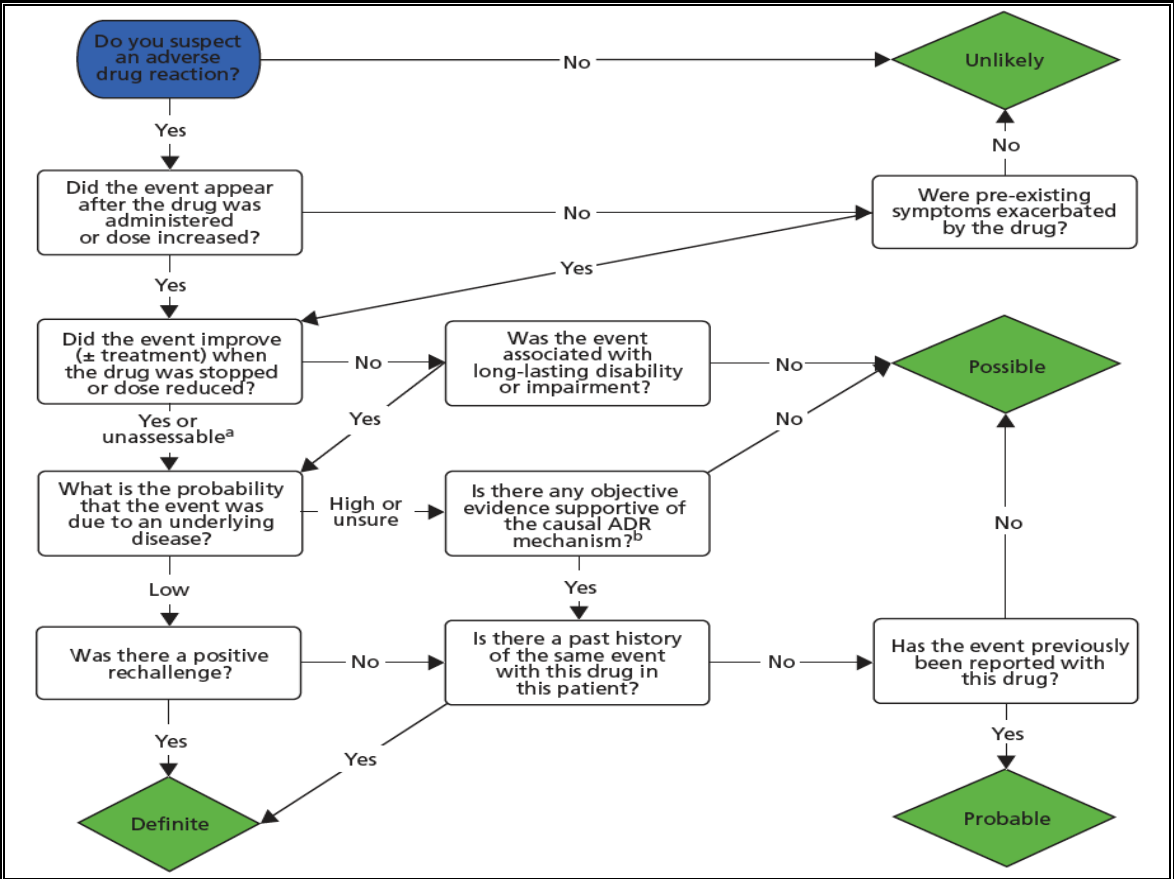
Suspected ADEs were identified initially through daily screening of medication charts of all inpatients admitted to the study PICUs, along with identification and investigation for any alerts to the occurrence of ADEs. Medical notes, laboratory reports, patient safety incident reports and conversations with staff/patients/families were also used to identify events daily.

Further inspection of any suspected ADEs included examination of all relevant patient records such as prescription orders or medication administration records, case note entries and attending multidisciplinary unit rounds. Any identified event or trigger (e.g. low potassium levels or a ME) was recorded and followed up by the clinical pharmacists during the stay of the involved patient in PICU. These events were considered ADEs only if they caused a harmful outcome due to use of a drug. The pharmacists also provided data on the apparent causes, severity and preventability of each ADE they identified as shown in Appendix 11.

5.3.6 Assessment of causality, preventability and severity

A multidisciplinary expert panel reviewed each recorded event that data collectors suspected as harm related to medication use. The expert panel included two experienced PICU clinical pharmacists and one consultant paediatric intensivist. Each panel member reviewed each adverse event independently in meetings that were held to assess causality, preventability and severity of identified events. Panel members discussed any disagreement to achieve consensus (Appendix 12).

The Liverpool ADR causality assessment tool [337] (Figure 5.2) was used to assess the causal relationship between use of drugs and adverse events. This causality algorithm classifies detected ADEs/ADRs into unlikely, possible, probable, and definite. Definite or probable ADE categories underwent preventability assessment. This was performed by the expert panel using the feasible Schumock and Thornton preventability scale (Table 5.1).[338]



Unassessable refer to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressant).

**Examples of objective evidence: positive laboratory investigation of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient.

Abbreviations: ADR: Adverse drug reaction.

Figure 5.2 Liverpool ADR causality assessment tool.

(Source: Ruairi et al (2011))[337]

The expert panel also assessed each ADEs severity using categories E though I of the NCC MERP classifications index (Table 5.1).[249]

Table 5.1 Criteria used to assess preventability and severity of probable and definite ADEs.

Preventability criteria according to Schumock and Thornton scale *	
1	Was there a history of allergy or previous reactions to the drug?
2	Was the drug involved inappropriate for the patient's clinical condition?
3	Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4	Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5	Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
6	Was a drug interaction involved in the reaction?
7	Was poor compliance involved in the adverse drug reaction?
Harm categories based on the NCC MERP classifications index.	
Category E	Harm that required intervention and resulted in temporary patient harm.
Category F	Harm that required initial or prolonged hospitalisation and resulted in temporary patient harm.
Category G	Harm that resulted in permanent patient harm.
Category H	Harm that resulted in near-death event and required intervention to sustain life.
Category I	Harm that resulted in the death of a patient.

Abbreviations: ADE: Adverse drug event; NCC MERP: National Coordinating Council for Medication Error Reporting and Prevention.
* The assessed ADE was considered preventable if any answer to one or more of the questions was "yes".

5.3.7 Statistical analysis

The statistical analyses were performed using STATA v15®.[339] Descriptive statistics were calculated for characteristics of the patients, such as age, length of follow-up period and number of medications. Dependent on their distributional form, we presented either mean and standard deviation or median and IQRs, plus the range. It was not known exactly how long some patients (4%) stayed in PICU (e.g. some patients remained in PICUs after the study stopped) and, therefore, it has been assumed that they stayed for 90 days (the duration of data collection).

The incidence rate per 1000 patient days was calculated by dividing the total number of ADEs or preventable ADEs detected by the total number of patient days in PICU and multiply the result by 1000. To express the rates as percentages, the total number of patients who experienced one or more ADE or preventable ADE was divided by the total number of included patients and multiplied by 100.

The estimated crude and adjusted (for follow up period and PICU site) incident rates of ADEs were calculated per 1000 patient-days and per 100 patients, along with 95% CI. A null regression model was used to determine rates adjusted for duration of follow up and PICU site. This is in order to control for the different numbers of patients from each PICU as well as the differing duration of follow up from patient-to-patient.

Medications associated with the occurrence of ADEs and preventable ADEs were described and reported according to the BNF-C.[59] The severity of detected ADEs and involved stages of medication use process were presented as numbers and percentages. Additionally, cross-tabulations were used to describe associations between variables such as stage of medication use process and severity of ADEs.

Associations between independent variables and ADEs detected in this study were investigated using univariable (direct association between outcome variable and each covariate independently) and multivariable (control for other covariates) logistic regression models. Two classifications of the dependant variable (ADE) were considered. The first classification involved both types of ADEs (preventable and non-preventable) versus no ADEs, and the second was preventable ADEs versus non-preventable and no ADEs. Independent variables were categorised into groups involving five groups of patients' age (≤29 days, one month – 12 months, 13 months – 60 months, 61 months – 144 months and >144 months), three groups of follow up periods (one – six days, seven – 14 days and ≥15 days), three groups of number of medications on admission (one – eight, nine – 13 and 14 – 23 medications).

Additionally, univariable and multivariable multinomial regression was carried out. This is because there were actually three possible classifications (no ADE, preventable ADE, non-preventable ADE), but there is no natural ordering to them. Analyses used patients without ADEs as a base outcome and examined two classifications (no ADE vs preventable ADE and no ADE vs non-preventable ADE). It was controlled for PICU site, duration of follow up, age and number of medications in the multivariable multinomial analysis.

Only patients who experienced ADEs that were classified as definite or probable were included in the regression analysis. The findings of the regression analysis were presented as odds ratios (OR) and 95% CI. A p-value <0.05 was considered to represent statistical significance.

5.3.8 Ethical consideration

This study was granted ethical approvals by Health Research Authority (approval reference: NHS001521) and the Research and Development/Audit Departments from each participating NHS trust sites (Appendix 13).

5.4 Results

5.4.1 Patient characteristics

A total of 302 patients across the three participating PICUs were included during the study period. The patients' age ranged from two days to 18 years old with a median of 365 days (IQR 60 days – 6 years). The median number of medications prescribed for patients on admission was 9 [IQR (7 – 12); range = 1 to 23]. In total 3,000 medications had been prescribed to the study sample. The range of follow up was between two and 90 days with a median of six days (IQR 3 – 14). Only 12 of the 302 patients (4%) stayed on the PICU for the entire follow-up period (90 days). Table 5.2 summarises the characteristics of the patients, both overall and by participating PICU.

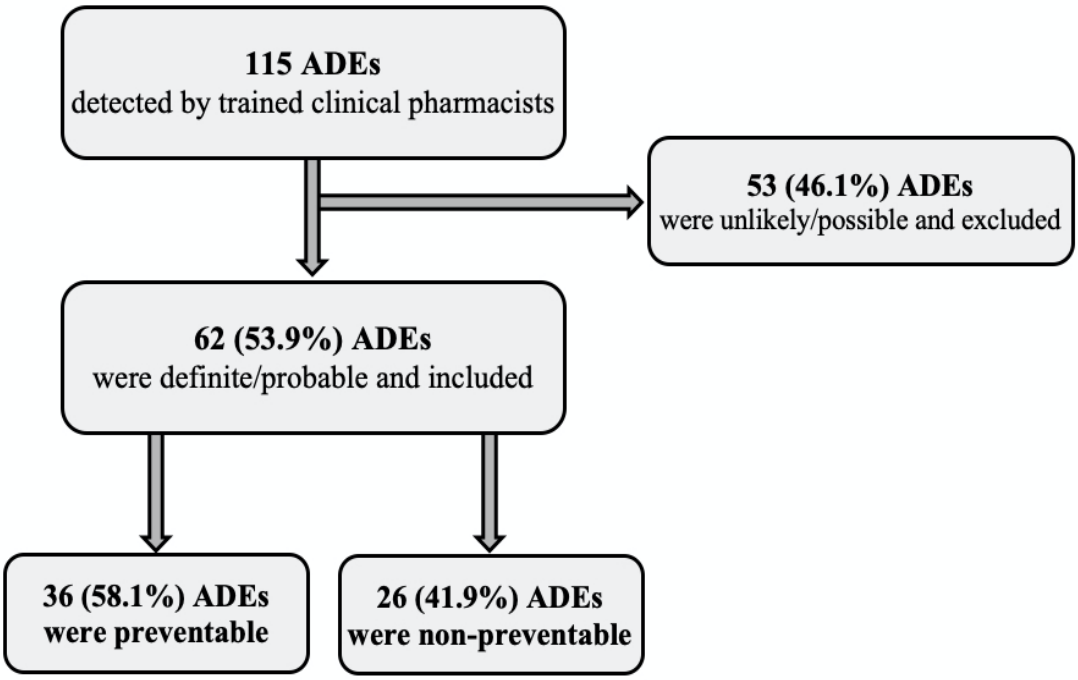
Table 5.2 Characteristics of included patients.

Participating PICUs	Number of patients No. (%)	Age – years Median (IQR)	Follow up period – days Median (IQR)	Number of medications on admission Median (IQR)
PICU – A	81 (26.8%)	0.5 (0.08 – 5.06)	5 (3 – 10)	8 (6 – 11)
PICU – B	100 (33.1%)	1.01 (0.16 – 8.61)	6.5 (3 – 15)	10 (8 – 14)
PICU – C	121 (40.1%)	1.83 (0.32 – 7.09)	6 (3 – 14)	9 (7 – 13)
Total	302 (100%)	1.01 (0.16 – 6.1)	6 (3 – 14)	9 (7 – 12)

Abbreviations: PICUs: paediatric intensive care units; IQR: interquartile range.

5.4.2 Rate and nature of adverse drug events

In total, 115 ADEs were detected by the clinical pharmacists during the study's follow up period. Of these, 53 (46.1%) were deemed unlikely or possible causality and were excluded from further assessment. The remaining 62 (53.9%) ADEs were confirmed by the expert panel and classified as definite (7/62, 11.3%) and probable causality (55/62, 88.7%) as shown in Figure 5.3.



Abbreviations: ADE: adverse drug event.

Figure 5.3 Results of causality and preventability assessment of detected events.

The characteristics of patients experiencing no ADEs, unlikely or possible causality ADEs and definite or probable ADEs are presented in Table 5.3. One in six patients (47/302, 15.6%) experienced at least one confirmed ADE (definite and probable causality) during PICU stay. Eleven patients (3.6%) were affected by more than one ADE. Given that these multiple ADEs were not common and not related to each other (e.g. caused different

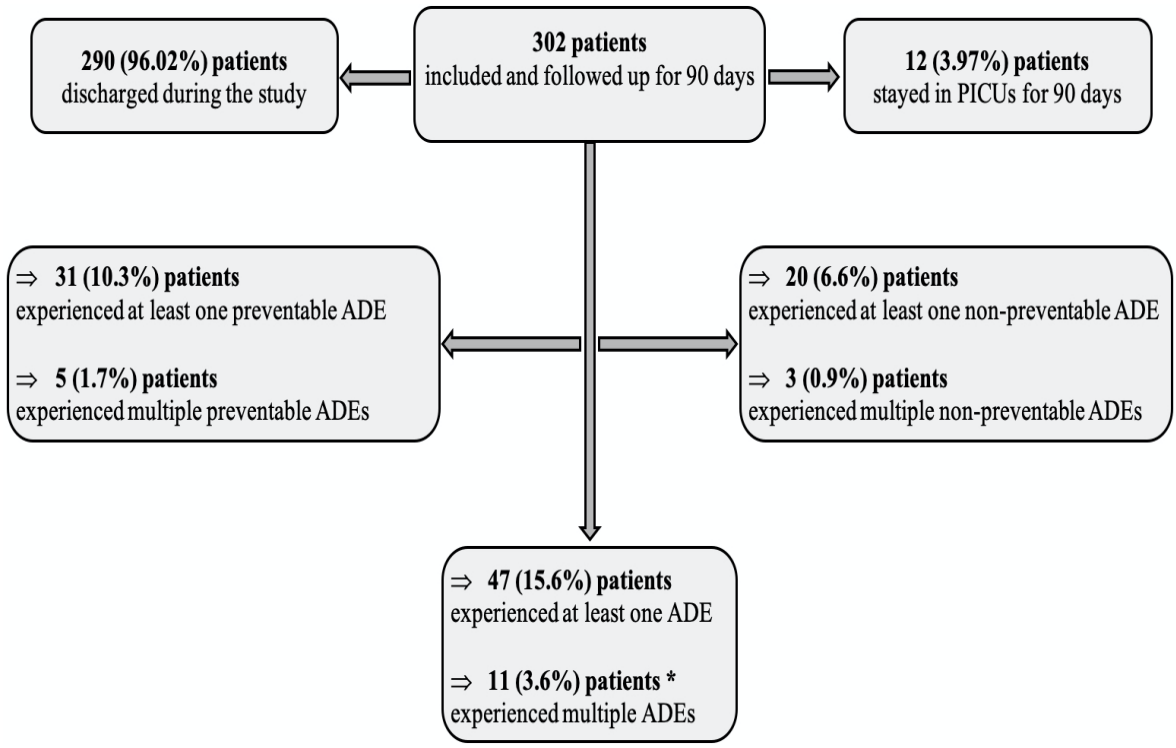
patient harm by different medications), they were treated as independent events. Figure 5.4 illustrates screened patients, and proportions of patients affected by ADEs.

Table 5.3 Characteristics of patients without ADEs, with unlikely or possible ADEs and with definite or probable ADEs.

Variable		Patients without ADEs (n=255)	Patients with unlikely or possible ADEs [a] (n=42)	Patients with definite or probable ADEs [b] (n=47)
Age in years. Median (IQR) [Range: 2 days – 18 years]		1.01 (0.16 – 7.1)	2.3 (0.31 – 11.2)	1.7 (0.31 – 6.1)
Follow up period in days. Median (IQR) [Range: 2 – 90 days]		5 (2 – 10)	15 (7 – 34)	15 (8 – 32)
Number of medications on admission. Median (IQR) [Range: 1 – 23 drugs]		9 (7 – 12)	10 (8 – 15)	12 (8 – 15)
Involved PICUs (n, %)	PICU – A	63 (24.7%)	20 (47.6%)	18 (38.3%)
	PICU – B	87 (34.1%)	8 (19.04%)	13 (27.6%)
	PICU – C	105 (41.2%)	14 (33.3%)	16 (34.04%)

Abbreviations: ADEs: adverse drug events, IQR: interquartile range, PICUs: paediatric intensive care units.
[a] Unlikely or possible causality ADEs as classified by the study's expert panel were excluded from further assessment.
[b] ADEs with definite or probable causality as classified by the study's expert panel were included in the study analysis.

As presented in Table 5.4, the crude and adjusted (for duration of follow up and PICU site) ADE rates per 100 patients were 20.5 ADEs (95% CI, 16.1 – 25.5) and 20.5 (95% CI, 15.32 – 27.55), respectively. The crude rate of ADEs per 1000 patient-days was 15.6 (95% CI, 11.9 – 20.1) and the adjusted rate for PICU site and follow up period was 16.7 per 1000 patient-days (95% CI, 9.35 – 29.95).



Abbreviations: ADE: adverse drug events. PICU: paediatric intensive care unit.
* Three of those patients experienced one preventable and one non-preventable ADEs.

Figure 5.4 Screened patients and proportions of patients experienced ADEs.

The prescribing stage was most commonly associated with confirmed ADEs (29/62, 46.8%) as shown in Table 5.5. Monitoring medicines was the second most common stage involved with confirmed ADEs (18/62, 29.03). The majority of confirmed ADEs (42/62, 67.7%) caused temporary patient harm (the lowest level of severity) with the remaining ADEs causing prolonged hospitalisation and temporary harm (13/62, 20.9%), permanent harm (4/62, 6.4%) and near-death events (3/62, 4.8%). None of the confirmed ADEs resulted in death events.

Table 5.4 Crude and adjusted rates of ADEs per 100 patients and 1000 patient-days.

Category	Rate of ADE per 100 patients (95% CI) [a]		Rate of ADE per 1000 patient-days (95% CI) [a]	
	Crude rate	Adjusted rate [b]	Crude rate	Adjusted rate [b]
All ADEs	20.5 [c] (95% CI, 16.1–25.5)	20.5 [c] (95% CI, 15.3–27.5)	15.6 [d] (95% CI, 11.9–20.1)	16.7 [d] (95% CI, 9.3–29.9)
Preventable ADEs	11.9 [c] (95% CI, 8.4–16.1)	11.7 [c] (95% CI, 6.7–20.1)	9.08 [d] (95% CI, 6.3–12.5)	9.43 [d] (95% CI, 4.02–22.1)

Abbreviations: ADEs: adverse drug events, CI: confidence intervals.
[a] The 95% C.I.'s to give the degree of uncertainty in these calculations (e.g. between 9.3 and 29.9 new ADE's per 1,000 patients per day).
[b] Adjusted rate for follow up period and paediatric intensive care unit site.
[c] Number of patients in every 100 patients will have an ADE during the course of their observation.
[d] New ADE's per 1,000 patients per day.

Seven ADEs (7/62, 11.3%) caused the most severe ADEs (permanent harm and near-death events). The medicines administration stage was commonly involved with the most severe ADEs (4/7, 57.1%) (three ADEs caused permanent patient harm and one led to a near death event). The monitoring stage was associated with one ADE that resulted in permanent patient harm and one led to a near death event (2/7, 28.6%). One further ADE resulted in near-death harm and was associated with the prescribing stage (1/7, 14.3%).

The most commonly involved drug classes associated with ADEs were medicines for central nervous system (14/62, 22.6%), infections (13/62, 20.9%) and cardiovascular system (12/62, 19.4%). ADEs that caused severe patient harm (permanent harm and near-death events) were associated with using anti-infectives and cardiovascular agents, with some considered as high-risk medicines (e.g. adrenergic antagonists and aminoglycosides) as shown in Table 5.6 and Appendix 14.

5.4.3 Rate and nature of preventable adverse drug events

The majority of the confirmed ADEs were preventable (36/62, 58.1%). Few patients (5/302, 1.7%) experienced more than one preventable ADE (Figure 5.4). The estimated crude and adjusted (for follow up period and PICU site) rates of preventable ADEs per 100 patients were 11.9 (95% CI, 8.4 – 16.1) and 11.7 (95% CI, 6.7 – 20.1), respectively. The crude rate of preventable ADEs per 1000 patient-days was 9.08 (95% CI, 6.3 – 12.5) and the adjusted rate for PICU site and follow up period was 9.43 per 1000 patient-days (95% CI, 4.02 – 22.1) as shown in Table 5.4.

The severity of confirmed preventable ADEs ranged between categories E (temporary harm to patient) through H (near-death event) on the NCC MERP index (Table 5.5). Most of the preventable ADEs (21/36, 58.3%) caused temporary harm to patients (category E). Ten ADEs (27.8%) fell into category F, which required prolonged hospitalisation and resulted in temporary patient harm. A smaller proportion of preventable ADEs resulted in severe harm that caused permanent patient injury (category G) and a near-death event (category H) and accounted for 11.1% (4/36) and 2.7% (1/36), respectively.

Preventable ADEs were mostly associated with the medicines prescribing stage (17/36, 47.2%) followed by the administration stage (13/36, 36.1%). The near-death preventable ADE incident was associated with the prescribing stage (1/17, 5.9%). Four preventable ADEs resulted in permanent patient injuries; three were associated with the administration stage (3/13, 23.1%) and one with monitoring (1/6, 16.7%) stage (Table 5.5).

Table 5.5 Stage of medication use process and severity of harm associated with ADEs.

All ADEs	Stage of medication use process No. (%)			Total No. (%)
	Prescribing	Administration	Monitoring	
	29 (46.8%)	15 (24.2%)	18 (29.03%)	62 (100%)
Severity (NCC MERP index) No. (%)				
E (temporary patient harm)	20 (47.6%)	8 (19.05%)	14 (33.3%)	42 (67.7%)
F (prolonged hospitalisation and temporary harm)	8 (61.5%)	3 (23.08%)	2 (15.4%)	13 (20.9%)
G (permanent harm)	0 (0.0%)	3 (75%)	1 (25%)	4 (6.4%)
H (near-death)	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (4.8%)
Preventable ADEs	Stage of medication use process No. (%)			
	Prescribing	Administration	Monitoring	Total No. (%)
	17 (47.2%)	13 (36.1%)	6 (10.3%)	36 (58.1%)
Severity (NCC MERP index) No. (%)				
E (temporary patient harm)	11 (52.4%)	7 (33.3%)	3 (14.3%)	21 (58.3%)
F (prolonged hospitalisation and temporary harm)	5 (50%)	3 (30%)	2 (20%)	10 (27.8%)
G (permanent harm)	0 (0.0%)	3 (75%)	1 (25%)	4 (11.1%)
H (near-death)	1 (100%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

Abbreviations: ADEs: adverse drug events,
NCC MERP: National Co-ordinating Council for Medication Error Reporting and Prevention,
E: Harm that required intervention and resulted in temporary patient harm,
F: Harm that required initial or prolonged hospitalisation and resulted in temporary patient harm,
G: Harm that resulted in permanent patient harm,
H: Harm that resulted in near-death event and required intervention to sustain life,
I: Harm that resulted in the death of a patient.

Medications for the central nervous system were the most common agents involved with preventable ADEs (10/36, 27.8%) followed by cardiovascular system agents (9/36, 25%)

and medicines to treat infections (5/36, 13.9%) as shown in Table 5.6. Drug classes involved with the most severe preventable ADEs (permanent patient harm or near-death event) were cardiovascular system agents (3/5, 60%) and anti-infectives (2/5, 40%). Complications (e.g. sedation withdrawal events) associated with using medications that have sedative effects (e.g. benzodiazepines and opioid analgesics that are considered high-risk medications) were the most frequently reported preventable ADEs (11/36, 30.6%) in PICUs. Seven of these ADEs led to prolonged hospitalisation for the involved patients. Appendix 14 summarises preventable ADEs, drug classes involved, associated level of severity and explanation of their preventability.

Table 5.6 Commonly involved drug classes with preventable and non-preventable ADEs and associated level of severity.

Drug class	Severity (NCC MERP index) No. (%)				Preventable ADEs No. (%)	Non-preventable ADE No. (%)	Total No. (%)
	E (temporary patient harm)	F (prolonged hospitalisation and temporary harm)	G (permanent harm)	H (near-death)			
Central nervous system	7 (50%)	7 (50%)	0 (0.00%)	0 (0.00%)	10 (27.8%)	4 (15.4%)	14 (22.6%)
Cardiovascular system	6 (50%)	2 (16.7%)	2 (16.7%)	2 (16.7%)	9 (25%)	3 (11.5%)	12 (19.4%)
Anti-infectives	10 (76.9%)	1 (7.7%)	2 (15.4%)	0 (0.00%)	5 (13.9%)	8 (30.8%)	13 (20.9%)
Total	(23/62, 37.1%)	(10/62, 16.1%)	(4/62, 6.5%)	(2/62, 3.2%)	(24/36, 66.7%)	(15/26, 57.7%)	(39/62, 62.9%)

Abbreviations: ADEs: adverse drug events,
NCC MERP: National Co-ordinating Council for Medication Error Reporting and Prevention,
E: Harm that required intervention and resulted in temporary patient harm,
F: Harm that required initial or prolonged hospitalisation and resulted in temporary patient harm,
G: Harm that resulted in permanent patient harm,
H: Harm that resulted in near-death event and required intervention to sustain life,
I: Harm that resulted in the death of a patient.

5.4.4 Associations between adverse drug events and covariates

In the univariable analysis, a significant association was found between duration of follow up and the occurrence of ADEs ($p<0.001$). Patient age and number of medications were not significantly associated with the occurrence of ADEs in the univariable logistic regression model (Table 5.7).

In addition, PICU site was not associated with experiencing one or more ADEs before controlling for the other covariates ($p=0.160$). Due to observed differences in patient characteristics (e.g. number of patients and age) between involved PICUs, it has been controlled for PICU site in the multivariable models to test the impact of these variations on ADE occurrence. PICU site was found to be significantly ($p=0.006$) associated with ADE occurrence adjusting for the four independent variables involved in the multivariable logistic regression. Patients admitted to PICU-B (OR 0.27, 95% CI 0.10 – 0.69) or PICU-C (OR 0.26, 95% CI 0.10 – 0.65) were less likely to experience ADEs than those residing within PICU-A.

Another significant association was found between duration of follow up and the occurrence of ADEs in the multivariable logistic analysis ($p<0.001$). Patients who were screened for one to two weeks (OR 6.29, 95% CI 2.42 – 16.32) or more than 15 days (OR 13.12, 95% CI 5.01 – 34.34) were more likely to experience ADEs than those who were followed up for shorter periods (one week or less) as shown in Table 5.7. The remaining two covariates (age and number of medications) remained not significantly associated with the occurrence of ADEs in the multivariable logistic regression model.

Similarly, an increased risk of a patient experiencing one or more preventable ADEs was only associated with duration of follow up in the univariate analysis ($p<0.001$). The remaining covariates (patient age, number of medications and PICU site) were not

associated significantly with risk of having ADE in the univariate analysis as described in Table 5.7.

Duration of follow up remained significantly associated with experiencing a preventable ADE ($p<0.001$) in the multivariable logistic regression model (Table 5.7). Patients were more likely to experience preventable ADEs if they were followed up in PICUs for seven to 14 days (OR 5.21, 95% CI 1.78 – 15.21) or more than 15 days (OR 8.02, 95% CI 2.68 – 23.96) compared to those who were followed up for less than seven days (1 – 6 days). PICU site was also found to be significantly associated with ADE occurrence in the multivariate analysis ($p<0.033$). Patients in PICU-B (OR 0.40, 95% CI 0.14 – 1.08) and PICU-C (OR 0.26, 95% CI 0.09 – 0.74) were at lower risk of having preventable ADEs than patients in PICU-A.

As longer stay or period of observation in intensive care may result in a greater chance of an ADE, these regression models have been refitted excluding duration of follow up. This has found that other variables (age ($p=0.890$), number of medications ($p=0.148$) and PICU site ($p=0.094$)) were not associated significantly with ADEs occurrence.

Table 5.7 Univariable and multivariable logistic regression analysis of ADEs.

Covariate	**Category**	**Univariable analysis**		**Multivariable analysis**	
		Odds Ratios (95% CI)	P- value*	Odds Ratios (95% CI)	P- value*
Preventable and non-preventable ADEs					
Age	≤29 days	Reference	0.787	Reference	0.493
	1 month – 1 year	1 (0.37 – 2.63)		1.03 (0.35 – 3.03)	
	1 (>12 months) – 5 years	1.5 (0.54 – 4.15)		2.21 (0.67 – 7.24)	
	5 (>60 months) – 12 years	0.85 (0.27 – 2.64)		0.99 (0.28 – 3.49)	
	12 (>144 months) – 18 years	1.38 (0.41 – 4.57)		1.68 (0.41 – 6.75)	
Follow up period (days)	1 – 6	Reference	<0.001	Reference	<0.001
	7 – 14	5.28 (2.12 – 13.14)		6.29 (2.42 – 16.32)	
	≥15	10.33 (4.3 – 24.57)		13.12 (5.01 – 34.34)	
Number of medications on admission	1 – 8	Reference	0.099	Reference	0.715
	9 – 13	1.2 (0.58 – 2.47)		1.33 (0.57 – 3.11)	
	14 – 23	2.4 (1.06 – 5.38)		1.4 (0.54 – 4.04)	
Involved PICUs	PICU – A	Reference	0.160	Reference	0.006
	PICU – B	0.52 (0.23 – 1.14)		0.27 (0.10 – 0.69)	
	PICU – C	0.53 (0.25 – 1.12)		0.26 (0.10 – 0.65)	
Preventable ADEs					
Age	≤29 days	Reference	0.873	Reference	0.981
	1 month – 1 year	0.70 (0.25 – 1.93)		0.75 (0.25 – 2.27)	
	1 (>12 months) – 5 years	0.54 (0.16 – 1.83)		0.75 (0.19 – 2.89)	
	5 (>60 months) – 12 years	0.58 (0.17 – 1.98)		0.72 (0.19 – 2.72)	
	12 (>144 months) – 18 years	0.62 (0.14 – 2.60)		0.63 (0.12 – 3.15)	
Follow up period (days)	1 – 6	Reference	<0.001	Reference	<0.001
	7 – 14	4.87 (1.72 – 13.78)		5.21 (1.78 – 15.21)	
	≥15	6.66 (2.43 – 18.18)		8.02 (2.68 – 23.96)	
Number of medications on admission	1 – 8	Reference	0.304	Reference	0.604
	9 – 13	0.61 (0.24 – 1.54)		0.76 (0.29 – 2.02)	
	14 – 23	1.46 (0.56 – 3.79)		1.3 (0.42 – 4.06)	
Involved PICUs	PICU – A	Reference	0.105	Reference	0.033
	PICU – B	0.58 (0.24 – 1.40)		0.40 (0.14 – 1.08)	
	PICU – C	0.37 (0.14 – 0.93)		0.26 (0.09 – 0.74)	

PICUs: paediatric intensive care units, ADEs: adverse drug events.

* P-value is a 'composite' and represents the significance of the overall association between the covariate and the outcome (and not pairwise contrasts between the reference category and other individual categories).

Non-preventable ADEs were found to be rare in the two youngest age groups (≤29 days and 1 month to 1 year). Therefore, these two age groups were combined and four age categories were used when adjusting for this variable in the multinomial logistic regression models.

The findings of the multinomial regression analysis are in line with the logistic regression presented in Table 5.7. Among the four independent variables, the follow up period was the only variable associated with the occurrence of both preventable ADEs and non-preventable ADEs identified in the univariate analysis ($p<0.001$) as shown in Table 5.8.

The follow up period remained significantly associated with ADE occurrence of both preventable ADEs and non-preventable ADEs after controlling for the other covariates ($p<0.001$). The multivariable multinomial regression analysis also showed that PICU site was associated with occurrence of both preventable ADEs and non-preventable ADEs ($p<0.017$). The multivariable analysis did not show association between either preventable ADEs or non-preventable ADEs and the remaining variables (age and number of medications).

Table 5.8 Univariable and multivariable multinomial logistic regression analysis of ADEs.

Covariate	**Category**	**Univariable analysis**		**Multivariable analysis**	
No ADEs (base outcome)		Coef. (95% CI)	P- value*	Coef. (95% CI)	P- value*
Preventable ADEs					
Age	≤ (12 months)1 year	Reference	0.154	Reference	0.139
	1 (>12 months) – 5 years	-0.26 (-1.031 – 0.77)		0.19 (-0.09 – 1.34)	
	5 (>60 months) – 12 years	-0.28 (-1.33 – 0.75)		-0.08 (-1.2 – 1.04)	
	12 (>144 months) – 18 years	-0.57 (-2.09 – 0.94)		-0.41 (-2.0 – 1.23)	
Follow up period (days)	1 – 6	Reference	<0.001	Reference	<0.001
	7 – 14	1.64 (0.601 – 2.68)		1.77 (0.69 – 2.86)	
	≥15	2.01 (0.98 – 3.03)		2.27 (1.14 – 3.40)	
Number of medications on admission	1 – 8	Reference	0.139	Reference	0.398
	9 – 13	-0.087 (-0.96 – 0.79)		-0.14 (-1.11 – 0.82)	
	14 – 23	0.48 (-0.47 – 1.44)		0.26 (-0.88 – 1.41)	
Involved PICUs	PICU – A	Reference	0.122	Reference	0.017
	PICU – B	-0.58 (-1.47 – 0.301)		-1.09 (-2.10 – -0.07)	
	PICU – C	-1.12 (-2.10 – -0.15)		-1.58 (-2.67 – -0.50)	
Non-preventable ADEs					
Age	≤ (12 months)1 year	Reference	0.154	Reference	0.139
	1 (>12 months) – 5 years	1.57 (0.29 – 2.84)		1.85 (0.38 – 3.32)	
	5 (>60 months) – 12 years	0.29 (-1.43 – 2.02)		0.26 (-1.58 – 2.11)	
	12 (>144 months) – 18 years	1.6 (0.17 – 3.07)		2.02 (0.29 – 3.75)	
Follow up period (days)	1 – 6	Reference	<0.001	Reference	<0.001
	7 – 14	1.72 (0.004 – 3.45)		1.89 (0.11 – 3.68)	
	≥15	2.9 (1.39 – 4.48)		3.01 (1.35 – 4.68)	
Number of medications on admission	1 – 8	Reference	0.139	Reference	0.398
	9 – 13	1.59 (0.043 – 3.15)		1.54 (-0.14 – 3.23)	
	14 – 23	1.99 (0.35 – 3.62)		1.02 (-0.83 – 2.89)	
Involved PICUs	PICU – A	Reference	0.122	Reference	0.017
	PICU – B	-0.83 (-2.30 – 0.63)		-1.79 (-3.45 – -0.13)	
	PICU – C	0.076 (-1.06 – 1.21)		-0.97 (-2.36 – 0.41)	

PICUs: paediatric intensive care units, ADEs: adverse drug events.

* P-value is a 'composite' and represents the significance of the overall association between the covariate and the outcome (and not pairwise contrasts between the reference category and other individual categories).

5.5 Discussion

This chapter presents findings from the first UK based study to establish the rate, nature and predictors of ADEs in critically ill children admitted to PICUs. ADEs were found to be common in PICU patients; one in six patients experienced one or more ADEs with an estimated rate of 20.5 per 100 patients and 16.7 per 1000 patient-days. Most of the identified ADEs were preventable (58.1%) at a rate of 9.43 per 1000 patient-days and associated commonly with the medicines prescribing stage. Nearly one third of identified ADEs (20/62, 32.3%) contributed to patients' prolonged hospitalisation and temporary harm, permanent harm and near-death events. Longer duration of PICU stay was also associated with the risk of experiencing an ADE.

Medicines targeting the central nervous system, infections and cardiovascular system were the most commonly involved drug classes with both preventable and non-preventable ADEs. High risk medicines such as anticoagulants, adrenergic antagonists and aminoglycosides were involved with preventable ADEs of a major severity (permanent harm or near-death event) in this study.[45] In addition, the most frequently reported preventable ADEs (e.g. over sedation or agitation) were associated with using high-risk medications with sedative effects (e.g. opioid analgesics and benzodiazepines).[44,45] The medication classes identified in this study have also been reported in other published studies to be commonly involved with MEs and preventable ADEs in children's ICU.[155,288,315,317,340]

Anticoagulants, aminoglycosides and opioid analgesics are frequently used in ICU settings and are defined by the Institute for Safe Medication Practices (ISMP) as bearing a heightened risk of causing significant patient harm when they are used in error.[44] The

continuing safe use of these drugs is, therefore, a clear target for ongoing medication safety improvement to reduce patient harm.

A large proportion of ADEs in this study were preventable, with estimated rates of 11.7 per 100 patients and 9.43 per 1000 patient-days. These rates are lower than those reported by single-site studies that collected ADE data prospectively originating from a PICU in the USA (29 preventable ADEs per 1000 patient-days) [187] and a New Zealand NICU (14.38 per 1000 patient-days).[312] Lower rates of preventable ADEs have been reported in PICUs following a retrospective single site USA study (2.3 preventable ADEs per 100 patients) [307] and across two Japanese NICUs (0.47 per 1000 patient-days).[155] However, a higher rate (21 preventable ADEs per 1000 patient-days) was reported by a USA multicentre retrospective study.[186] Other studies utilised different methods of detecting ADEs such as voluntary incident report analysis and direct comparison was not practical [167,287,308,341,342], varied in definition [343], examined only non-preventable ADEs [336] or reported ADE rates with different denominators (e.g. assessed MEs that resulted in ADEs).[288]

Standardised detection methods and definitions in future studies are, therefore, needed to allow direct comparison between estimates within and between countries.[344] Standardisation may play a part alongside other factors such as variability in delivering care (e.g. variable dosing guidelines and policies) across different health care organisations, which may need to be addressed to help make the standards of care, where it is possible, harmonised between centres. This would help in providing precise estimates and actionable recommendations for improvement.[62,110,345]

The findings from this study can support national efforts to reduce preventable medication-related harm.[46] It has examined multiple PICUs to enhance generalisability of findings and utilised a prospective cohort design, using a standardised data collection method, which

may help in detecting more ADEs than a retrospective design.[344,346-348] Additionally, this study did not apply any restrictions on the medications or type of events that could be recorded during the screening for ADEs, which helped in identifying a wide range of events. This study identified potential risk factors, high-risk medications involved with ADEs and unsafe medication practices that could be the focus of further research in PICUs (e.g. assessing the causes of ADEs). However, this study did not examine all possible factors (e.g. severity of illness and route of drug administration) that could be associated with the risk of ADEs in PICU. A larger future study examining a wider range of factors could add further understanding.

There were 12 out of the 302 patients included in this study who stayed in PICU for more than the 90-day study period, hence the calculated incidence rates may be over-estimates. However, given that this only applies to 4% of patients, this is not likely to have a significant effect/difference on the calculated rate. In addition, eleven patients (3.6%) were affected by more than one ADE in this study. It is acknowledged that this study treated these as independent events (even though they might not have been) for analytical purposes, given that they were so few in number. If this had been more common, this study would have had to have accounted for it using a multi-level model which will account for the potential correlation of ADE's within patients.

Considering that the data collectors for this study were ward-based clinical pharmacists, errors that may have had the potential to cause ADEs may have prompted intervention by pharmacists before reaching patients. For example, a rising level of creatinine is one of the signs that pharmacists would record and follow up to identify any actual harm (e.g. nephrotoxicity) that could be related to this trigger. Pharmacists would normally intervene and correct any ME before causing harm. This may result in a lower rate of preventable ADEs or more serious ADEs identified in this study.

Recording the exact number of prescribed medications for each patient was challenging, and was, therefore, determined by a single count after the medication reconciliation had been completed for included patients. This was mainly due to nature of ICU where patients' medications were frequently evaluated and changed. Additionally, variation between ADEs collected by different clinical pharmacists participated in this study was expected. However, training data collectors on the standardised ADE detection method developed for this study as well as the use of a multidisciplinary expert panel to review and confirm collected ADEs were applied to enhance reliability of data.

In conclusion, this study has determined the rate and nature of ADEs in PICUs in the UK. It found that the risk of experiencing ADEs is significantly associated with longer length of PICU stay. The majority of identified ADEs were judged preventable and their consequences were often severe, resulting in patients' prolonged hospitalisation and temporary harm, permanent harm and near-death events. Increasing length of PICU stay, use of high-risk medications that are associated with risk of patient harm when used in error and prescribing practices and processes have been highlighted as targets for remedial interventions to reduce the risk of avoidable patient harm in this setting. The next chapter will build on these findings and explore the underlying contributory factors of preventable ADEs from a national incident reporting database.

Chapter 6. Medication safety incidents reported in neonatal and children's intensive care units: Findings from a mixed-methods analysis of the National Reporting and Learning System

6.1 Introduction

The previous chapters have established the rate and nature of MEs and ADEs in NICU and PICUs and understanding their underlying contributory factors is important to guide improvement strategies and minimise risk to vulnerable patients. Such understanding could highlight targets and prioritise high-risk areas for medication safety improvement in critically ill children. There has been limited research exploring the contributory factors to MEs and related harm involving this high-risk patient population as described in Chapter 2.[121,162]

Medication-related safety incidents are commonly reported as the most frequent incident type in hospitals, and are more likely to cause harm in children than adults.[35,42] The risk of experiencing these incidents may be greater for children admitted to ICU than those on general wards due to factors that were described earlier in Chapters 1, 2 and 3.

The NRLS is considered the largest and most comprehensive patient safety incident report database worldwide and it receives around 65,000 incident reports involving paediatric patients every year.[214] As described in Chapters 2 and 3, incident reports can be an important source of information to understand human and systems factors that underpin errors in health care.[227,265,266,349] To date, there has been no systematic analysis examining the nature and contributory factors of medication-related safety incidents reported from neonatal and children's intensive care settings of NHS hospitals. Previous studies have analysed incidents affecting children in primary care [214], adult critical care [350], and specific children's inpatient units (e.g. neonatal units).[351] These earlier studies did not focus specifically on children in ICU.[352]

6.2 Aim and objectives

This study aimed to examine the nature and contributory factors of medication-related incidents that involved children admitted to hospital intensive care settings and submitted to the NRLS from NHS organisations in England and Wales over a nine-year period.

The objectives of this study were:

- To describe the nature of medication safety incidents including:
    - Age groups of children involved with reported incidents,
    - Stages of medication use process (e.g. prescribing, dispensing, administration and monitoring) including error types involved with each stage,
    - Medication classes associated with incidents,
    - Severity of harm reported for the incidents.
- To explore the potential contributory factors for the reported incidents associated with any patient harm,
- To identify targets for interventions to improve medication safety in children's ICUs.

6.3 Methods

6.3.1 Study design, settings and data source

A retrospective mixed methods study was carried out. This included analysis of data from medication-related incidents that involved children (≤18 years of age) admitted to hospital intensive care settings and submitted to the NRLS database from NHS organisations in England and Wales over a nine-year period (1st January 2010 and 31st December 2018). This period was chosen as it provides a sufficiently large dataset from recent years [353] and

represents the period since mandatory reporting of serious harm and death incidents in NHS organisations was implemented (June 2010).[263]

Intensive care services for children can be divided into two fields - neonatal intensive care and paediatric critical care. In England and Wales these are advanced and mature services providing critical care for both neonates (≤28 days old) and children up to 18 years old with severe illnesses. For example, across the UK PICUs, approximately 140,000 bed days were delivered annually between 2016 and 2018.[65] Critical care units provide care at a regional level and annual admission rates have increased dramatically in recent years due in part to an increased number of children being born prematurely, or children with complex medical conditions requiring intensive care.[16]

The NRLS defines a patient safety incident as "any unintended or unexpected incident that could have or did lead to harm for one or more patients receiving NHS-funded healthcare".[354] Anonymised incident reports were obtained from the NRLS and related only to use of medication in hospital paediatric critical care settings (paediatric and neonatal ICU). Because of the way NRLS code incident data from neonatal and paediatric intensive care, it is impractical to separate the data into separate groups (neonatal and paediatric ICU) reliably, therefore the data has been processed together. NHS Improvement approved the study protocol and the sharing of anonymised NRLS data with the University of Manchester (approval reference: DSA.5047).

6.3.2 Screening process and descriptive analysis

Patient safety incidents are mostly reported by health care professionals in NHS organisations to their local risk management system using existing coding frameworks. The NHS organisations analyse and anonymise incidents reports, and then submit them to

the NRLS. All incidents reported by NHS organisations are aligned to the NRLS classification system.[355] The final codes recorded in the NRLS classification system were utilised in this study without amendments by the research team as described in Appendices 15 and 16.

Two authors (AAA and AS) of the study independently screened all incidents and excluded those that were not medication-related. In the first stage of data analysis, two authors (AAA and AS) coded medication(s) within each report using the BNF-C categorisation system for medication classes.[59] Existing coded data from the NRLS framework for patient age, harm level, stage of medication use and error category were extracted by two authors (AAA and AS) independently (Appendices 15 and 16).

6.3.3 Contributory factors associated with incidents resulting in patient harm

In the second phase of the study, all incident reports associated with any patient harm (low harm, moderate harm, severe harm and death) were reviewed and content analysis of the free text incident descriptions (what happened, contributory factors, planned actions preventing reoccurrence) were carried out to understand potential contributory factors.

The contributory factors framework within the PISA system was applied to the selected incident reports.[257] This has been successfully used in previous studies examining NRLS medication incident data.[214,356-358] To assess the feasibility of using PISA in our study, we applied the framework to a sample of the incidents and found that it captured all factors reported in the reports. The PISA framework was then applied to each incident by one author (AAA) with a random sample of 500 reports independently coded by another author (AS). Any disagreements between the reviewers were discussed until consensus was reached.

6.3.4 Data analysis

6.3.4.1 Descriptive analysis

Descriptive analyses were conducted using STATA v15®.[339] Frequency distributions and cross-tabulations were used to assess relationships between categories. Due to lack of information about the specific incident location or speciality in which incident occurred, the data were analysed according to children's age group (Figure 6.1).

Cross-tabulations were generated between three patient age groups (under 28 days, one month to one year and two to 18 years old), medication use process stage (supply, prescribing, advice, preparation/dispensing, administration, and monitoring), degree of harm (severity) and error type (Appendix 15). Further analysis explored the three most common BNF-C medication sub-classes involved across the medication use process stages (Appendix 16). Cross-tabulations were also generated between medications involved in reported incidents and the degree of harm to identify medication classes commonly involved with harmful events.

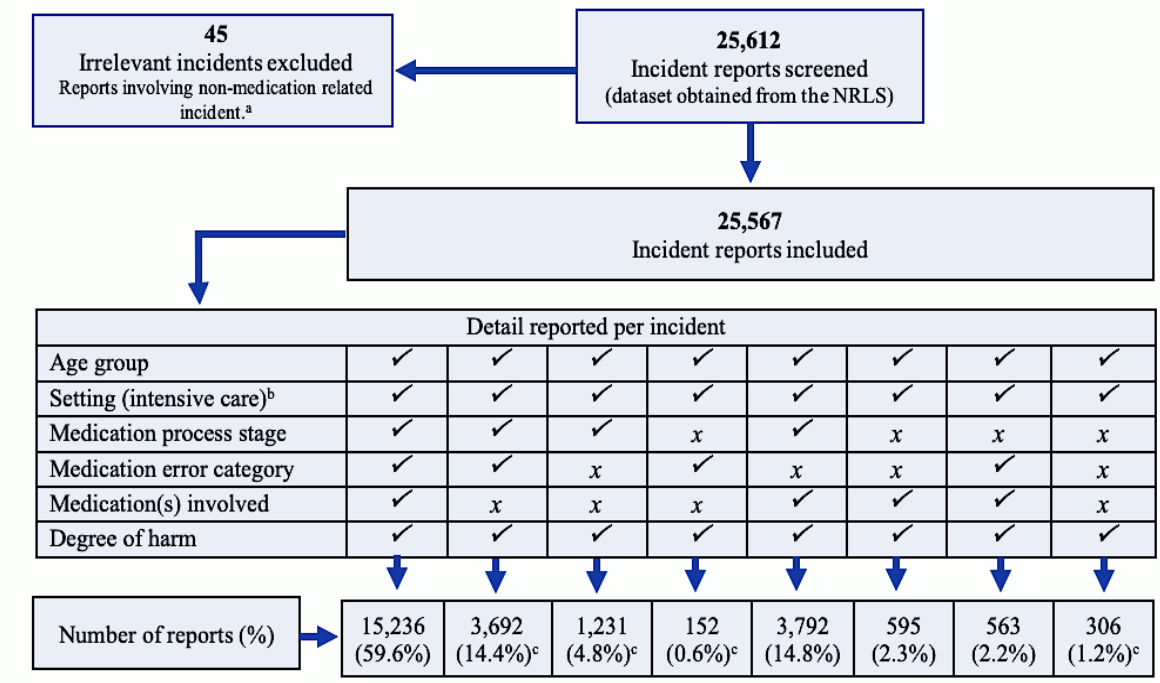
6.3.4.2 Content analysis of incidents involved patient harm

The four main domains of the PISA classification system contributory factors list (patient, staff/individual, equipment and organisation related factors) and their sub-categories were applied to the sub-set of incidents associated with harm. Reason's theoretical model of accident causation [234] was used to classify and present emerging contributory factor categories as active failures (proximal causes of incidents) associated with individuals and organisational (latent) systems failures that were described in the reports. Categorising these failures further (e.g. slips or lapses for active failures) was not possible due to insufficient information in the incident reports.

6.4 Results

6.4.1 Descriptive findings

A total of 25,612 incident reports were obtained from the NRLS database. Of these, 25,567 (99.8%) were medication-related and deemed eligible for inclusion and the remainder (0.2%) were excluded as they were not associated with the use of medication (e.g. infant feeds (breast milk, formula)). Figure 6.1 illustrates the screening process, including capture of key information with each report. Reports with complete category fields comprised 59.6% (15,236/25,567) of the dataset. The remaining reports (40.4%) contained at least one missing category detail (stage of medication process, error type or medication involved).



NRLS: National Reporting and Learning System.
✓: reported x: not reported
[a] Non-medication incidents reports involving products such as infant feeds (breast milk, formula).
[b] Speciality was specified in 2.2% (565/25,567) and 12.9% (3,322/25,567) of reports as neonatal and paediatric intensive care settings, respectively.
[C] Incidents reports with unknown medication(s): 5,381/25,567 (21.1%).

Figure 6.1 Categories of incident reports containing key information.

Most incident reports involved infants less than 28 days old (12,235/25,567, 47.9%) and children aged between one month and one year (9,337/25,567, 36.5%). Most of reported incidents related to medicines administration (13,668/25,567, 53.5%) and prescribing (7,412/25,567, 29%) with drug omission (4,812/25,567, 18.8%), wrong dose (4,475/25,567, 17.5%) and wrong frequency (3,193/25,567, 12.5%) as the most common error types as described in Table 6.1. Further details about age groups, stages of medication use process, types of errors and severity of harm involved with incidents are presented in Appendix 17.

Most incidents did not cause patient harm (22,438/25,567, 87.8%). Of 3,129 (12.2%) harmful events, 2,833 (90.5%) resulted in low harm, 286 (9.1%) caused moderate harm and 10 incidents (0.31%) led to severe harm/patient death. Anti-infective medications (6,483/25,567, 25.4%) were commonly involved with incidents followed by medications affecting nutrition and blood (4,505/25,567, 17.6%) and agents acting on the central nervous system (2,613/25,567, 10.2%). The majority of incidents involving anti-infectives were antibacterial agents (6,002/6,483, 92.6%), with most of these belonging to the aminoglycoside sub-class (2,470/6,002, 41.2%). Medication classes involved and the level of harm caused by each drug category are shown in Table 6.1. Appendix 18 presents further details regarding drug and sub-classes in reported incidents and the level of harm caused by each drug category.

Table 6.1 Descriptive statistics of the incident reports dataset including age groups, common stages of medication use process, common error types, severity and medication classes.

Category	Number of incidents (%)				
Incident reports per age group					
Under 28 days	12235 (47.9%)				
1 month to 1 year	9337 (36.5%)				
2 years to 18 years	3995 (15.6%)				
Commonly involved stages of medication use process		Commonly reported error category per stage			Number of incidents (%)
Administration	13668 (53.5%)	Omitted medicine			3590 (26.3%)
		Wrong frequency			1810 (13.2%)
		Wrong dose			1674 (12.2%)
Prescribing	7412 (29%)	Wrong dose			2450 (33.1%)
		Wrong frequency			1156 (15.6%)
		Wrong quantity			614 (8.3%)
Incident reports per degree of harm (severity)					
No harm	22438 (87.8%)				
Low	2833 (11.1%)				
Moderate	286 (1.1%)				
Severe/death	10 (0.04%)				
Medication classes involved with reported incidents and degree of harm per drug class					
Category (British National Formulary for Children)	Degree of harm (severity) per drug class				Number of incidents (%)
	No harm	Low	Moderate	Severe/death	
Gastro-intestinal system	790 (89.2%)	90 (10.2%)	6 (0.7%)	0	886 (3.5%)
Cardiovascular system	2144 (86.8%)	297 (12%)	28 (1.1%)	0	2469 (9.7%)
Respiratory system	770 (89.4%)	84 (9.8%)	7 (0.8%)	0	861 (3.4%)
Central Nervous System	2283 (87.4%)	301 (11.5%)	29 (1.1%)	0	2,613 (10.2%)
Infections	5709 (88.1%)	728 (11.2%)	44 (0.7%)	2 (0.03%)	6,483 (25.4%)
Endocrine System	716 (84.7%)	118 (13.9%)	11 (1.3%)	0	845 (3.3%)
Obstetrics, gynaecology, and urinary-tract disorders	2 (66.7%)	1 (33.3%)	0	0	3 (0.01%)
Malignant disease and immunosuppression	117 (89.3%)	12 (9.2%)	2 (1.5%)	0	131 (0.5%)
Nutrition and blood	3948 (87,6%)	502 (11.1%)	51 (1.1%)	4 (0.09%)	4,505 (17.6%)
Musculoskeletal and joint diseases	132 (88.6%)	15 (10.1%)	2 (1.3%)	0	149 (0.6%)
Eye	102 (92.7%)	7 (6.4%)	1 (0.9%)	0	110 (0.4%)
Ear, nose, and oropharynx	16 (94.1%)	1 (5.9%)	0	0	17 (0.1%)
Skin	130 (90.9%)	13 (9.1%)	0	0	143 (0.6%)
Immunological products and vaccines	150 (88.8%)	15 (8.9%)	4 (2.4%)	0	169 (0.7%)
Anaesthesia	696 (89.2%)	72 (%)	12 (%)	0	780 (3.1%)
Multiple drug categories involved	18 (81.8%)	3 (13.6%)	1 (4.5%)	0	22 (0.1%)
Unknown drugs	4715 (87.6%)	574 (10.7%)	88 (1.6%)	4 (0.1%)	5,381 (21.1%)

6.4.2 Incidents reported by age group (less than 28 days, one month to two years, and two to 18 years old)

Medication administration and prescribing were reported as the stages of the medication use process most commonly involved with incidents across all age groups, with drug

omissions and wrong doses as the common error types as described in Table 6.2. Across both prescribing and administration stages, anti-infectives were the most commonly involved medications with reported incidents in youngest age groups (under 28 days (3,399/9,941, 34.2%) and one month to two years of age (1,427/7,819, 18.2%)).

In older children (>two years old), medicines belonging to the central nervous system (637/3,320, 19.2%) followed by anti-infective classes (555/3,320, 16.7%) were most commonly reported in incidents involving both prescribing and administration stages.

Across all medication use process stages, most of incidents associated with using anti-infective medications were reported to involve neonates aged ≤28 days (4,153/6,483, 64.1%). Aminoglycosides were the most commonly involved anti-infectives reported in this age group (2,007/4,153, 48.3%).

Half of all harmful incidents (1,570/3,129, 50.2%) involved neonates aged ≤28 days and a third (1,055/3,129, 33.7%) involved children aged between one to two years. Children older than two years of age were not commonly involved with the reported harmful incidents (504/3,129, 16.1%) when compared to the other age groups. Across all age groups, harmful incidents were, most frequently, reported to occur during medicines administration (1,955/3,129, 62.5%), and commonly involved medications to treat infections (774/3,129, 24.7%), and wrong dosing (608/3,129, 19.4%), drug omission (606/3,129, 19.4%) and wrong frequency (454/3,129, 14.5%) error types.

Detailed information about incidents reported in each age group including commonly involved medication use process stages, levels of harm, drug classes and error types is presented in Table 6.2. Further detailed results of the incidents analysis that was carried out for patients aged ≤28 days, one month to two years and older than two years are presented in appendices 19, 20 and 21, respectively.

Table 6.2 Summary of the descriptive analysis of incident reports by age group.

Category		**No. of incidents (%)**							
Under 28 days of age		12,235 (47.9%) reported incident							
Degree of harm (severity)									
No harm		10,665 (87.2%)							
Low		1,402 (11.5%)							
Moderate		163 (1.3%)							
Severe/death		5 (0.04%)							
Commonly involved stages of medication use process	**No. of incidents (%)**	**Degree of harm (severity) No. of incidents (%)**				**Common error types**	**No. of incidents (%)**	**Commonly involved drug classes in each stage**	
		No harm	Low	Moderate	Severe/death			Drug class	No. of incidents (%)
Administration	6,465 (52.8%)	5,491 (84.9%)	865 (13.4%)	104 (1.6%)	5 (0.08%)	Omitted medicine	1,750 (27.1%)	Anti-infectives	2,146 (33.2%)
						Wrong frequency	1,067 (16.5%)	Nutrition and blood	1,206 (18.7%)
						Wrong dose	721 (11.2%)	Cardiovascular system	381 (5.9%)
Prescribing	3,476 (28.4%)	3,159 (90.9%)	285 (8.2%)	32 (0.9%)	0 (0.00%)	Wrong dose	1,011 (29.09%)	Anti-infectives	1,253 (36.1%)
						Wrong frequency	667 (19.19%)	Nutrition and blood	690 (19.9%)
						Wrong quantity	302 (8.69%)	Central Nervous System	236 (6.8%)
Total	9,941 (81.2%)	8,650 (87.01%)	1,150 (11.6%)	136 (1.4%)	5 (0.05%)	5,518 (55.5%)		5,912 (59.5%)	
One month to two years of age		9,337 (36.5%) reported incidents							
Degree of harm (severity)									
No harm		8,282 (88.7%)							
Low		967 (10.4%)							
Moderate		84 (0.9%)							
Severe/death		4 (0.04%)							
Commonly involved stages of medication use process	**No. of incidents (%)**	**Degree of harm (severity) No. of incidents (%)**				**Common error types**	**No. of incidents (%)**	**Commonly involved drug classes in each stage**	
		No harm	Low	Moderate	Severe/death			Drug class	No. of incidents (%)
Administration	5,082 (54.4%)	4,419 (86.9%)	600 (11.8%)	61 (1.2%)	2 (0.04%)	Omitted medicine	1,443 (28.39%)	Nutrition and blood	900 (17.7%)
						Wrong dose	622 (12.24%)	Anti-infectives	869 (17.1%)
						Wrong frequency	579 (11.39%)	Cardiovascular system	696 (13.7%)
Prescribing	2,737 (29.3%)	2,493 (91.1%)	231 (8.4%)	12 (0.4%)	1 (0.04%)	Wrong dose	965 (35.26%)	Anti-infectives	558 (20.4%)
						Wrong frequency	379 (13.85%)	Nutrition and blood	450 (16.4%)
						Omitted medicine	208 (7.60%)	Central Nervous System	376 (13.7%)
Total	7,819 (83.7%)	6,912 (74.02%)	831 (10.6%)	73 (0.93%)	3 (0.04%)	4,196 (53.7%)		3,849 (41.2%)	
Older than two years of age (2–18 years old)		3,995 (15.6%) reported incidents							
Degree of harm (severity)									
No harm		3,491 (87.4%)							
Low		464 (11.6%)							
Moderate		39 (1.0%)							
Severe/death		1 (0.03%)							
Commonly involved stages of medication use process	**No. of incidents (%)**	**Degree of harm (severity) No. of incidents (%)**				**Common error types**	**No. of incidents (%)**	**Commonly involved drug classes in each stage**	
		No harm	Low	Moderate	Severe/death			Drug class	No. of incidents (%)
Administration	2,121 (53.1%)	1,803 (85.0%)	294 (13.9%)	23 (1.1%)	1 (0.05%)	Omitted medicine	397 (18.7%)	Central Nervous System	411 (19.4%)
						Wrong dose	331 (15.6%)	Anti-infectives	302 (14.2%)
						Wrong quantity	195 (9.2%)	Nutrition and blood	292 (13.8%)
Prescribing	1,199 (30.0%)	1,084 (90.4%)	104 (8.7%)	11 (0.9%)	0 (0.0%)	Wrong dose	474 (39.5%)	Anti-infectives	253 (21.1%)
						Wrong frequency	110 (9.2%)	Central Nervous System	226 (18.8%)
						Omitted medicine	100 (8.3%)	Cardiovascular system	152 (12.7%)
Total	3,320 (83.1%)	2,887 (86.9%)	398 (11.9%)	34 (1.02%)	1 (0.03%)	1,607 (48.4%)		1,636 (49.3%)	

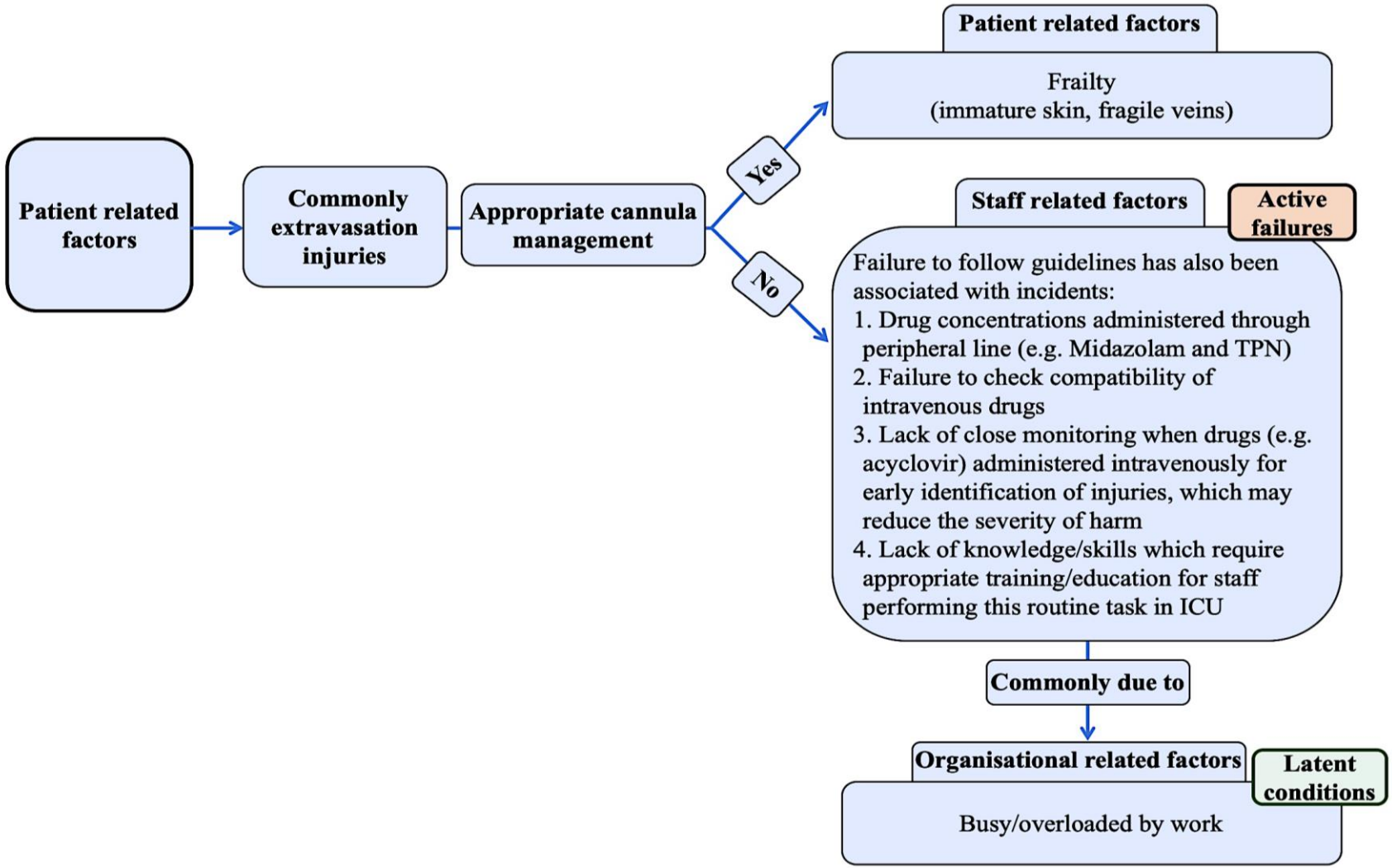
6.4.3 Contributory factors for incidents involved patient harm

Of the 12.2% of harmful incidents, 1,765 reports (56.4%) were included as they stated explicit contributory factors whilst the remaining 1,364 reports (43.6%) were excluded due to lack of sufficient description of reported incidents.

Three main categories emerged from the content analysis that explored contributory factors; namely, factors related to patients (62/1,765, 3.5%), medical staff/individual factors (1,212/1,765, 68.7%) and organisational factors (482/1,765, 27.3%). Some incident reports were related to impractical/faulty equipment or inadequate medication storage (9/1,765, 0.5%). Incidents that involved multiple contributory factors were common across the harmful incidents examined and common combinations of these were staff and organisational related factors. Of 1,212 reported incidents that stated staff related contributory factors, 807 (66.6%) incidents also involved organisational-related factors.

6.4.3.1 Patient-related factors

Patient factors featured in incidents involving dose omissions and extravasation injuries as described in Figure 6.2. Challenging venous access in neonates led to dose omissions and consequently delays in treatment (Example 1.1, Table 6.3). Due to undeveloped skin and fragile vasculature in this patient group, extravasation injuries were reported commonly in neonates despite following correct cannula management procedures (Example 1.2, Table 6.3).



TPN: Total parenteral nutrition.
ICU: Intensive care unit.

Figure 6.2 Contributory factors related to patients that emerged commonly in incident causing doses omissions and extravasation injuries.

6.4.3.2 Staff-related factors

Staff factors included cognitive issues (e.g. perception, memory or thinking), inadequate skill set/knowledge and failure to follow/adhere to protocols or procedures. These active failures were reported frequently to be caused by organisational-related factors (latent conditions) such as work pressures and issues related to using paper-based prescribing systems (e.g. design of prescription or illegible handwriting). Figure 6.3 illustrates multi-directional interactions between active failures and latent conditions.

Failure to follow protocols or procedures (active failures), commonly involving prescribing, administering or monitoring anti-infective medication, were the most common contributory factors directly involving staff. At times, staff did not monitor drug levels as recommended in protocols or follow safety procedures (e.g. independent double checking) for medication administration (Examples 2.1 and 2.2, Table 6.3). Cognitive issues such as distraction, inattention and oversight were other common contributory factors (Example 2.3, Table 6.3).

Active failures (such as, inappropriate cannula management) was also associated with some incidents. For example, lack of monitoring of cannula sites regularly for early signs of extravasations injuries (Example 2.4, Table 6.3) and failure to follow guidelines for administering IV medications (Example 2.5, Table 6.3) contributed to some incidents. However, these active failures were commonly associated with latent conditions. Medical staff being busy or overloaded by work were often reported as contributory factors for these failures, which were often associated with many distractions and oversights to secure venous access or follow safe cannula management procedures (Example 2.6, Table 6.3).

Errors (active failures) also occurred commonly during patient transfer between units or at handover between shifts. Most of these failures included poor quality of documentation such as doses that were given and not documented, or administration records lost during handovers or patient transfer to ICU (Example 2.7, Table 6.3). These active failures were notably reported as being associated with latent conditions such as heavy workloads (staff busy with other prioritised commitments) and inadequate patient record documentation systems.

Staff also reported errors in medication administration and monitoring due to inadequate knowledge, such as those with specific safety requirements in dosing or administration process (e.g. phenytoin) (Example 2.8, Table 6.3).

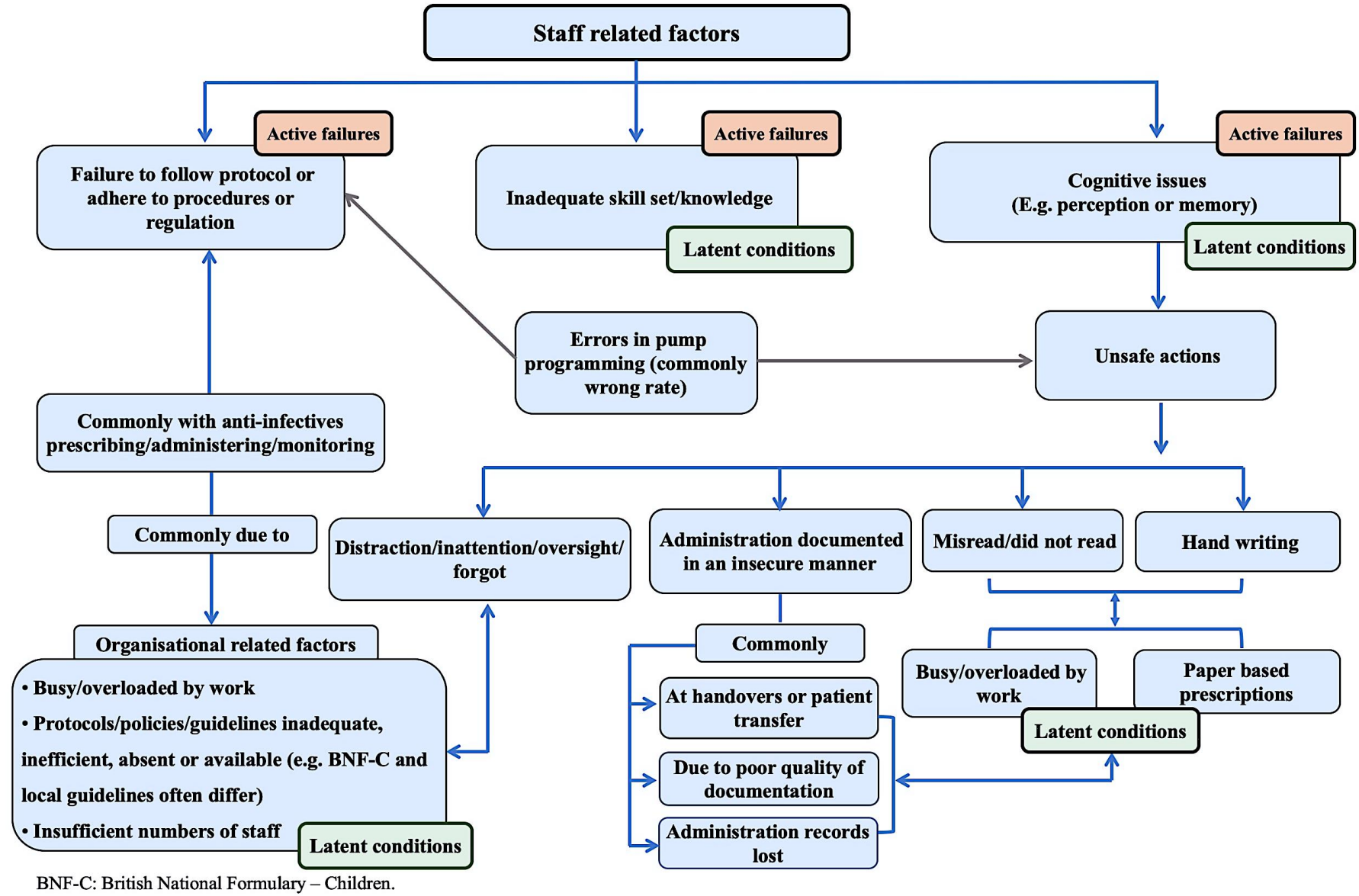


Figure 6.3 Contributory factors related to medical staff and interactions with organisational related factors.

6.4.3.3 Organisational-related factors

Pressurised work environments of ICU and shortage of staff often contributed to medication omissions and failures to follow safety policies (Example 3.1, Table 6.3). Incidents were also associated with errors during shift handovers due to inadequate protocols for this process and poor communication between medical staff (Example 3.2, Table 6.3). Newly qualified staff working in ICU that lacked training and familiarity about the setting's policies and procedures were also described as a contributory factor associated with specific incidents (Example 3.3, Table 6.3).

It became apparent that in some cases, children, mostly neonates, were transferred routinely from other hospital areas (e.g. general or post-natal wards) to ICU for single dose administration before being returned. Incidents occurring during this process were often reported due to poor documentation of doses given in either the ward or ICU or loss of medicines administration records (Example 3.4, Table 6.3).

Other important contributory factors were categorised under poor continuity of care between ICU and hospital departments such as pharmacy and test laboratories. This involved delay in medicines supply from pharmacy or inadequate dispensing protocols (Example 3.5, Table 6.3) as well as delays in providing results of blood tests from laboratories (Example 3.6, Table 6.3), which mainly caused dose omissions.

The design of prescription forms and use of paper-based documentation systems contributed commonly to the reported incidents. Ambiguous handwriting as well as poor design of prescriptions were reported as causes of confusion which led to MEs (Example 3.7, Table 6.3). Unavailability of protocols and inadequate and variable guidelines were also notable contributory factors (Examples 3.8, 3.9 and 3.10 Table 6.3). Organisational-

related contributory factors commonly associated with reported incidents are described in Figure 6.4.

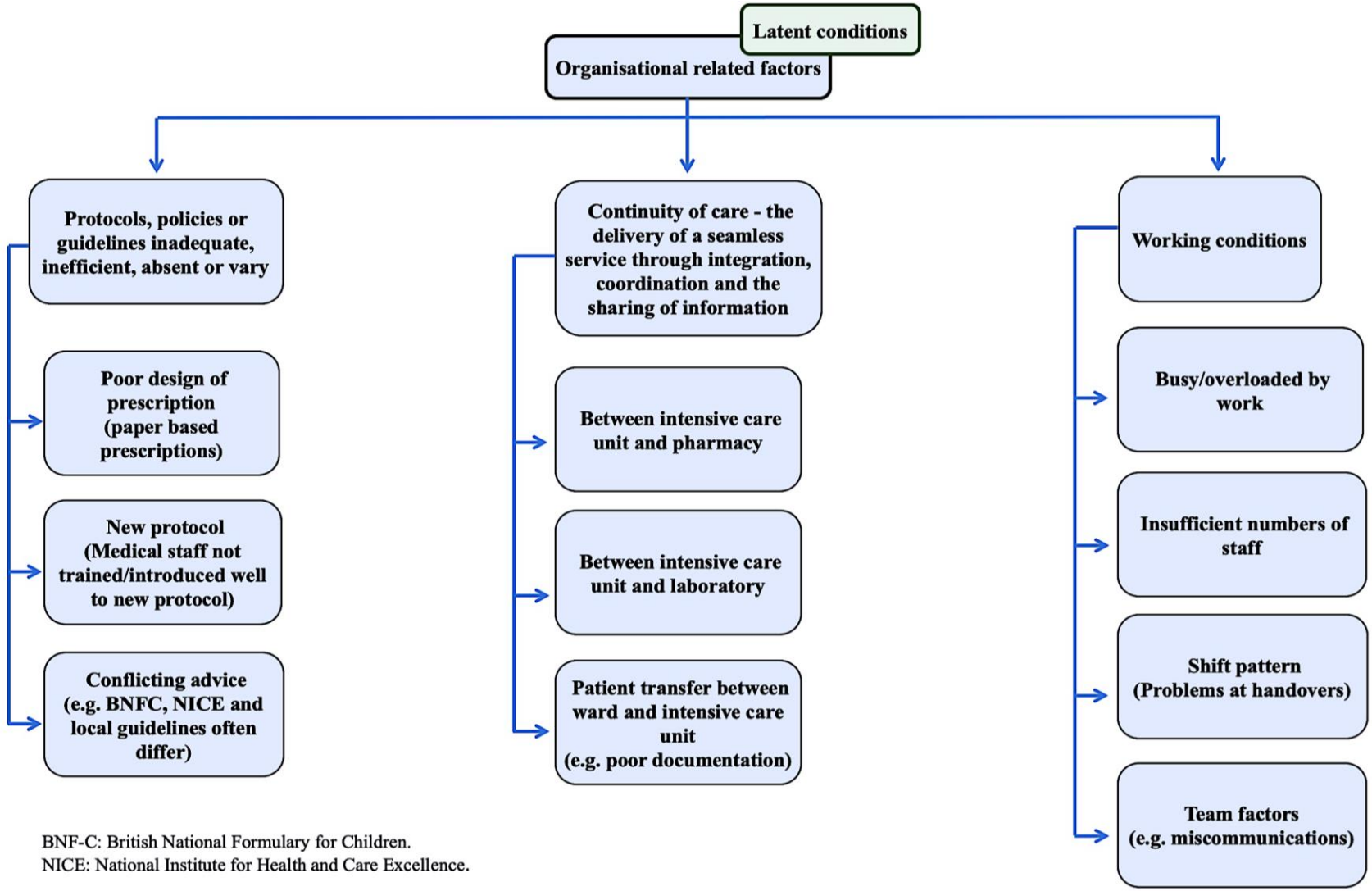


Figure 6.4 Organisational-related contributory factors commonly involved with reported incident.

Table 6.3 Extracted examples of incident descriptions.

1. Patient related factors
Example 1.1: Doses omissions due to difficult venous access
"Baby cannula tissues so it was removed. Dr informed new cannula attempted on numerous occasions overnight unsuccessful, we handed over to day staff and they made further attempts but continued to be unsuccessful. The baby then went 52 hours without intravenous antibiotics."
Example 1.2: Non-preventable extravasation injury
"This extravasation injury seemed unavoidable through the documentation in the nursing notes. The nurse checked the insertion site every 30 minutes as per the guideline (documented in the nursing notes). Ten minutes after her last check, the baby was very active and when she went to check, she found the injury. The parenteral nutrition was discontinued immediately and the doctors informed. The plastics team were called to review the wound site and carried out an infiltration of the wound and dressed it."
2. Staff related factors
Example 2.1: Failure to follow policy
"Third dose of Gentamicin was given. However, drug level was not taken prior to administration."
Example 2.2: Failure to follow policy
"An incident occurred when the nurses changed the infusion at the infusion pump. Instead of taking the Potassium Acid Phosphate infusion down they mistakenly removed the Potassium Chloride infusion which was infusing on the pump below the Potassium Acid Phosphate infusion. Therefore, this resulted in two Potassium Acid Phosphate infusions running simultaneously. This was not noticed for 8 hours and was noted during nursing handover to the next shift. Nurses reminded that two nurses must go to the infusion pump to check that the correct infusion has been changed."
Example 2.3: Misread/distraction error
"The prescription had been written in a very stressful, busy situation with the child being extremely unstable. Two-part error: 1) Prescribing misread theatre syringe as 50 when actually 500 micrograms in 50 ml. Also, not signed and no rate written up but interrupted numerous times when prescribing. Either way prescription written as 50 micrograms in 50 ml. 2) Administration nursing staff misread prescription as 500 micrograms in 50 ml drew this up but labelled as 50 micrograms in 50 ml. However, the pump programmed as 500 micrograms in 50 ml."
Example 2.4: Extravasation injury caused by failure to follow protocol
"Infusion of fluconazole is being infused, checked only on completion of infusion. When flushing line, it was noted that the arm was red and swollen around cannula site."
Example 2.5: Extravasation injury caused by error
"Intravenous potassium was given by nurse and documented as being given centrally but line clearly attached to cannula in the dorsum of patient left wrist. I was alerted to the error near the beginning of my night shift. I found 30 ml of infusion had been given and dark red patch of skin on dorsum of baby's left hand."
Example 2.6: Lack of venous access contributed to dose omission
"Baby came around for antibiotics, flushed cannula this was leaking and could not be saved and therefore removed. Medical staff informed and asked to site another cannula. Doctors were busy, so they asked a nurse able to do cannulas to put one in. The nurse was busy, but when she was free she tried a few times without success. Doctors were informed and asked several more times that the baby needed a cannula as the antibiotics were over two hours late. Both medical staff went to another intensive care room and it was another 40 minutes before the night doctors came on duty and sited the cannula."
Example 2.7: Administration documented in an insecure manner
"I received a phone call from staff on ward informing me that they had found a drug chart for a baby (usually kept on the neonatal intensive care unit) with the baby's documentation, and that intravenous antibiotics had been prescribed but not given."
Example 2.8: Inadequate knowledge
"Patient prescribed maintenance oral phenytoin given as charted. No specific instructions provided on prescription chart, Phenytoin level checked as requested by team - remained out of range. Neurology team suggested that if we weren't giving medication 30 minutes before food or after 3 hours could indicate why level low". Reported cause: "Unit staff reminded of requirements for phenytoin as some staff not used to medication and optimal giving procedures"

Table 6.3. continued.

3. Organisational related factors
Example 3.1: Busy/overloaded by work/insufficient number of staff
"On reviewing the medical and nursing notes from the time of admission that there have been a number of omissions. Staffing was an issue due to sickness and Shift Coordinator had made attempts to increase the level of staff on duty over the week end shifts."
Example 3.2: Shift pattern/communication failure
"Due to communication failure of handover, second drug chart found at 04:00, drug dose missed at 20:00 last night which should have been given on previous shift. Not handed over that baby was on vancomycin or that there was a second drug chart."
Example 3.3: Shift pattern/new staff
"At morning handover, I was told that the patient lipid infusion had been switched off which I interpreted as being complete. Normal practice is to restarted after 4 hours so morning bloods will not give high results. As a new starter to paediatric intensive care unit, my previous practice had Total Parenteral Nutrition on for 24 hours and was only stopped once complete."
Example 3.4: Patient transfer
"Baby went from post-natal ward to intensive care unit for intravenous Benzylpenicillin and Gentamicin, baby returned to ward, when I checked drug chart baby had not received the Gentamicin intravenous antibiotic."
Example 3.5: Issues between intensive care unit and pharmacy
"Patient intravenous Busulphan chemotherapy was due for 22:30. Staff checked chemotherapy fridge and it was not there. All other possible fridges checked and other paediatric wards rang to see if it had been delivered to them in error but still not found. I spoke to on-call pharmacist who was also dealing with another call for missing chemotherapy and explained the situation. We were informed there was no documentation of the drug being made in pharmacy although the ward had received a phone call at 17:00 asking if we wanted the chemotherapy delivered by a porter to which we agreed. After discussion with on-call consultant and patient consultant, it was decided that tonight's dose would be missed and added on at the end of the regime."
Example 3.6: Issues between intensive care unit and laboratory
"Pre-second dose level for gentamicin was due at 04:00 which was a level and hold as per prescription, level taken by porters to the laboratory. According to biochemistry the sample did not reach them until 06:00. Biochemistry was called at approximately 10:00 regarding the level results, blood was being processed. Biochemistry called the unit at 13:30 was unable to process gentamicin level as not enough blood. Therefore, the dose at 04:00 was not given."
Example 3.7: Issues with using paper-based systems
"Missed dose of cefotaxime for baby when giving flucloxacillin, due to large crossings out on above prescription making it look like cefotaxime was also crossed off."
Example 3.8: Inadequate/variable guidelines
"Phenobarbital prescribed, protocol states to dilute 60mg/ml vial to 10 times the volume. 2mls of 60 mg/ml diluted to 20 ml. Protocol does not state that the syringe now contains 60mg/10mls. Therefore, both myself and checker calculated drug as being 60mg/ml. Baby only received 2mg/kg instead of 20mg/kg."
Example 3.9: Inadequate/variable guidelines
"The Nurse in Charge was asked to query the infusion dose several hours later by the bedside nurse as the bedside nurse had found several protocols with difference dose amounts and concentrations. After extensive calculations, it was established that the ketamine syringe was running at 8.26 mls/hr which equated to 23mcg/kg/min. The pump was actually programmed as 1400 mcg/kg/hr. This is 4.6 times more than the upper dose of 5mcg / kg / min on the Acute Pain Programme. During the 3 hours that this syringe was infusing, the patient received 225 mg of Ketamine which should have been delivered over 13hours if at a rate of 5mcg/kg/min."
Example 3.10: Inadequate/variable guidelines
"Issues with lack of clear guidelines/calculation formulas regarding corrected phenytoin levels - several formulas for correction available in internet each calculating a different level. No agreement as to which formula has been agreed for use in paediatric intensive care unit."

6.5 Discussion

This study presents the first detailed analysis of medication-related incident data reported to the NRLS database from neonatal and children's intensive care settings over a nine-year period. It found that incidents relating to medication administration and prescribing stages, and those involving medication omissions, wrong doses and wrong frequency were the most common across all age groups. Most incidents were reported to have not caused patient harm. Neonates aged less than 28 days were associated with most of reported incidents and affected by most harmful incidents. Anti-infective medications followed by medications affecting nutrition and blood were the most involved medication classes in both harmful and no-harm incidents.

Contributory factors for incidents reported as harmful were explored in this study to help facilitate understanding about medication safety in this environment, and illuminate the complexity of neonatal and children's intensive care settings. Challenging physiology in neonates, working conditions (e.g. heavy workload), variable or inadequate guidelines and systems, and poor continuity of care between ICU and other hospital departments were the most frequently documented contributory factors associated with harmful incidents.

Challenging venous access was found as a contributory factor to harmful medication incidents, which commonly involved neonates aged less than 28 days and was frequently associated with drug omission errors. Aminoglycoside anti-infective medications such as gentamicin were commonly involved with this type of incidents, which are considered as high-risk medications in PICU.[45] The most commonly reported contributory factors to harmful incidents were related to ICU staff. Most of these were associated with failures to follow safety procedures and policies in prescribing, administering and monitoring anti-infective medications. Common errors that result from these failures were wrong doses and

drug omission errors. These failures were, notably, found to occur due to organisational-related factors.

Routine tasks such as securing and monitoring venous access, checking and acting on drug levels, and medication administration double checking procedures were adversely affected by organisational factors such as staff shortages and consequent heavy workload leading to incidents, along with inadequate dosing guidelines and prescribing systems. Policies such as shift handovers and patient transfers between hospital's general wards and ICU were other organisational factors that were associated with errors (e.g. documentation errors).

In this study, a large dataset covering a nine-year period was analysed. This has generated important understanding of the nature and contributory factors associated with medication safety incidents occurring in children's ICU which may be used to support efforts to reduce MEs and related patient harm in this area. The main limitation of this study is the reliance on retrospective, spontaneous incident reporting that is subject to under-reporting and poor quality of reporting.[359] However, of the majority of incident reports utilised in this study (59.6% for the descriptive analysis and 56.4% for the content analysis) contained sufficient information for analysis.

In conclusion, this study identified clear targets for interventions to improve medication safety in children's ICUs, focussed on neonates, medicines administration and prescribing, and anti-infective medications. These interventions will need to address prevailing organisational factors (e.g. improvement in staffing and workload and design of systems and processes) in order to facilitate improvements in medication safety.

Chapter 7. General discussion and overall conclusion

7.1 Discussion

7.1.1 Introduction

This PhD programme aimed to provide an understanding of the burden, nature and risk factors of MEs and preventable ADEs among critically ill neonates and children admitted to ICU. Such understanding will help identify targets and inform an action agenda for medication safety improvement in these vulnerable patient populations. Generating a detailed understanding of frequency, nature and risk factors of MEs and related ADEs in children's intensive care settings, and then moving towards understanding at a national level the nature and contributory factors of these events, is a fundamental part of the process towards developing theory informed, targeted interventions with greatest chance of success.[46,48,49]

Therefore, this PhD programme started by examining the available evidence on the global prevalence and nature of both MEs and preventable ADEs in PICUs and NICUs. This was achieved by conducting a systematic literature review, which also identified gaps in the current knowledge base (e.g. lack of evidence about the burden and nature of preventable ADEs in PICU and NICU in the UK) and informed the future plan for this research programme. Consequently, the first prospective observational study to establish the incidence, nature, preventability and severity of ADEs occurring in critically ill children at UK hospitals was carried out. To add further understanding, this was followed by a detailed analysis of medication-safety incidents reported in children's intensive care settings at a national level in order to identify the nature and contributory factors associated with these incidents.

This chapter provides a summary of the key findings of the studies that were carried out during this PhD programme and a general discussion on the implications of the findings

for policy and clinical practice as well as the contribution of this research to the existing literature. This chapter also discusses the strengths and limitations of this research programme. In addition, this chapter highlights areas that require further research in the future to improve the safe use of medications in critically ill children.

7.1.2 Key findings

7.1.2.1 Prevalence and nature of medication errors and preventable adverse drug events in NICU and PICU

The systematic literature review presented in Chapter 4 identified 35 unique studies that examined MEs or preventable ADEs using direct observation, medication chart review or a mixture of methods in children ≤18 years of age admitted to PICU or NICU for inclusion. These studies were published between 2000 and 2017 with the majority of them being published from January 2010 onwards. This may indicate that examining preventable medication-related events in children's ICU is a developing area.[334] In addition, included studies in this systematic review were more frequently undertaken in the USA (10/35, 28.6%) [35,164,186,187,307,316,317,323-325] followed by the UK (6/35, 17.1%) [143,212,213,318-320] than other countries. Table 7.1 summarises the reported rates of MEs and preventable ADEs in both settings.

Table 7.1 Rates of MEs and preventable ADEs in NICU and PICU.

Event	Rate *
PICU	
Medication errors	Median: 14.6 per 100 medication orders (IQR 5.7 – 48.8) (n=3) [35,91,317]
	Range: 6.4 – 9.1 per 1000 patient-days (n=2) [155,286]
Prescribing errors	Median: 13.25 per 100 medication orders (IQR 9.5 – 29.35) (n=12) [91,145,164,185,188,212,301,315,316,318,320,321]
Dispensing errors	0.78 per 100 medication orders § [91]
Transcription errors	4.88 per 100 medication orders § [91]
Medication administration errors	Different denominators used in the identified studies [91,301]
Preventable adverse drug events	Range: 21 – 29 per 1000 patient-days (n=2) [186,187]
NICU	
Medication errors	Range: 5.5 – 77.9 per 100 medication orders (n=2) [35,204]
	Range: 4 – 35.1 per 1000 patient-days (n=2) [155,286]
Prescribing errors	Median: 14.9 per 100 medication orders (IQR 4.25 – 29.9) (n=6) [146,213,301,303,315,325]
Prescribing & dispensing errors	0.7 per patient § [306]
Medication administration errors	Median: 31.4 per 100 administrations (IQR 8.2 – 84.8) (n=3) [301,326,327]
Preventable adverse drug events	Range: 0.47 – 14.38 per 1000 patient-days (n=2) [155,312]

Abbreviations: PICU: paediatric intensive care unit; NICU; neonatal intensive care unit; IQR: interquartile range.
* Range of rates or median of medication errors/preventable adverse drug events rates and IQRs were calculated for studies that used same denominators.
§ Only one study provided event rate.

This systematic review found that MEs are common in PICUs and NICUs (occurring frequently during medication prescribing and administration stages) and may lead to patient harm. Dosing errors and the use of anti-infective medications were identified as priority areas for medication safety improvement in these settings. This review also

identified a number of areas that require further exploration to evaluate the safe use of medications in both PICU and NICU. In both settings, the majority of the included studies focused on MEs, specifically prescribing errors, with few targeting preventable ADEs. The scale and nature of preventable ADEs in particular, were found to be unknown in UK children's intensive care as all of the identified studies that reported such data were carried out in other countries (mostly in the USA).[186,187,307,323] The systematic review also highlighted the need for standardised definitions and methods in future studies examining MEs and preventable ADEs in children's ICU settings to allow direct comparison of estimates within and between countries.

7.1.2.2 Incidence and nature of adverse drug events across three PICUs in England

Chapter 5 presented the findings from the first prospective epidemiological study that examined the incidence, nature, preventability and severity of ADEs occurring in PICUs in the UK hospitals. This was informed by the findings of Chapter 4 which identified limited data in the published literature concerning ADEs in PICU worldwide, and specifically in UK hospitals.[334] This study was carried out over a three-month period during 2019 and included 302 patients (≤18 years of age) who stayed for a minimum of 24-hours across three PICUs in England. Intensive surveillance for suspected ADEs was performed by trained clinical pharmacists. An expert panel assessed causality, preventability and severity of detected events.

Of 302 patients included, one or more ADEs was detected in 47 (15.6%) patients. A total of 115 events were identified by clinical pharmacists. Of these 62 ADEs were confirmed by the expert panel (definite and probable causality), with an estimated rate of 20.5 per 100 patients and 16.7 per 1000 patient-days. The majority of ADEs were preventable (58.1%). The estimated rate of preventable ADE was 11.7 per 100 patients and 9.43 per 1000

patient-days. Most ADEs (67.7%) caused temporary harm. The remaining ADEs (32.3%) caused prolonged hospitalisation and temporary harm, permanent harm and near-death events with no death events associated with detected ADEs.

Most ADEs were associated with prescribing (46.8%). Medication classes commonly involved with ADEs included medicines for the central nervous system, infections and cardiovascular system. High-risk medications such as anticoagulants and sympathomimetics were associated with preventable harm that caused serious patient injuries (e.g. permanent harm or near-death event). Other high-risk medications (e.g. opioid analgesics) were associated with the most frequently reported preventable ADEs and commonly led to harms that prolonged stay of patients in PICU. Increased length of PICU stay was significantly associated with ADE occurrence; children with a hospital stay of seven or more days were more likely to experience an ADE compared to patients with a stay of one to six days. In addition, rates of ADEs varied among the three participating PICUs ($p=0.006$) and risk of experiencing an ADE was higher in one of the involved PICUs than the remaining two PICUs.

With the understanding about the scale, nature and risk factors of preventable ADEs that was described in this study, there is a necessary need to explore underlying contributory factors associated with these events in children's ICU settings in order to identify targets for remedial interventions. Additionally, long PICU stay, use of high-risk medications and prescribing errors were identified as targets for preventive strategies to reduce the risk of avoidable patient harm in this setting.

7.1.2.3 Analysis of medication safety incidents reported in children's intensive care settings to the NRLS

Given that rates of MEs and ADEs in children's intensive care settings were established in Chapters 4 and 5 of this thesis, Chapter 6 added further understanding of these events by examining their nature and underlying contributory factors. This was achieved by carrying out a mixed methods study to describe and understand medication-related safety incidents reported in critically ill neonates and children at a national level using one of the largest patient safety incident reporting databases worldwide. This study provided important learning concerning the types of medication-related safety incidents that occur, as well as the environmental, organisational and inter-personal antecedents that lead to these incidents arising in neonatal and children's ICUs.

A total of 25,567 eligible medication-related incident reports were examined. Most incident reports involved infants less than 28 days old. Incidents commonly occurred during medicines administration and prescribing stages, and involved drug omission and wrong dose errors as the most common error types. Anti-infectives were the most commonly implicated agents in the reports. Antibacterial agents, with most of these belonging to the aminoglycoside sub-class, were the most commonly anti-infective medications involved with incidents. Neonates aged ≤28 days were remarkably involved with incidents associated with anti-infective medications, particularly aminoglycoside agents.

Incidents that were reported to cause patient harm accounted for 12.2% and commonly affected neonates aged less than 28 days. Common contributing factors to harmful incidents comprised staff-related factors such as failure to follow protocols or errors in documentation, which were associated often with working conditions and inadequate

guidelines, design of systems and protocols. Other contributory factors associated with reported incidents involved challenging venous access in neonates which led commonly to dose omission errors.

This extensive analysis of medication-related safety incidents generated important findings about the nature and contributory factors of medication safety incidents in children's intensive care that could inform preventive strategies. Improvements in staffing and workload, design of systems and processes and the use of anti-infective medications were identified strategies that may reduce this risk.

7.1.3 Overall interpretation of findings

As outlined by Chapters 1, 2, and 3 of this thesis, the first step to improve medication safety on the national [46,48] and international [24] agendas is assessing the extent and nature of MEs and related patient harm occurring in hospitalised patients in order to target future interventions to improve patient safety. This research programme has achieved this objective in critically ill neonates and children who are at increased risk for these events. The NHS has launched the Medication Safety Improvement Programme in response to the WHO global campaign 'Medication Without Harm'.[46] The NHS programme has established a national project that aims to collect data about three main areas; namely high-risk drugs, high-risk parts of the medication use process and high-risk patient populations.[46] The current research programme focusing on critically ill paediatric patients is supporting such efforts by providing data concerning the three main areas that the NHS is prioritising in improving the safe use of medicines and reduce avoidable patient harm. It has identified medication classes, stages of medication use process and patient's age group frequently involved with MEs and related ADEs that could be the target for future medication safety interventions. This also included understanding the underlying

contributory factors and risk factors associated with MEs and preventable ADEs that could guide future efforts to reduce these events in PICU and NICU.

This programme of research contributed to the literature by identifying and summarising the available evidence on the global prevalence and nature of both MEs and preventable ADEs across neonatal and paediatric intensive care settings (Chapter 4).[334] This was followed by conducting the first UK based study that provided epidemiological data on the frequency, nature, preventability and severity of ADEs in PICUs (Chapter 5). Data concerning preventable ADEs are limited [29], and this work provided new data that informs estimates of burden of such events on NHS and identifies areas for improvement. In addition, this was supported by insights from the first exploration of the type, and underlying contributory factors of medication-related safety incidents reported in children's ICUs at a national level (Chapter 6).

The findings of this research programme have identified targets for improvement that may inform the planning of future safety interventions and generated recommendations for future studies aiming to improve the safe use of medications in neonatal and children's intensive care settings.

7.1.3.1 Extent of medication errors and adverse drug events in children's intensive care settings

This research programme found that MEs occur frequently in critically ill children admitted to PICU and NICU. It has also found that ADEs occur frequently in children's ICU with most of them being associated with MEs (preventable ADEs). This type of harm contributes to extended length of hospital stay and additional costs. In the UK, it was recently estimated that preventable ADEs cost the NHS an additional £98.5 million per year.[29] Understanding preventable harm has greater significance for identifying key

challenges to improve patient care. This would enable development of successful remedial interventions to reduce harmful MEs and associated costs, ultimately supporting the third WHO safety global campaign to improve patient safety.[24]

Comparing the findings presented in Chapter 5 about the nature and risk factors with other PICU studies was not practical due to variable designs of studies.[155,187] In addition, wide variability was observed in many reported MEs rates in the existing literature due to variation of definitions, denominators and event detection methods used in the published studies (Chapter 4). These variations make comparisons of the extent of MEs in PICU and NICU challenging. Hence, there is a need for methodological standardisation in future studies examining these events, which will be discussed in more detail later in this chapter. Another possible reason for the variability of outcome rates may be related to differences in health care systems between countries, hospitals or even medical teams on hospital wards.[360,361] For example, Chapter 4 identified two studies conducted in Iran and the USA using the same study design, non-electronic prescribing systems, over a similar period time with a similar sample size reported notable differences in ME rates of 48.8% and 14.6%, respectively.[91,317]

Furthermore, the findings presented in Chapter 5 showed variation in ADE rates between PICUs. This variation may be explained by differences between wards in terms of the unit size and variation in specialised care provided by centres (e.g. cardiac critical care). However, this variation in ADE rates prompts the need for further investigation to explore underlying factors between different PICUs that may influence the emergence of ADEs and the effective implementation of safety interventions. Hence, addressing variations between centres is recommended and organisations should evaluate their own local clinical practices to support successful implementation of national medication safety policies.[362]

7.1.3.2 Nature of medication errors and adverse drug events in children's intensive care settings

Types and severity of medication errors and adverse drug events

Chapters 4 and 6 of this research programme found that the most common types of MEs in these settings were medicines prescribing and administration errors, with dosing errors and drug omission as the most frequent error sub-types. Most of the identified ADEs across NHS PICUs were preventable. Problems with prescribing medication were also commonly implicated with preventable ADEs as described in the study presented in Chapter 5 and in previous studies that examined MEs in PICU.[334] Factors that contribute to prescribing errors in PICU have been explored recently in the UK.[121] Distractions and interruptions in the paediatric intensive care environment that contribute to mental fatigue of prescribers were found as potential factors that lead to prescribing errors. Hence, it was recommended that future interventions should consider mitigating cognitive load on prescribers and enhancing team performance to reduce such errors and associated harm.

Dosing errors were reported as being a common subtype of MEs in previous studies conducted in the paediatric population [38,160,169,197] and the findings of this programme of research (Chapters 4, 5 and 6) reflect this and reinforce recommendations that have previously been made to prioritise interventions designed to reduce dosing errors in clinical practice.[197,363] A previous systematic review published in 2004 demonstrated that some healthcare professionals were not competent in calculating correct doses (e.g. weight-based) in paediatric patients, which could result in 10-fold errors.[153] Providing training programmes on medication dosing calculations and calculation aids (e.g. technological-based dosing calculation aids) for PICU and NICU staff may help improve their skills and reduce risk of MEs.[168,364] In addition, common dosing errors also often

involve the use of off-label and unlicensed drugs in children as a common associated factor.[365] Safe and effective dosing of these medications has been reported to be difficult due to variable scientific recommendations and a lack of appropriate formulations for children [366,367] and may thus lead to errors in prescribed or administered doses and ultimately harmful events.[368,369] Standardised dosing guidelines in children's ICU may reduce risk of MEs as the variability of the existing guidelines was identified by this research programme (Chapter 6) as a contributory factor to medication-related incidents in these settings.[370]

Fortunately, most MEs occurring in critically ill children were harmless (87.8% of MEs and ADEs in Chapter 6 were harmless). In addition, the harm associated with MEs (preventable ADEs) as described in Chapter 5 was frequently minor (58.1% caused temporary patient harm). This is a commonly reported finding across studies examining MEs in children.[371] This could be explained by the early interception of errors before they cause patient harm as well as the chance that errors did reach the patient but did not cause actual harm.[247] However, it is thought that errors causing actual harm may be reported less frequently than harmless MEs due to the prevailing reporting cultures among staff.[125]

Medication classes involved with medication errors and adverse drug events in children's intensive care settings

Identifying particular medications associated with higher risk of patient harm is a key component to the global WHO challenge (Medication Without Harm) and the NHS Medicines Safety Improvement Programme to reduce preventable harm.[24,46] In both NICU and PICU, the evidence presented in Chapter 4 showed that medications to treat infections are commonly involved with both MEs and preventable ADEs. There was a limited number of studies that reported data concerning commonly involved medications with

these events in Chapter 4 across both PICU and NICU.[334] However, the identified risk of MEs and preventable ADEs associated with the use of anti-infective medications in Chapter 4 was supported by the findings of Chapter 6. This class of medications was commonly involved with reported medication safety incidents in children's intensive care settings, particularly in neonates aged ≤28 days. Anti-infectives were also one of the most common medication classes involved with preventable ADEs in the study presented in Chapter 5. This may be because infection-related illnesses are common in paediatric patients and anti-infective agents are frequently prescribed in critically ill patients.[7] This medication class also involves certain agents that have been found to be more likely associated with MEs and ADEs in children (e.g. aminoglycosides) due to their narrow dosing ranges and the need for close monitoring of their serum levels.[372] Previous systematic reviews exploring MEs in paediatric patients have also reported that antibiotics were the most common drug class associated with MEs [197] and antimicrobials with medication administration errors [211], which suggests that future efforts in reducing MEs/preventable ADEs in critically ill paediatrics could target this group of medications.

Additionally, Chapter 5 has identified medications that have been classified as high-risk (e.g. adrenergic agonists/antagonists and anticoagulant agents), which were involved with preventable ADEs that caused serious patient harm. In addition, medications such as opioid analgesics were associated with the most frequently reported preventable ADEs in the study presented in Chapter 5. Excessive dosing of opioid analgesics was found to be associated with harm such as over sedation and agitation, which frequently caused prolonged patients' PICU stay. These drugs were classified as high-risk medications by the ISMP.[44] However, the list of the ISMP is not defined particularly for paediatric patients. A list of high-risk medications specified for PICU patients were presented in a study conducted by Franke et al. (2009), which involved 19 drug classes, some of them were not

identified by the ISMP list.[45] One of these drug classes was aminoglycoside anti-infective agents (e.g. gentamicin) that were considered as high-risk medications in PICU. In support of the Franke et al. study, this research programme found these anti-infective agents to be involved with risk of harmful preventable ADEs and medication safety incidents in critically ill neonates and children (Chapters 5 and 6).

If organisations such as ISMP produced some separate lists specific for different patient groups, particularly paediatric patients, this may help support efforts to reduce their risk to patient safety. Errors in using high-risk medications pose significant risk to NICU and PICU patients and generating a list of these drugs is only the first step to minimise this risk. It has been recommended that following the identification of high-risk medications, safety strategies to minimise associated risk of using them should be developed and tested.[373] This may include implementing several safety interventions. For example, using standardised medication concentrations for these medications, computerized physician order entry and Clinical Decision Support (CDS) systems with dosing guides (including maximum doses) and forcing functions, and training programmes for ICU staff about the safety of using these medications may minimise associated risk of errors and related harm.[175,316,374] This research programme reinforces this recommendation and presents an action agenda to address this issue by clinical staff and policy makers that will be discussed in more detail later in this chapter.

7.1.3.4 Risk factors and contributory factors to medication errors and preventable adverse drug events in children's intensive care settings

Chapter 5 of this thesis reported a statistically significant association between the risk of ADE occurrence and length of PICU stay. In addition, when an ADE occurs, it has been reported that it is likely to cause extended stay of the patient in hospital.[206] Nearly one third

of identified ADEs that were described in Chapter 5 contributed to patient harm that caused prolonged patient stay in the PICU. It has been estimated that the cost of an ADE in ICU is around 9000 USA Dollars.[375] These ADEs also adversely affect the delivery of care by reducing the capacity for health care providers and the optimal use of beds.[362]

Furthermore, Chapter 6 of this research programme found that harmful medication incidents occurring in neonatal and children's intensive care settings may have origins in challenging venous access in neonates (leading commonly to drug omission), failure of ICU staff to follow safety protocols (commonly contributing to errors in prescribing, administering or monitoring anti-infective drugs). These factors were, notably, due to ICU excessive workload, shortage of staff and inadequate policies (e.g. handover process, transferring patient to ICU for a single dose administration or medication dispensing and blood test policies) or systems (e.g. prescribing system).

Another common contributory factor associated with MEs was transferring patients between ICU and other clinical hospital areas. In this research programme, common errors occurred during this process were documentation error of patients' records, which has been also found as a frequent error that occur during children transfer between hospital wards.[376] Transition of care is a key area that the current WHO global campaign has highlighted for countries to prioritise when developing interventions to prevent medication-related harm.[24] The NHS in its Long Term Plan is moving toward digitisation of such processes, which may help minimise the risk of errors (e.g. poor documentation and loss of medicines administration records) identified by this research program in critically ill neonates and children.[73]

The unique nature of neonatal and children's intensive care has been illuminated by factors that this research has identified such as pressurised working environment of ICU and

challenging physiology in neonates which commonly contributed to MEs and related patient harm. These settings involve high-risk patient populations and are a priority target for medication safety improvement. Interventions should be designed specifically for these settings considering systemic organisational factors to support effective implementation. Recommendations for improvement include redesign of systems and policies (e.g. transfer of care processes between wards and ICU, medicines prescribing and patient records documentation systems) as well as the use of certain medications (e.g. anti-infective and high-risk medications). Reducing length of PICU stay as well as problems associated with challenging venous access in neonates (e.g. drug omission errors) are also targets for improvement in children's ICU to reduce avoidable patient harm. Improvement of working conditions in children's ICU (e.g. inadequate staffing) is needed to help implement medication safety interventions effectively in these settings.

This thesis has identified risk factors and salient relationships between common ME types and factors contributing to their occurrence in neonatal and children's intensive care settings (Chapters 5 and 6). This highlighted areas that should be prioritised by future interventions designed to reduce MEs and related harm in these setting. The approach of utilising a mixed methods study design that included quantitative descriptive analysis alongside content analysis of free text incident descriptions has provided the opportunity to learn from medication safety incidents at a national level. This has generated important recommendations to improve patient safety by understanding their underlying antecedents and prioritising high-risk areas, and is a process used successfully elsewhere.[214,259,300,350,356]

7.1.4 Main strengths and limitations of the research programme

This research programme adds important knowledge about medication safety in neonatal and children's intensive care settings that was not known or understood before.

Specifically, this includes understanding the frequency, nature and underlying contributory factors of MEs and preventable ADEs occurring in these settings. This has given the opportunity to identify high risk areas and generate novel recommendations for improvement to make these settings safer environments. The objectives of this research programme were achieved by utilising appropriate methodologies such as mixed-methods analysis [377] and prospective cohort designs [346].

The systematic review presented in Chapter 4 searched several databases as well as grey literature, along with reference lists of included studies in order to minimise the risk of missing relevant data.[334] Two of the review authors (AAA and RNK, DMA or AS) extracted relevant data independently and authors of included studies were contacted when additional data were required. The broad focus of this systematic review in examining rate and nature of MEs (across all stages of the medication use process) as well as related ADEs in both NICU and PICU has allowed building a more complete overview of medication safety issues in these settings. It has also helped in identifying areas for further investigation such as the frequency and nature of preventable ADEs in UK PICUs.

This research programme collected ADE data (Chapter 5) from multiple PICUs across England that provide regional critical care services to enhance validity and generalisability of the findings. However, the applicability of these findings may be restricted to UK practice due to variable clinical practice in children's ICU between countries.

The extensive analysis of medication safety incidents presented in Chapter 6 covering a nine year-period has provided system-wide learning from a national incident reporting system. It has supported the identification of areas of risk to patients and offered more understanding on the nature and contributory factors associated with medication safety incidents in children's ICU. However, it was not possible to determine whether incidents

were MEs or ADEs in all cases, and if reported harm was actual or potential. In addition, the poor quality of reporting speciality (neonatal or paediatric ICU) where incidents occurred limited the ability to separate out data from the two settings and to generate distinct improvement recommendations (Chapter 6). This was a limitation for the whole research programme. PICU and NICU are potentially two distinct settings as they may involve different ICU staff and patient populations. For example, NICU are often staffed by neonatologists and neonatal nursing staff who are trained to provide specialised care for critically ill term and preterm new-born patients. Due to factors such as different anatomical and physiological considerations compared to older children, critically ill neonates, ideally, need specialised medical practitioners in ICU.[378] However, there is substantial crossover between neonatal and paediatric intensive care in the UK because some services (e.g. congenital cardiac surgery) are provided on a national basis by specialised units. For example, the observational study presented in Chapter 5 was based specifically in PICU, however 16.2% of screened patients across the three involved PICUs were neonates (aged less than 29 days). In addition, while this research programme separated NICU and PICU data in Chapter 4,[334] clinical heterogeneity was observed across both settings (involving neonates in PICU studies and vice versa). This source of heterogeneity also prevented meta-analysis across included studies.

7.1.5 Implications of the findings for clinical practice and policy

There are important implications of the research findings presented in this thesis, which will be discussed in this section, for clinical staff and health care leaders to promote the safe use of medications in neonatal and children's intensive care units.

7.1.5.1 Target medications to improve safety of patients in children's intensive care settings

Prescribing, administration and monitoring of anti-infective drugs are routine duties in children's ICUs. It is estimated that around 70% of children patient receive anti-infective medications during PICU stay.[379] This research programme found these medications commonly involved with MEs and preventable ADEs in critically ill children (Chapters 4, 5 and 6). It, therefore, highlights the use of anti-infective medications as an area of high risk to children in ICU, particularly neonates aged less than 28 days, with a high proportion of aminoglycosides implicated in reported medication safety incidents in this age group (Chapter 6). Aminoglycosides are considered as high-risk medications [45], and are widely used to treat infections in neonates.[380] In the UK, a national survey across neonatal units in England (published in 2010) indicated that 89% of 180 participating units were using IV gentamicin (aminoglycoside agent) to treat infections in neonates.[175]

Aminoglycosides have a narrow therapeutic window and require frequent dosing adjustments that are based on monitoring their serum levels, which involve performing new calculations every time the dose is changed.[381] Dosing and monitoring errors that involve these medications may cause serious injury (e.g. nephrotoxicity), some of which may be irreversible.[382] National co-ordinated guidance was implemented in 2010 by the NPSA to reduce incidents associated with using aminoglycosides in neonates.[383] Chapter 6 of this thesis shows that despite this intervention, incidents involving this drug class still persist and were also identified in Chapter 5 to be involved with preventable ADEs of a significant severity (e.g. permanent patient harm). This, therefore, should prompt further investigation to evaluate the use of safer alternative antimicrobials in critically ill neonates or improving the safety measures in the use of these medications. In addition, Chapters 5 and 6 of this research programme found that the most common error type in using

aminoglycoside medications were the omission of monitoring pre and/or post dose level of aminoglycosides by ICU clinical staff. Chapter 6 explored the commonly associated contributory factors to errors in using these medications to be due to excessive ICU workload, shortage of staff and challenging venous access in neonates. This makes addressing issues concerning working conditions in ICU by health care leaders vital to promote successful implementation of interventions designed to reduce the risk associated with using these medications.

Other high-risk medications (e.g. opioid analgesics and adrenoceptor blocking medications) were found by this research programme to be associated with greater severity of preventable ADEs and prolonged the stay of critically ill neonates and children in ICU (Chapters 5 and 6).

Specific safety measures should be implemented for the use of these medications in NICU and PICU to reduce the risk of errors in prescribing, preparing, administering and monitoring them. Several interventions may be considered for employment in high-acuity environments such as NICU and PICU to address such risk.[384,385] Given the complexity of the medication management system in these settings, using known medication safety measures such as smart infusion pumps alone may not be sufficient to prevent errors and serious harm associated with these medications.[386,387] For example, one of the preventable ADEs (bleeding) due to use of high-risk medication (parenteral anticoagulants) identified by the epidemiological study presented in Chapter 5 was associated with using an infusion pump. The error occurred in setting up the rate of administration of a heparin dose and the patient harm associated with this error was classified as permanent. Independent double-checking strategies when programming infusion pumps may have prevented errors like these and the avoidable harm they create. This could be layered together with other strategies such as colour-coded labelling of these drugs, which is a well-recognised policy

that may help PICU staff to be more vigilant when preparing, administering and monitoring these medications.[388] In addition, using standardised medication concentrations for medications commonly administered via infusion pump in paediatric patients was found effective in reducing overdosing errors.[374,389] In a study by Larsen et al. (2005) that examined the impact of this strategy over two years in hospitalised children, the researchers reported a reduction in the rate of 10-fold errors (from 0.41 to 0.08 per 1000 doses).[374]

Providing additional training for ICU staff involved in prescribing and administering high-risk medications is also recommended to increase their knowledge about actions that should be taken in monitoring blood drug levels of these medication to reduce the risk of errors associated with their use.[175,386] For example, the NPSA developed a training pack that was published with their alert in 2010.[383] Undertaking this training should be made a requirement for PICU and NICU clinical staff involved with using aminoglycoside medications.

7.1.5.2 Improvement of working conditions in children's intensive care settings

Commonly identified error types in this research programme such as wrong doses and dose omissions were often found to be associated with ICU pressurised work environments (Chapter 6). Hence, this research programme suggests that improvements in staffing and workload is an important target to improve medication safety in NICU and PICU. Previous studies have found that heavy workload and inadequate staffing, and related staff fatigue, were significantly associated with missed care for critically ill children. [121,390-392]

Children's ICUs including high dependency beds in England and Wales routinely exceed the standard limit of bed occupancy (85-100% occupancy), which should be less than 85%

and thus are often considered overloaded.[65,115] Though admission rates have remained broadly stable over the past three years (~20,000 children/144,000 patient bed days per year in the UK) there is a trend towards paediatric intensive care patients having more long term complex care needs.[393] A better understanding of safe working conditions, and their influence on implementation of medication safety improvements in these settings is needed. Manageable workload and adequate staffing, which has been associated with improved patient safety in ICU [158,394,395], should be considered by policy makers in children's critical care settings to reduce MEs and related ADEs.

Cognitive burden on prescribers due to interruptions and distractions in PICU were described as a principal underlying cause of prescribing errors by a recent UK study.[121] Prescribing errors in PICU due to interruptions or distractions was found to occur at a rate of 19.6 per 100 medication orders in the UK.[396] A zero tolerance prescribing strategy was applied in a single UK PICU and evaluated by a prospective pre- and post-intervention study was found effective in reducing prescribing errors.[143] This strategy was designed to reduce interruptions and distractions during medicines prescribing by implementing a dedicated quiet area for prescribers equipped by necessary resources (e.g. PICU guidelines and up-to-date dosing reference). Another part of this strategy was providing feedback to prescribers on any error intercepted by pharmacists. A significant reduction in prescribing errors (absolute risk reduction of 44.5%) was found after applying this intervention in PICU. This strategy was adapted by another study and found improvement in medicines prescribing practice in PICU without a statistically significant reduction in MEs.[212] However, this study was published as a conference abstract without reporting sufficient information about the method used in implementing and evaluating the intervention. The intervention was reported to be less expensive than those based on technological innovations (e.g. computerised physician order entry) and its primary results in reducing

MEs in PICU were promising.[143,396] This strategy targeted a common error type (prescribing errors) by addressing one of the main associated contributory factors (excessive interruptions and distractions in a pressurised working environment). It could be adopted more widely as an intervention in which policymakers aim to create safer environments for patient care rather than relying only on efforts by individual teams.[62]

In addition, medication administration errors are one of the most common ME types as identified by this research programme (chapters 4, 5 and 6) and across published literature.[160,169,177] It is thought that interruptions during medication preparation and administration stages are a contributory factor associated with errors during these stages.[397] There have been several safety interventions to reduce interruptions to nurses during medication preparation and administration stages such as 'quiet/no interruption zone' and using 'no interruption signs/vests'.[398-400] In a systematic review that was conducted in 2013 to evaluate the effectiveness of such interventions, it was concluded that evidence is weak (in reducing interruptions and related MEs). This was principally due to methodological issues across the examined studies (10 studies) and controlled trials are needed to evaluate the value of available interventions before they could be rolled out.[401]

Furthermore, application of principles from the field of human factors and ergonomics could support the redesign of systems and processes to achieve improved safety in complex work settings like ICU.[222,402] This research programme, therefore, recommends that future safety policies should focus on improving human factors knowledge in this area which should help ICU staff to communicate well and carry out their routine tasks (e.g. monitoring vascular access or prescribing/administering anti-infective drugs) in the right way, and consequently improve medication safety. For example, working toward implementing the current NHS Patient Safety Strategy is needed which has highlighted the need for education in patient safety for the workforce. The NHS strategy is expecting that

improving the understanding of health care workers about the importance of delivering care safely to patients rather than asking them to follow specific safety rules will have a significant impact to improve patient safety.[25]

7.1.5.3 Interventions to reduce medication errors and related harm in children's intensive care settings

Technology-based interventions

The systematic review presented in Chapter 4 included studies that examined MEs in PICU and NICU using paper-based and electronic prescribing systems, and compared MEs rates between ICUs using these different systems.[334] However available data about ICUs that use electronic prescribing systems was provided only by a small number of studies (only two studies in PICU and one in NICU). The systematic review identified four studies with a pre-post intervention design [188,316,320,324], one of which was rated as high-quality [316], that assessed the impact of introducing electronic medication charts on prescribing errors in paper-based ICUs. All these studies found a significant reduction in prescribing error rates (e.g. from 8.24 to 1.4 per 100 medication orders)[188] following introduction of electronic prescribing systems. The introduction of electronic prescribing systems has been associated with significant reduction of certain types of errors such as illegible prescriptions.[192] Evidence on the clinical effectiveness (mitigating patient harm) of these strategies utilising technological innovations including computerised physician order entry and CDS systems are still limited.[168,209,403]

The use of technological interventions might be helpful in carrying out fewer dosing calculations by clinical staff, which has been associated with common dosing errors in paediatric patients.[153] However, most electronic systems (e.g. computerised physician order entry) are designed by medical software vendors for adult hospitals.[125] The

successful implementation of such interventions may be enhanced by developing electronic prescribing systems that are supported by CDS systems designed specifically for the paediatric patient population. This may help in minimising the risk of errors in prescribing particular medications such as those identified by this research programme (e.g. anti-infectives) to be commonly involved with MEs and preventable ADEs. For example, implementing maximum doses in these systems for medications that are likely associated with overdosing errors in neonates may help prescribers to follow standardised dosing guidelines consistently and prevent such errors. Opioids are widely used in NICU and PICU as sedating agents and are an example of those medications that are commonly involved with overdosing errors in neonates [306], which has also been identified by this research programme (Chapter 5). This intervention may enhance awareness among prescribers about the risk associated with using these drugs and decrease potential harmful events. For example, a study that prospectively examined more than 13,000 medication orders reported a significant reduction in prescribing errors (from 30.1 to 0.2 per 100 orders) and potential ADE (from 2.2 to 1.3 per 100 orders) after implementing a computerized physician order entry system in PICU.[316] This included CDS with automated dosing guide and forcing functions that have been designed for paediatric patients. Implementing such systems in children's ICU is thought to be helpful in preventing MEs due to human factors.[404]

However, such interventions may only target the prescribing stage and would not prevent errors during drug administration. Technology may not reduce the risk of error when there is a need to manipulate the drug products.[132] For example, 5 mg/mL is the lowest concentration of diamorphine IV opioid that is licenced in the UK.[405] The recommended dose of diamorphine for children (e.g. 1 – 2 months old) is 20 micrograms/kg. Hence, one ampoule of this drug could cause a significant overdosing error, the like of which has been

reported previously to cause death incidents in neonates and children in the UK.[153] The availability of drug strength that is appropriate for use in neonates and children was found effective in minimising such risk.[406] This could be recommended for pharmaceutical companies with financial support by governments, as developing such formulations may not be a desirable investment due to financial issues.[407] In addition, using the NHS Pharmacy aseptic services that make 'ready to use IV medications' may also help reduce MEs that occur in NICUs and PICU, particularly in frequently used IV medications (e.g. anti-infectives and analgesics).[408]

Furthermore, prescribing remains largely paper-based in the UK hospitals.[409] Handwriting was one of the factors commonly involved with reported medication-related safety incidents as described in Chapter 6. In addition, CDS is offered in the UK children's intensive care primarily in the form of administrative policies and guidelines, many of which are not standardised across interfaces of care. In a recent multi-centre study of the causative factors of prescribing errors in paediatric intensive care in England, a core feature of these decision support systems was their intellectual and physical inaccessibility.[121]

Moving toward implementing technological support in clinical processes is a main part of the recently announced NHS Long Term Plan to improve patient safety.[73] For example, there is ongoing implementation and rollout of electronic prescribing and medication administration systems in UK hospitals, which is expected to reduce MEs and ADEs by 50% in NHS England.[74] Until the effectiveness of these preventive strategies is evaluated [74,410], there is an urgent need for medication safety improvement in the current clinical practice in NICU and PICU.

Furthermore, the NHS is undertaking a national transformation programme (Digital Child Health Transformation Programme) to make paediatric patients records available electronically by 2021.[411] The pace of implementing this programme may be affected by the impact of the current coronavirus disease (COVID-19) pandemic and will resume in the future.[412] This would support patient care improvement by making children's health data accessible by health care providers where digital information could be shared to deliver safe care for patients. This effort with support of the NHS Long Term Plan in implementing electronic systems for clinical processes (e.g. electronic prescribing and medication administration systems) would promote paediatric patient safety.[73]

Non-technology based interventions

High risk areas identified by this research programme such as medicines dosing for neonates could be the target for improvement in ICU clinical staff using non-technology approaches. Risk of MEs associated with lack of ICU staff knowledge was identified by the study presented in Chapter 6 of this thesis. Strategies such as enhancing competency of NICU and PICU clinical staff in weight-based dosing calculations and their knowledge about the safety procedures in using commonly prescribed medications (e.g. anti-infectives) and high-risk medication may minimise this risk. This could be achieved by developing continuous competency-based educational programmes for frontline healthcare staff in ICU, which has been reflected in the current NHS Patient Safety Strategy.[25,413] For example, physicians in their earlier years of residency programme (first to third year of training) in a paediatric hospital were found to be commonly involved with prescribing errors, particularly in PICU, due to their lack of paediatric dosing skills.[414] Training and educational programmes for medical staff have been found to have positive impact on medication safety improvement.[415,416] In addition, medical staff registration authorities and

academic institutions could also incorporate special training curriculum for future health care professionals in dealing with medications for paediatric patients as part of their educational programmes.[417]

Developing specific induction programmes for new ICU staff on local drug safety policies, and verifying compatibility and appropriate route of administration of IV medications may also promote safer use of medications in NICU and PICU.[265] For example, Chapter 6 of this thesis found that some new ICU staff were not familiar with their unit's policies and guidelines which contributed to medication incidents. Facilitating development and supporting implementation of these strategies could be the role the Patient Safety Specialists who are currently being identified and trained by the NHS. Patient Safety Specialists are a key component of the recent NHS Patient Safety Strategy.[25] They will be enrolled in training programmes to improve their knowledge and skills about patient safety so that they can lead on patient safety improvement at their local health care settings. This initiative has been made previously in the NHS by creating a role of Medication Safety Officer in 2014.[258] The benefits of such initiative on medication safety activities have been described in a large USA medical centre.[418] The implementation of the role of these safety officers as part of the current NHS Patient Safety Strategy need to consider specifically critically ill children as a vulnerable and at-risk patient population. Specialised training for those safety officers is recommended (considering the understanding generated by this research programme about medication safety in children's ICU) to enhance their knowledge in developing and adapting safety interventions for this environment.

Significant variation in risk of preventable medication-related harm across PICUs, as the findings of this research programme have shown (Chapter 5), could be addressed by the Patient Safety Specialists strategy. Those specialists may have a better opportunity to identify deficiencies within their local systems, which may not be similar to other

centres.[419] In addition, Patient Safety Specialists will, subsequently, join patient safety networks at a national level so that they can share experiences and good practice, which may help further in improving patient safety across NHS organisations.

7.1.5.4 Reducing length of children's stay in intensive care unit

This research programme found a significant association between risk of experiencing a preventable ADE and increased patient stay in PICU (Chapter 5). Several factors may influence length of stay of patient in ICU such as severity of illness.[420] Complications associated with use of medications (e.g. sedation) is another factor that may contribute principally to increase patients length of stay in neonatal and children's intensive care settings.[421] In a study that screened 20 PICUs in the UK (2007), 13% of 338 patients experienced sedation withdrawal ADEs.[422] The study presented in Chapter 5 of this thesis found that the most frequently identified preventable ADEs in PICUs (30.6%) were associated with using medications that have sedative effects and most of these ADEs led to prolonged stay of patients in PICU.

In NICU and PICU, patients frequently require the use of mechanical ventilation and this is often associated with the use of sedative medications. Weaning from ventilation and sedative medication must be attempted as soon as the patient condition improves. However, evaluating the readiness of ventilated patients to begin the weaning process is a complex task with lack of robust evidence on the effectiveness of existing weaning protocols.[423] Failure of sedation weaning processes are usually associated with undesirable over sedation events (e.g. withdrawal syndrome), which consequently delay recovery (e.g. increase length of ventilation) and prolong PICU stay.[424]

In NHS PICUs, the sedation weaning process is largely a non-protocol-based practice without specific criteria and rely mainly on the clinical judgment of the medical team.[425,426] However, there is a national protocol-based intervention that is being implemented in the UK to promote optimal sedation weaning in critically ill children receiving mechanical ventilation.[427] Evaluating the effectiveness of this intervention is underway through a large clinical trial involving 17 PICUs across the UK. A similar intervention was found promising in managing length of stay in both PICU and adult ICU.[428-430] Hence, if implemented successfully in NICU and PICU, this intervention may contribute to overall medication safety improvement in these settings by reducing length of stay (this has been observed in adult ICU) [431] and associated risk of experiencing preventable ADEs. This may also help to reduce risk of excessive dosing of sedative medications as addressing this issue in PICUs is a requirement to implement the new protocol-based intervention.[427]

Furthermore, the NHS published a five-year plan in 2017 to improve quality of care and one of this plan's objectives was to effectively enhance hospitals' productivity by reducing number of delayed discharges.[72] After publication of this plan, the NHS announced recently (2019) that within two years, length of stay of patients who were hospitalised for more than 21 days reduced and this strategy made around 2000 beds available for new patients.[73] This plan involves reviewing admitted patients frequently to assess whether the care could be provided in less intensive hospital settings, which may help in reducing length of ICU stay.[432] The results of such efforts seem promising for medication safety improvement in NICU and PICU by targeting reduction of patient hospital stay, thus minimising risk of experiencing ADEs. In addition, the current NHS medication safety improvement programme may help support these efforts to reduce length of hospital stay by reducing risk of experiencing ADEs, which may prolong patients stay as identified by this research programme.

7.1.5.5 Challenging vascular access in children

Peripheral and central venous access is a regularly required procedure for critically ill neonates and children in ICU.[433] This procedure involves insertion of catheter into a vein for several medical reasons including medication administration. This research programme found failure in securing venous access was associated with drug omission errors in neonates admitted to ICU (Chapter 6). MEs and ADEs were also associated with administering drugs through peripheral lines, which frequently were not appropriate for some drug concentrations and caused extravasation injuries. For example, some parenteral nutrition concentrations should be administered via central venous access in neonates to avoid undesirable complications (e.g. extravasation harm).[434]

Securing central venous access is a challenging procedure and clinicians, including nurses, undertaking this procedure should have enough knowledge about anatomical insertion sites in neonates and experience in doing such a procedure. In addition, using ultrasound imaging in inserting central venous catheter was found effective method in decreasing the number of attempts and complications associated with failure of this procedure.[435-437] In 2002, the National Institute for Health and Care Excellence (NICE) has recommended using this technique as a preferred way for inserting central venous catheters in children.[438] NICE recommends that all NHS children's hospitals should locate their ultrasound units appropriately and train their health care professionals on using them in undertaking this procedure. Such an approach may also help preventing the need for surgical procedures and related complications in securing venous access for children.

The current infrastructure of NHS hospitals may be ready for implementing this technique as hospitals are equipped with ultrasound scanning devices. This research programme reinforces the NICE recommendation to use such available equipment and optimise skills

of health care professionals in using this technique. This may help in preventing drug omission errors and harm such as extravasation events in critically ill neonates and children, and consequently improve safe use of mediations in this vulnerable patient population. However, it has been nearly two decades since the publication of the NICE guidance. This prompts the need for further research to explore whether NHS hospitals are following this approach and reasons that may prevent the implementation of this intervention in practice.

7.1.6 Recommendation for future research

7.1.6.1 Research implementation into clinical practice

There are existing interventions and policies to improve medication safety in children's intensive care that have shown limited impact. Examples of such interventions are those aimed to improve the use of aminoglycoside anti-infectives and using ultrasound scanning for central venous access to reduce associated complications (e.g. drug omission).[190,212,383,438,439] This could be due to failure of the implementation process into clinical practice rather than deficit in the interventions themselves, which is a commonly reported phenomenon in the literature.[440] To bridge the gap between research and clinical practice, theoretical understanding may help in providing useful guidance to implement new or existing evidence-based interventions in health care.

Examining a health care issue, identifying targets for improvement and designing an intervention to minimise risks should be accompanied by an implementation plan for clinical usage, which needs a focused effort. The field of implementation science addresses issues associated with implementing research into the real world.[441] This science is defined as 'the study of methods and strategies to promote the uptake of interventions that have

proven effective into routine practice, with the aim of improving population health'.[442] Hence, this science provides important understanding of how to implement safety interventions into clinical practice effectively. It also examines the overall impact of interventions (including the wider practicality of the intervention by considering impact on people and processes, as well as outcomes of interest) and test ways to improve their implementation. This involves testing different outcome variables of implementation such as acceptability, appropriateness and feasibility.[440]

Importantly, this science is also mindful to questions that may arise from experience by health care practitioners or policy makers as it recommends identifying such questions or concerns at the early stages of developing intervention or safety policies.[443] Co-designing an intervention in partnership with relevant local practitioners and policy makers would help in judging the relevance of the intervention and integrating it within their health care practice.[441] Furthermore, researchers should be prepared for changes over time in factors that could influence the implementation process and, subsequently, the impact and sustainability of an intervention. For example, new health care professionals joining PICU/NICU teams may need education and training programmes on an implemented safety intervention or guidelines, which is a recommended strategy by implementation science.[440] In addition, changes in usual clinical practice or systems by implementing new intervention may involve unintended consequences that implementers should identify and address them to tackle any barriers that could affect the implementation process.[444,445] For example, introduction of electronic prescribing and advanced decision support systems may produce new errors (e.g. wrong patient/drug selection) due to factors such as the poor adoption by users of a new technology or lack of technical support.[403,446] Such unintended consequences are commonly associated with implementing technology-based interventions in health care.[447,448]

Intervention implementation is a multi-step process and there are several theoretical approaches in implementation science that have been developed to potentially be used in translating research into practice.[449-452] These approaches were categorised into five main areas that cover different aspects of implementation; namely process models, determinant frameworks, classic theories, implementation theories and evaluation frameworks. These categories were developed by Nilsen (2015) to help researchers to distinguish between different approaches and appropriately select the right type to achieve different aims in implementing interventions.[453] Figure 7.1 created by Nilsen describes these categories and their links to the aims of implementation science.

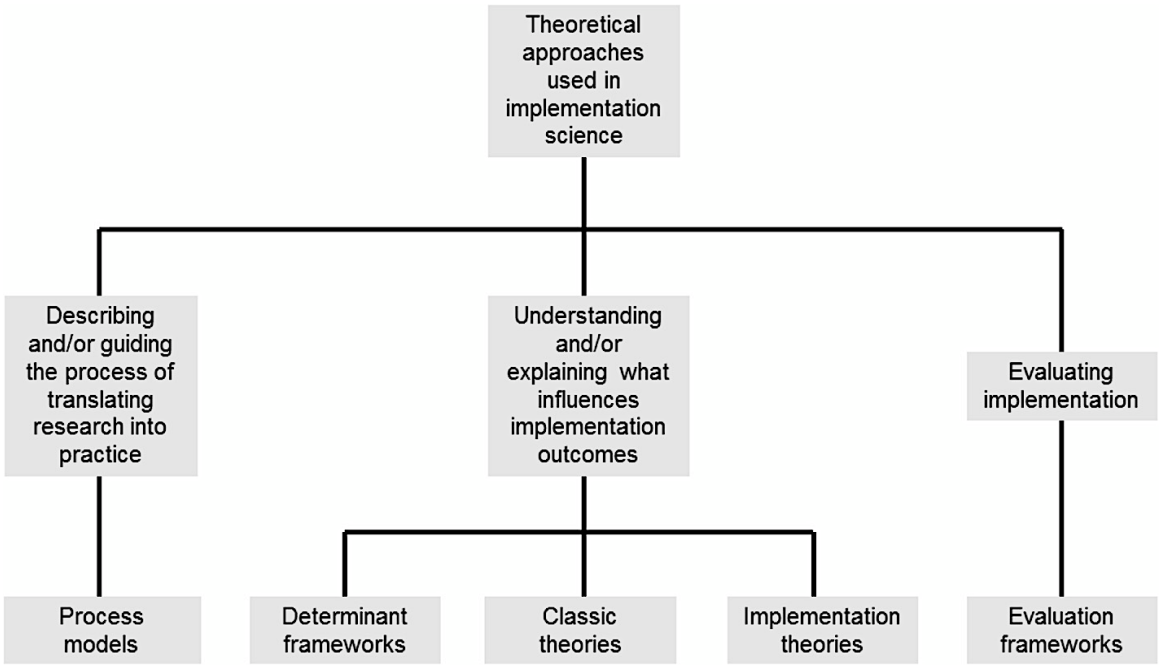


Figure 7.1 Categories of approaches developed to achieve aims of implementation science. (Sources: Nilsen (2015))[453]

Implementation science is a form of 'real world' research and mainly sheds light on factors that can influence implementation of interventions. It helps understand the context of the environment where an intervention will be implemented. Different health care providers have variable capacities and diverse contexts to implement a preventive intervention.[426]

Understanding contextual factors is crucial as they are principally associated with intervention implementation issues.[454,455] For example, positive contexts in healthcare environment described by supportive leadership, empowering culture and effective feedback on performance (evaluation of following safety policies) were found associated with successful implementation of research into practice and improved patient safety.[456-458]

Using this knowledge, for example, to improve safe use of anti-infectives in critically ill children, may require changing practitioners' fundamental understanding of how to use these medications in the safe way. For example, ICU nurses may find administering an IV anti-infective medication (e.g. aminoglycoside agent) without carrying out a double-check process would save time for other urgent tasks. This deviation from medication safety policies was found as a common contributory factor associated with MEs (Chapter 6). Changes to reduce these unsafe practices may require complex interventions that include multiple components such as interventions to change behaviour of health professionals (e.g. medication prescribing and administration behaviour) and enhancing adherence of practitioners to safety policies and guidelines.[459,460]

For example, several studies have successfully utilised the Medical Research Council framework to develop and evaluate complex interventions.[443,461-463] This framework involves multiple phases starting with identifying and using an appropriate theory for an intervention. It is also important to identify the existing evidence at this stage about similar interventions to inform the development of the intervention.[464] This is followed by a modelling phase to identify relevant components of the intervention and the potential interactions between them. In this phase, it has been suggested that methods such as surveys, interviews, focus groups are useful to explore obstacles in developing behavioural change interventions for health care professionals.[460] The next phase utilises data from the previous stages about the identified components to inform the development of the

intervention and the optimal study design. This involves exploratory work about the developed intervention by conducting a pilot study to examine factors that may affect the feasibility of implementing the intervention and acceptability by patients and health care providers. Addressing such factors is crucial as they may also prevent the intervention from being eligible to be replicated in other contexts or delivered at a larger scale.[465] Implementers then should evaluate the intervention in a robust manner (e.g. using randomised controlled trials) to provide evidence on the effectiveness. Long term monitoring to assess the effectiveness of intervention in practice is also recommended as a final stage of the implementation to test its stability and identify any unintended effects.[460]

A greater interest in the field of implementation science is, therefore, recommended by this research programme for future research to help in developing and implementing medication safety interventions effectively in children's intensive care settings.

7.1.6.2 Effectiveness of medication safety interventions in children's intensive care settings

Technology-based intervention

There are systematic reviews that have evaluated the effectiveness of existing interventions to reduce MEs in children; one focusing on paediatrics and ICU settings (including adults) published in 2009 [209], one on PICUs published in 2014 [190], two on paediatrics including ICUs published in 2014 [466] and 2015 [168] and one on neonatal settings involving NICUs and PICUs published in 2018.[189] These reviews found that implementing technological innovations (e.g. computerised physician order entry or CDS systems) might help in reducing MEs. However, all these reviews concluded that the evidence remains limited, with methodological variations identified across the reviewed studies which prevented a more thorough assessment. In addition, these reviews identified a limited number of

studies from the UK children's ICU settings. For example, Manias et al. (2014) [190] and Nguyen et al. (2018) [189] found four UK based studies (published in 2000 [167], 2004 [467], 2011 [320], and 2012 [143]). Only one of these studies examined the impact of technological-based intervention in a PICU (implementing electronic prescribing system) and reported a reduction in certain types of MEs (medication omission and illegible prescription errors), but new types of errors were identified (e.g. selecting wrong infusion rate).[320] This highlights the need for future medication safety research to focus on critically ill children in the UK health care using theory driven approach.

Furthermore, a systematic review published in 2015, which assessed the effectiveness of existing interventions to reduce medication administration errors in hospitalised children including PICU patients, found that the impact of available approaches remain limited.[211] The review concluded that medication administration is a multifaceted process, which includes, for example, preparation technique and right patient, drug and dose, which may need better understanding to target the most susceptible stage to errors. A key gap identified by this review was that there were very limited studies that focused on reducing medication administration errors in children's intensive care setting, particularly in the UK (only one study that was carried out 10 years ago).[320] Errors at the medication administration stage were found to be one of the most common ME types in NICU and PICU (Chapters 4, 5 and 6). Hence, it is recommended that future efforts should target medication administration errors in designing and evaluating interventions to improve medication safety in PICU and NICU.

Due to lack of evidence concerning the effectiveness of medication safety interventions that were examined by the aforementioned systematic reviews, recommending an ideal intervention(s) to adopt in NICU and PICU is currently challenging. Therefore, robust

approaches in developing and evaluating medication safety interventions for these settings is recommended for future research to achieve the desired clinical and cost effectiveness.

Technological improvement efforts in the UK health care system may support safe use of medications in critically ill children. For example, successfully developed and evaluated technological-based medication safety interventions led by pharmacists in the UK could be emulated and customised for NHS children's intensive care practice.[290,468] One of these interventions is the Pharmacist-led Information Technology Complex Intervention (PINCER) programme, which is a good example of medication safety intervention that has been developed and evaluated successfully by utilising the guidance provided by implementation science.[469] PINCER was evaluated in 72 general health care practices and found effective method in reducing MEs. The development and evaluation of this intervention using robust approach contributed to its success in reducing MEs and subsequently to its wide rollout to general practices in the UK. This intervention is designed to identify at-risk patients and help preventing potential prescribing errors by integrating medication safety indicators into the prescribing systems. For instance, adequate blood test monitoring is a key part of PINCER intervention. This could be beneficial for children's intensive care practice in preventing inadequate drug level monitoring for high-risk medications such as aminoglycosides, which was found commonly associated with MEs and preventable ADEs by this research programme (Chapters 5 and 6).

Fox et al. (2016) developed a list of medication prescribing indicators for paediatrics in the UK using two rounds electronic consensus method.[470] The list included 41 paediatric prescribing indicators of potential harm with dosing errors as the most common error type and anti-infectives as the most common medication classes within the indicators. High-risk medications that have been identified by this research programme to be associated with

MEs and harmful preventable ADEs (e.g. anticoagulants, aminoglycosides, opioid analgesics) were among the high-risk indicators developed by Fox et al. These medication safety indicators could be used in the development of technological-based prescribing safety interventions for paediatric patients such as those developed for other areas (e.g. PINCER and the pharmacist-led Safety Medication Dashboard).[290,468]

Clinical pharmacist intervention

Pharmacists play a vital role in improving patient safety and their interventions to reduce preventable patient harm were found effective across different health care areas.[471-473] Clinical pharmacy services are normally provided in the NHS hospitals, but the role of these services in medication safety for the UK's children's intensive care settings is not well understood.

Involvement of clinical pharmacists in medication management processes such as validating prescriptions, participating in ward rounds and developing educational programmes for medical teams have yielded encouraging results in reducing MEs in hospitalised children including PICU patients.[191,474] However, the volume and quality of this evidence is still limited and further studies evaluating the role of clinical pharmacy services on medication safety in children, particularly in those admitted to ICU, are warranted.[475]

In the UK PICUs, the only control against MEs was identified as the bedside nurse or unit pharmacist in a study that explored the human factors of prescribing errors across two PICUs.[121] However, these controls may be constrained by staff shortages and whether pharmacy services are established on an "office hours" basis. The estimated rate of prescribing errors intercepted by pharmacists in neonatal and paediatric health care settings

in the UK accounted for 8.7 per 100 medication order (20.6 per 100 patients).[476] This was reported by a prospective multicentre study that recruited pharmacists voluntarily across 13 NHS children's hospitals to record prescribing errors that they identified and intercepted as part of their usual working routine. However, this study was published as a conference abstract and did not report sufficient information about the methods used or paediatric clinical settings involved.

In a study originated from the USA, pharmacists made 1,315 interventions in two months to prevent MEs in paediatric patients (including NICU and PICU patient) and prevented 311 MEs out of 322 MEs with around half of the errors being classified to have the potential to cause serious patient injuries.[414] Furthermore, clinical pharmacists' interventions may have a positive impact on reducing cost associated with MEs in children's intensive care settings.[477,478] For example, in a Brazilian study that examined the impact of clinical pharmacist interventions in PICU over one-year period, estimated cost of MEs prevented by pharmacists accounted for 4,828 USA Dollars (3% of total cost of PICU patient's treatment).[479]

PICU/NICU pharmacists may help address major safety areas identified by this research programme (Chapters 4, 5 and 6) such as prescribing and administering high-risk medications (aminoglycoside and opioid analgesics). This may include several activities such as involvement in therapeutic drug monitoring and validating doses and route of administration. Clinical pharmacists may help intercept MEs that have been reported in this thesis to result in preventable patient harm. The role of pharmacists in children's ICU needs to be evaluated in order to be used effectively in reducing MEs and related ADEs in the NHS hospitals. For example, in a study that evaluated the impact of unit-based pharmacist intervention in a USA PICU, a significant reduction of preventable ADEs (from 29 to 6 preventable ADEs per 1000 patient-days) was associated with the

employment of full-time PICU pharmacist.[187] However, no reduction in these events was observed with PICU pharmacist available on a part-time basis.

In a recent meta-analysis (2020), 19 studies were included in examining the impact of clinical pharmacists on reducing MEs in paediatric inpatients (11 studies were carried out in NICU/PICU) worldwide.[191] None of the identified studies by the review originated from the UK. In addition, a recent investigation on the role of ward-based clinical pharmacist services in England to reduce high-risk prescribing errors found a lack of understanding on the optimal use of these services to improve patient safety in NHS hospitals.[480] Therefore, this research programme highlights evaluating the effect of clinical pharmacy services on MEs prevention and cost-saving in children's intensive care settings in the NHS hospitals as a priority area for future research.

7.1.6.3 Areas for further studies to examine the scale of medication errors and related harm in children's intensive care settings

Among all phases of the medication use process, prescribing was examined more frequently in both NICU and PICU with comparatively little focus on the drug dispensing phase as described in Chapter 4.[334] Only two studies examined dispensing errors in PICU and NICU and none of them were carried out in the UK.[91,306] Thus, examining the frequency, type and severity of medication dispensing errors is warranted to add further understanding about errors that may occur within the medication use process and effectively guide efforts to reduce such events across both NICU and PICU settings.

In addition, PICUs and NICUs are complex and dynamic environments with a strong humanistic element. A recent qualitative study explored causative factors in prescribing errors in PICU and identified that systems in PICU to support safe medication practice were ineffective.[121] This study supported the findings of Manias's review, which also

identified limited effectiveness of interventions to mitigate ME in PICU.[190] The complex interplay of systems also means that the consideration of prescribing errors, dispensing errors and medication administration errors as separate processes and phenomena may be misleading and lead to tokenistic interpretation of the causes. Therefore, a multi-system approach to understanding the underlying causes of MEs in critically ill children may be an area for investigation. This may include mapping the medication use systems in children's intensive care and also how ICU staff work and interact with one another.

Chapter 6 of this thesis found that transferring patients between ICU and other hospital wards was involved commonly with medication-related incidents. The transition of care process has been highlighted by the WHO global campaign as a target for improvement to reduce avoidable patient harm.[24] This research programme recommends understanding the rate and nature of preventable ADEs that occur during this process as a priority area for future research. These recommendations would support efforts in the development of effective intervention approaches and successful prioritisation of their implementation.

7.1.6.4 Standardising clinical practice and methodologies for medication safety research in children's intensive care settings

Methodological variations in medication safety research

Issues with study heterogeneity were identified in the systematic review presented in Chapter 4.[334] There were marked differences in definitions and research methodologies used across the studies included in the review in detecting MEs and preventable ADEs, which likely contributed to wide variability in reported rates and made direct comparisons between different studies challenging. For instance, the highest overall ME rate (77.9% of medication orders) was reported in a NICU study [204], which employed chart review for prescribing errors and direct observation of nurses preparing and administering

medications for medication administration errors. This detailed two-stage screening could have resulted in an overall high rate of MEs. In addition, direct observation of nursing practice is known to identify more medication administration errors than other approaches such as reviewing medication administration records.[481] Similar issues in ME research have been noted in other systematic reviews.[33,38,211]

Furthermore, the definitional variation may have an important impact on effect estimates. One study defined prescribing error according to the Institute Of Medicine definition including any errors during the prescribing or transcribing phases in physicians' orders containing pharmacological (e.g. medications) and non-pharmacological (e.g. nutritional supplements) items.[145] The broad definition used in this study that encapsulated transcription could have had influenced the rate of prescribing error (59.4%), which was higher than the rate reported in another study (8.24%) using a more specific prescribing error definition "incomplete or illegible prescription that required additional clarification to be executed".[188] Defining MEs explicitly is usually a challenging task in studies focussing on paediatric patient populations. This is mainly due to the wide variety of existing dosing recommendations for paediatric patients due to lack of evidence supporting suitable doses for different age and weights in this patient population.[170,482] This makes defining MEs (e.g. wrong doses) difficult and this, subsequently, contribute to variability of reported estimates across studies.

Lower prescribing error rates were also found in retrospective studies.[188,212,306,324,325] The limitations of this approach (such as risk of poor quality documentation and missing data) is acknowledged.[344] This may lead to low accuracy of detection and underestimation of the prevailing error rate. Prospectively designed studies with pharmacists collecting data are associated with higher rates of prescribing errors.[145,146,303,316,321] Subsequently, this approach has been found to be sensitive in detecting MEs and ADEs.[33,328]

Chapter 4 of this thesis also identified methodological heterogeneity in methods used to assess severity of MEs and preventable ADEs in children's ICU.[334] This methodological variation hindered judgment as to which patient group(s), stage(s) in the medication process or particular medication class(es) may be more vulnerable to MEs and preventable ADEs. Consequently, this research programme recommends that future studies use standardised approach to assess severity of preventable medication-related events to help identify targets for serious adverse events.

This thesis, therefore, highlights a need for researchers in the field to work towards greater standardisation to help ensure future ME and preventable ADE studies in critically ill children utilise more consistent study designs and definitions. This would facilitate greater comparability of studies and align will a call for greater standardisation that have been made in other ME or ADE systematic reviews.[90,92,177] For example, it has been recommended that future studies examining medication administration errors should utilise definitions that have been previously used in other studies.[92] This has been concluded by a systematic review that has assessed the methodological variations in studies examining medication administration errors in the UK hospitals. This would facilitate more direct comparison between studies and provide a better understanding of common targets for improvement.

Clinical practice standardisation

Chapter 5 observed significant variation in the rates of preventable ADEs that may indicates variable clinical practices across NHS PICUs. Additionally, Chapter 6 found that variable medication administration policies across PICUs was a contributory factor associated with reported medication safety incidents. For example, a new nurse joined a PICU discontinued administration of Total Parenteral Nutrition dose that should be

restarted after four hours due to previous experience in another PICU where medication is continuously administered over 24 hours. Examining the underlying causes associated with this variation is needed. This may explore factors that could guide NHS organisations to work toward standardising clinical practice (where it is practical and appropriate) across paediatric critical care services.[195] For example, there were variable recommendations for critical care nurse staffing that have been produced (between 2001 and 2005) by different UK professional organisations (e.g. Royal College of Nursing and British Association of Critical Care Nurses). These organisations worked collaboratively and provided a set of minimum standards for ICU nurse staffing in 2010, which has been found to be associated with patient safety improvement in critical care.[483]

7.1.6.5 Examining the burden of medication errors and preventable adverse drug events across different countries

This research programme has highlighted knowledge gaps from individual countries concerning the burden and nature of MEs and preventable ADEs in NICU and PICU.[334] Comparable insights from different health care systems internationally are needed to support the global campaign to reduce preventable medication-related harm in NICU and PICU.

In the systematic literature review presented in this thesis (Chapter 4) [334], it is apparent that MEs and preventable ADEs in patients admitted to PICU and NICU were more frequently examined in the USA than other countries. There is still little focus on these patient populations in the rest of the world. For example, only three studies identified by the systematic review were undertaken in Africa and none from Australia. Therefore, more work is needed in individual countries to understand the frequency and nature of MEs and preventable ADEs in PICUs and NICUs. In addition, there have been wider calls for more

research in the developing world to assess preventable medication-related harm. For example, in two large meta-analyses that assessed preventable medication-related harm worldwide (published in 2019 and 2020), very limited data have been originated from developing countries.[19,30] More research from these countries on medication use and safety is needed to support the current WHO call to reduce preventable medication-related harm and improve patient safety.

7.2 Summary of recommendations for medication safety improvement in neonatal and children's intensive care

The recommendations, summarised in Table 7.2, were generated based on this programme of research to inform clinical practice, policy makers and future research in designing safety measures to reduce MEs and related ADEs in critically ill neonates and children.

Table 7.2 Informed recommendations generated by this research programme to improve medication safety in neonatal and children's intensive care.

Targets for improvement	Recommendations	Recommendations relate to
Medication prescribing stage Common safety issues: Wrong dosing due to interruptions/distractions, inadequate prescribing system, variable dosing guidelines and lack of knowledge (e.g. dose calculation skills).	➢ Developing electronic prescribing systems that are supported by Clinical Decision Support systems designed specifically for the paediatric patient population. These could include dosing guides (e.g. maximum doses) and forcing functions that may help prescribers to follow standardised dosing guidelines consistently.[316]	Policy makers/NHS Trust/clinical practice (e.g. ICU leaders)
	➢ Developing standardised dosing guidelines and providing training programmes on medication dosing calculations and calculation aids (e.g. technological-based dosing calculation aids) for PICU and NICU staff.[168]	
	➢ Reducing cognitive burden on prescribers due to interruptions and distractions in NICU and PICU: ⇨ For example, testing interventions such as using a dedicated quiet area for prescribers in NICU and PICU.[143]	
Medication administration stage Common safety issues: Drug omission error, wrong dose/rate due to interruptions/distractions, lack of appropriate IV medications strength for paediatrics/knowledge about local drug safety policies.	➢ Reducing interruptions and distractions during medication preparation and administration stages: ⇨ For example, testing existing interventions such as 'quiet/no interruption zone' and 'no interruption signs/vests' to reduce interruptions during medication preparation and administration stages.[401]	
	➢ Improving vascular access practices: ⇨ For example, evaluating the intervention recommended by the NICE in using ultrasound imaging in inserting central venous catheter, which has been found effective in reducing complications associated with failure of this procedure [435,436], to reduce problems associated with challenging venous access in neonates (e.g. drug omission errors).[438]	
	➢ Developing specific induction programmes for new ICU staff on local drug safety policies, and verifying compatibility and appropriate route of administration of IV medications.[265]	
	➢ Availability of standardised IV medication concentrations (e.g. frequently used IV medications such as anti-infectives and analgesics) that is appropriate for use in neonates and children, particularly, for infusion pump administration.[374]	Pharmaceutical companies with financial support by governments
Certain medication classes High-risk medications (e.g. aminoglycosides, opioid analgesics, adrenergic agonists/antagonists and anticoagulant agents).	➢ Investigating and evaluating the use of safer alternative antimicrobials instead of aminoglycosides in critically ill neonates or improving the safety measures in the use of these medications: ⇨ For example, providing additional training (e.g. the NPSA training pack) for ICU staff involved in prescribing and administering high-risk medications.[175] ➢ Applying and testing a mixture of interventions to reduce risk of errors associated with using high risk medications: ⇨ For example, independent double-checking strategies, colour-coded labelling of these drugs and using standardised medication concentrations.	NHS Trust/clinical practice (e.g. ICU leaders and prescribers)

Table 7.2 continued.

Overall medication safety improvement	➢ Redesign of transfer of care processes between wards and ICU, handover process, blood test policies and patient records documentation systems (e.g. digitisation of transfer process as highlighted by the NHS Long Term Plan).[73]	Policy makers/NHS Trust/clinical practice (e.g. ICU leaders)
	➢ Reducing length of patients stay in NICU/PICU, for example, by applying the following strategies: ⇨ Implementing protocol-based intervention to promote optimal sedation weaning in critically ill children receiving mechanical ventilation, which is currently applied in some UK PICUs.[427] ⇨ Following the NHS five-year plan (2017) by reviewing admitted patients to NICU/PICU frequently to assess whether the care could be provided in less intensive hospital settings.[72]	
	➢ Providing specialised training for Patient Safety Officers (part of the current NHS Patient Safety Strategy) considering the understanding generated by this research programme about medication safety in children's ICU to enhance their knowledge in developing and adapting safety interventions for this environment.	
	➢ Improvement in working conditions in NICUs and PICUs (e.g. inadequate staffing and consequent heavy workload): ⇨ There is a need for a better understanding of safe working conditions, and their influence on implementation of medication safety interventions in NICU and PICU to inform the development of manageable workload and adequate staffing policies.[390]	
	➢ Improving human factors knowledge in this area which should help ICU staff to communicate well and carry out their routine tasks in the right way.[222]	
	➢ Developing continuous competency-based educational programmes for frontline healthcare staff in ICU, as reflected in the current NHS Patient Safety Strategy.[25]	
	➢ Incorporate a special training curriculum for future health care professionals in dealing with medications for paediatric patients as part of their educational programmes.[417]	Educational institutions
Recommendations for future research		
➢ A greater standardisation of study methodology to support comparisons between studies for future global research examining medication safety in NICU and PICU. ➢ Exploring certain types of preventable medication-related events such as understanding the rate, type and severity of preventable ADEs at transition of care. This research programme found that transferring patients between ICU and other hospital wards was involved commonly with medication-related incidents and examining the frequency and nature of these events is important to inform the development of effective interventions. ➢ Further investigation to explore underlying factors between different PICUs that may influence the emergence of ADEs and the effective implementation of safety interventions. This thesis found variation in ADE rates between NHS PICUs and understanding the factors contributing to the differences between centres is needed for effective implementation of medication safety interventions. ➢ Evaluating the effect of clinical pharmacy services on MEs prevention and cost-saving in children's intensive care settings in the NHS hospitals. There is a lack of understanding on the optimal use of clinical pharmacy services in NHS hospitals and evaluating the impact of these services on patient safety in NHS NICUs and PICUs is needed.[480] ➢ A greater interest in the field of implementation science as well as using robust approaches in developing and evaluating medication safety interventions for NICU and PICU. ➢ More research from different countries (e.g. Africa and Australia) on medication use and safety to support the current global medication safety campaign.		

Abbreviations: ADEs: adverse drug events; ICU: intensive care unit; NICU: neonatal intensive care unit; PICU: paediatric intensive care unit; NPSA: National Patient Safety Agency; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; IV: intravenous.

7.3 Overall conclusion

In high-intensity settings such as NICU and PICU caring for patients with increased vulnerability for preventable medication-related events, understanding the rate, nature and underlying contributory factors of MEs and preventable ADEs is fundamental to effectively guide theory-driven efforts to reduce them. The aim and objectives of this research programme were fulfilled by providing knowledge and an action agenda to make care safer for this vulnerable group of patients.

This research programme found that MEs are common and persistent problems that may pose significant risk to critically ill neonates and children admitted to ICUs. Understanding the multi-factorial and complex pathways to ME in children's ICU has now been provided by this research programme. The informed recommendations generated by this research programme that can guide future efforts to make care safer in these settings include reducing length of children's ICU stay, redesign of polices (e.g. transition of care) and systems (e.g. medicines prescribing systems) and improving the safety of using certain medications (e.g. aminoglycoside anti-infectives) and vascular access practices in neonates. To support effective implementation of future interventions, there is a need to improve working conditions (e.g. inadequate staffing and consequent heavy workload) in NICUs and PICUs. This research programme has also identified opportunities for further research to explore certain types of preventable medication-related events (e.g. preventable ADEs at transition of care). It also highlighted the need for greater standardisation on study methodology to support comparisons between studies for future global research examining medication safety in these settings.

Clear targets for medication safety interventions in NICUs and PICUs were identified. Therefore, more efforts are now needed toward improvement using the knowledge generated by this research programme. This includes the development and evaluation of medication safety interventions in NICU and PICU that can be effectively implemented and rolled out widely.

References

1. World Health Organization. Investing in our future: A comprehensive agenda for the health and well-being of children and adolescents. https://www.who.int/publications/i/item/investing-in-our-future. Published 2020. Accessed 1 Jan, 2021.
2. Ibiebele I, Algert CS, Bowen JR, et al. Pediatric admissions that include intensive care: A population-based study. *BMC Health Services Research.* 2018;18(1):264.
3. Conti G, Heckman JJ. The developmental approach to child and adult health. *Pediatrics.* 2013;131(Supplement 2):S133.
4. Betz CL. Pediatric hospitals are not appropriate for adult admissions. *Journal of Pediatric Nursing.* 2003;18(5):303-304.
5. O'Hara K. Paediatric pharmacokinetics and drug doses. *Aust Prescr.* 2016;39(6):208-210.
6. Casimir G. Why children's hospitals are unique and so essential. *Front Pediatr.* 2019;7:305-305.
7. Coathup V, Boyle E, Carson C, et al. Gestational age and hospital admissions during childhood: Population based, record linkage study in england. *BMJ.* 2020;371:m4075.
8. Wolfe I, Sigfrid L, Chanchlani N, et al. Child health systems in the united kingdom (england). *The Journal of Pediatrics.* 2016;177:S217-S242.
9. Bucholz EM, Toomey SL, Schuster MA. Trends in pediatric hospitalizations and readmissions: 2010–2016. *Pediatrics.* 2019;143(2):e20181958.
10. Crow SS, Undavalli C, Warner DO, et al. Epidemiology of pediatric critical illness in a population-based birth cohort in olmsted county, mn. *Pediatric Critical Care Medicine.* 2017;18(3):e137-e145.
11. Coulthard MG, Varghese V, Harvey LP, et al. A review of children with severe trauma admitted to pediatric intensive care in queensland, australia. *PloS One.* 2019;14(2):e0211530-e0211530.
12. Fraser LK, Parslow R. Children with life-limiting conditions in paediatric intensive care units: A national cohort, data linkage study. *Archives of Disease in Childhood.* 2018;103(6):540.
13. National Coordinating Group on Paediatric Intensive Care. Paediatric intensive care: A framework for the future. London: Department of health. 1997.
14. Marshall JC, Bosco L, Adhikari NK, et al. What is an intensive care unit? A report of the task force of the world federation of societies of intensive and critical care medicine. *Journal of Critical Care.* 2017;37:270-276.
15. Peltoniemi OM, Rautiainen P, Kataja J, et al. Pediatric intensive care in picus and adult icus: A 2-year cohort study in finland. *Pediatric Critical Care Medicine.* 2016;17(2).
16. Davis P, Stutchfield C, Evans TA, et al. Increasing admissions to paediatric intensive care units in england and wales: More than just rising a birth rate. *Archives of Disease in Childhood.* 2018;103(4):341.
17. Kanthimathinathan HK, Plunkett A, Scholefield BR, et al. Trends in long-stay admissions to a uk paediatric intensive care unit. *Archives of Disease in Childhood.* 2020;105(6):558.
18. World Health Organization. Delivering quality health services: A global imperative for universal health coverage. https://apps.who.int/iris/handle/10665/272465. Published 2018. Accessed 25 Jan, 2021.

19. Panagioti M, Khan K, Keers RN, et al. Prevalence, severity, and nature of preventable patient harm across medical care settings: Systematic review and meta-analysis. *BMJ*. 2019;366:l4185.
20. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients: Results of the harvard medical practice study. *New England Journal of Medicine*. 1991;324(6):370-376.
21. Terry A, Mottram C, Round J, et al. A safer place for patients: Learning to improve patient safety. https://www.nao.org.uk/wp-content/uploads/2005/11/0506456.pdf. Published 2005. Accessed 24 Jan, 2021.
22. World Health Organization. Patient safety. https://www.who.int/news-room/facts-in-pictures/detail/patient-safety and https://www.who.int/news-room/fact-sheets/detail/patient-safety. Published 2019. Accessed 1 Jan, 2021.
23. Jha AK, Larizgoitia I, Audera-Lopez C, et al. The global burden of unsafe medical care: Analytic modelling of observational studies. *BMJ Quality & Safety*. 2013;22(10):809-815.
24. World Health Organization. Who global patient safety challenge: Medication without harm. https://www.who.int/patientsafety/medication-safety/en/. Published 2017. Accessed 17 Sep, 2020.
25. National Health Service (NHS). The nhs patient safety strategy: Safer culture, safer systems, safer patients. https://www.england.nhs.uk/patient-safety/the-nhs-patient-safety-strategy/. Published 2019. Accessed 28 Sep, 2020.
26. National Coordinating Council for Medication Error Reporting and Prevention. About medication errors: What is a medication error? https://www.nccmerp.org/about-medication-errors. Published 2008. Accessed 24 Jan, 2021.
27. Lisby M, Nielsen LP, Brock B, et al. How are medication errors defined? A systematic literature review of definitions and characteristics. *International Journal for Quality in Health Care*. 2010;22(6):507-518.
28. National Coordinating Council for Medication Error Reporting and Prevention. Contemporary view of medication–related harm. A new paradigm. https://www.nccmerp.org/sites/default/files/nccmerp_fact_sheet_2015-02-v91.pdf. Published 2015. Accessed 24 Jan, 2021.
29. Elliott R CE, Campbell F, Jankovic D, Martyn St James M, Kaltenthaler E, Wong R, Sculpher M, Faria R. Prevalence and economic burden of medication errors in the nhs in england. http://www.eepru.org.uk/prevalence-and-economic-burden-of-medication-errors-in-the-nhs-in-england-2/. Published 2018. Accessed 19 Jun, 2019.
30. Hodkinson A, Tyler N, Ashcroft DM, et al. Preventable medication harm across health care settings: A systematic review and meta-analysis. *BMC Medicine*. 2020;18(1):313.
31. U.S. Department of Health and Human Services - Office of Disease Prevention and Health Promotion. National action plan for adverse drug event prevention. https://health.gov/our-work/health-care-quality/adverse-drug-events. Published 2014. Accessed 28 Oct, 2020.
32. MacFie CC, Baudouin SV, Messer PB. An integrative review of drug errors in critical care. *Journal of the Intensive Care Society*. 2016;17(1):63-72.
33. Wilmer A, Louie K, Dodek P, et al. Incidence of medication errors and adverse drug events in the icu: A systematic review. *Quality and Safety in Health Care*. 2010;19(5):e7.

34. Wilson DG, McArtney R, Newcombe RG, et al. Medication errors in paediatric practice: Insights from a continuous quality improvement approach. *European Journal of Pediatrics.* 1998;157(9):769-774.
35. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA.* 2001;285(16):2114-2120.
36. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. *Archives of Disease in Childhood.* 1999;80(2):F142.
37. Nir-Neuman H, Abu-Kishk I, Toledano M, et al. Unlicensed and off-label medication use in pediatric and neonatal intensive care units: No change over a decade. *Advances in therapy.* 2018;35(7):1122-1132.
38. Santesteban E, Arenas S, Campino A. Medication errors in neonatal care: A systematic review of types of errors and effectiveness of preventive strategies. *Journal of Neonatal Nursing.* 2015;21(5):200-208.
39. Turner S, Gill A, Nunn T, et al. Use of "off-label" and unlicensed drugs in paediatric intensive care unit. *The Lancet.* 1996;347(9000):549-550.
40. Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in/out-patients: A systematic review and meta-analysis of prospective studies. *British Journal of Clinical Pharmacology.* 2001;52(1):77-83.
41. Conroy S. Association between licence status and medication errors. *Archives of Disease in Childhood.* 2011;96(3):305.
42. World Health Organization. Promoting safety of medicines for children. https://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf?ua=1. Published 2007. Accessed 27 June, 2020.
43. Manias E, Cranswick N, Newall F, et al. Medication error trends and effects of person-related, environment-related and communication-related factors on medication errors in a paediatric hospital. *Journal of Paediatrics and Child Health.* 2019;55(3):320-326.
44. Institute for Safe Medication Practices. High-alert medications in acute care settings. https://www.ismp.org/recommendations/high-alert-medications-acute-list. Published 2018. Accessed 18 Aug, 2020.
45. Franke HA, Woods DM, Holl JL. High-alert medications in the pediatric intensive care unit. *Pediatric Critical Care Medicine.* 2009;10(1):85-90.
46. National Health Service (NHS). The medicines safety improvement programme - the nhs patient safety strategy. https://www.england.nhs.uk/patient-safety/national-medicines-safety-programme/. Published 2019. Accessed 28 Sep, 2020.
47. Wise J. Government takes steps to reduce annual burden of medication errors in england. *BMJ.* 2018;360:k903.
48. Donaldson LJ, Appleby L, Boyce J. *An organisation with a memory: Report of an expert group on learning from adverse events in the nhs.* Stationery Office Norwich, United Kingdom; 2000.
49. Kohn L, Corrigan J, Donaldson M. To err is human: Building a safer health system. Committee on quality in america. Washington, dc: Institute of medicine. In: National Academy Press; 2000.
50. Office for National Statistics. Population estimates for the uk, england and wales, scotland and northern ireland: Mid-2019. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates. Published 2019. Accessed 3 Nov 2020.
51. Office for National Statistics. Provisional births in england and wales: 2020. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/

livebirths/articles/provisionalbirthsinenglandandwales/2020. Published 2020. Accessed 3 Jan, 2021.
52. The United States Census Bureau. Children within u.S. Census bureau data. https://www.census.gov/topics/population/children.html. Published 2020. Accessed 31 2020.
53. Centers for Disease and Control and Prevetion. A child's health is the public's health. https://www.cdc.gov/childrenindisasters/features/children-public-health.html. Published 2020. Accessed 31 Dec, 2020.
54. Knoppert D, Reed M, Benavides S, et al. Paediatric age categories to be used in differentiating between listing on a model essential medicines list for children. *Word Health Organization position paper.* 2007;1(5).
55. Rashed AN, Neubert A, Tomlin S, et al. Epidemiology and potential associated risk factors of drug-related problems in hospitalised children in the united kingdom and saudi arabia. *European Journal of Clinical Pharmacology.* 2012;68(12):1657-1666.
56. Contopoulos-Ioannidis DG, Baltogianni MS, Ioannidis JP. Comparative effectiveness of medical interventions in adults versus children. *The Journal of Pediatrics.* 2010;157(2):322-330. e317.
57. Rose K. The challenges of pediatric drug development. *Current Therapeutic Research.* 2019;90:128-134.
58. Williams K, Thomson D, Seto I, et al. Standard 6: Age groups for pediatric trials. *Pediatrics.* 2012;129(Supplement 3):S153-S160.
59. Paediatric Formulary Committee. British national formulary for children. Pharmaceutical Press, and RCPCH Publications. http://www.medicinescomplete.com/. Published 2020-21. Accessed 4 Nov, 2020.
60. Food & Drug Administration. Guidance for industry e11. Clinical investigation of medicinal products in the pediatric population. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population. Published 2000. Accessed 6 Nov, 2020.
61. World Health Organization. Developmental difficulties in early childhood: Prevention, early identification, assessment and intervention in low-and middle-income countries: A review. https://www.who.int/maternal_child_adolescent/documents/development_difficulties_early_childhood/en/. Published 2012. Accessed 6 Nov, 2020.
62. Illingworth J. Continuous improvement of patient safety - the case for change in the nhs. https://www.health.org.uk/publications/continuous-improvement-of-patient-safety. Published 2015. Accessed 19 Jun, 2019.
63. Tsankov BK, Allaire JM, Irvine MA, et al. Severe covid-19 infection and pediatric comorbidities: A systematic review and meta-analysis. *International Journal of Infectious Diseases.* 2021;103:246-256.
64. Keeble E, Kossarova L. Focus on: Emergency hospital care for children and young people - what has changed in the past 10 years? The Health Foundation. https://www.health.org.uk/publications/focus-on-emergency-hospital-care-for-children-and-young-people. Published 2017. Accessed 25 Jan, 2021.
65. Paediatric Intensive Care Audit Network. Annual reporting and publications. https://www.picanet.org.uk/annual-reporting-and-publications/. Published 2019. Accessed 17 Nov, 2020.
66. Jarvis S, Parslow RC, Carragher P, et al. How many children and young people with life-limiting conditions are clinically unstable? A national data linkage study. *Archives of Disease in Childhood.* 2017;102(2):131.

67. National Health Service (NHS Digital). Hospital admitted patient care activity 2018-19. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19. Published 2019. Accessed 4 Nov, 2020.
68. Paediatric Intensive Care Audit Network. A decade of data. https://www.picanet.org.uk/wp-content/uploads/sites/25/2018/05/PICANet_A_Decade_of_Data_2014_Annual_Report_Summary.pdf. Published 2014. Accessed 5 Jan, 2021.
69. National Patient Safety Agency. National Reporting Learning Service. *Safety in doses: Improving the use of medicines in the nhs.* National Patient Safety Agency; 2009.
70. Smith J, Cavell G. Building a safer nhs for patients: Improving medication safety. https://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4071443. Published 2004. Accessed 25 Jan, 2021.
71. National Patient Safety Agency. National Reporting Learning Service. Review of patient safety for children and young people. https://psnet.ahrq.gov/issue/review-patient-safety-children-and-young-people. Published 2009. Accessed 6 Nov, 2020.
72. National Health Service (NHS). Next steps on the nhs five year forward view. https://www.england.nhs.uk/wp-content/uploads/2017/03/NEXT-STEPS-ON-THE-NHS-FIVE-YEAR-FORWARD-VIEW.pdf. Published 2017. Accessed 2 Oct, 2020.
73. National Health Service (NHS). The nhs long term plan. https://www.longtermplan.nhs.uk. Published 2019. Accessed 29 Sep, 2020.
74. Healthcare Safety Investigation Branch. Electronic prescribing and medicines administration systems and safe discharge. https://www.hsib.org.uk/documents/157/hsib_summary_report_epma_systems_safe_discharge_v2.pdf. Published 2019. Accessed 20 Oct, 2020.
75. Lewis I, Lenehan C. Report of the children and young people's health outcomes forum - children and young people's health outcomes strategy. https://www.gov.uk/government/groups/children-and-young-peoples-health-outcomes-forum. Published 2012. Accessed 6 Nov, 2020.
76. Berwick D. A promise to learn–a commitment to act: Improving the safety of patients in england. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/226703/Berwick_Report.pdf. Published 2013. Accessed 6 Nov, 2020.
77. Audit Commission L. A spoonful of sugar medicines management in nhs hospitals. http://www.eprescribingtoolkit.com/wp-content/uploads/2013/11/nrspoonfulsugar1.pdf. Published 2001. Accessed 6 Nov, 2020.
78. National Health Service (NHS). Supporting treatment and appropriate medication in paediatrics (stamp). https://www.england.nhs.uk/learning-disabilities/improving-health/stamp/. Published 2018. Accessed 14 Jan, 2021.
79. Damiani G, de Belvis AG, Gainotti S. From the harvard medical practice study to the luxembourg declaration. Changes in the approach to patient safety. Closing remarks. *Italian Journal of Public Health.* 2012;2(3-4).
80. Wilson RM, Runciman WB, Gibberd RW, et al. The quality in australian health care study. *Medical Journal of Australia.* 1995;163(9):458-471.

81. Vincent C, Neale G, Woloshynowych M. Adverse events in british hospitals: Preliminary retrospective record review. *BMJ.* 2001;322(7285):517-519.
82. Leape LL, Berwick DM. Five years after to err is humanwhat have we learned? *JAMA.* 2005;293(19):2384-2390.
83. National Health Service (NHS). Patient safety. http://www.nrls.npsa.nhs.uk/. Accessed 25 Feb, 2018.
84. Kane-Gill S, Weber RJ. Principles and practices of medication safety in the icu. *Critical Care Clinics.* 2006;22(2):273-290.
85. Moyen E, Camiré E, Stelfox HT. Clinical review: Medication errors in critical care. *Critical Care.* 2008;12(2):208.
86. Lerner RBdME, Carvalho Md, Vieira AA, et al. Medication errors in a neonatal intensive care unit. *Jornal De Pediatria.* 2008;84(2):166-170.
87. Lisby M, Nielsen LP, Mainz J. Errors in the medication process: Frequency, type, and potential clinical consequences. *International Journal for Quality in Health Care.* 2005;17(1):15-22.
88. Keers RN, Williams SD, Cooke J, et al. Causes of medication administration errors in hospitals: A systematic review of quantitative and qualitative evidence. *Drug safety.* 2013;36(11):1045-1067.
89. Krähenbühl-Melcher A, Schlienger R, Lampert M, et al. Drug-related problems in hospitals. *Drug safety.* 2007;30(5):379-407.
90. Lewis PJ, Dornan T, Taylor D, et al. Prevalence, incidence and nature of prescribing errors in hospital inpatients. *Drug Safety.* 2009;32(5):379-389.
91. Haghbin S, Shahsavari S, Vazin A. Medication errors in pediatric intensive care unit: Incidence, types and outcome. *Trends in Pharmaceutical Sciences.* 2016;2(2):109-116.
92. McLeod MC, Barber N, Franklin BD. Methodological variations and their effects on reported medication administration error rates. *BMJ Quality & Safety.* 2013;22(4):278.
93. Morimoto T, Gandhi T, Seger A, et al. Adverse drug events and medication errors: Detection and classification methods. *BMJ Quality & Safety.* 2004;13(4):306-314.
94. Ferranti J, Horvath MM, Cozart H, et al. Reevaluating the safety profile of pediatrics: A comparison of computerized adverse drug event surveillance and voluntary reporting in the pediatric environment. *Pediatrics.* 2008;121(5):e1201-e1207.
95. Bonati M, Pandolfini C. Off-label drug use in children should be rational. *Archives of Disease in Childhood.* 2011;96(9):870.
96. Ceelie I, van der Starre C, Tibboel D, et al. Evaluation of drug formularies for pediatric intensive care. *Pediatric Critical Care Medicine.* 2011;12(1):e14-e19.
97. L Mukattash T, Q Nuseir K, S Jarab A, et al. Sources of information used when prescribing for children, a survey of hospital based pediatricians. *Current Clinical Pharmacology.* 2014;9(4):395-398.
98. McDonald KM, Davies SM, Haberland CA, et al. Preliminary assessment of pediatric health care quality and patient safety in the united states using readily available administrative data. *Pediatrics.* 2008;122(2):e416-e425.
99. Makary MA, Daniel M. Medical error—the third leading cause of death in the us. *BMJ.* 2016;353:i2139.
100. Sandars J, Cook G. *Abc of patient safety.* Vol 72: John Wiley & Sons; 2009.
101. Chapman SM, Fitzsimons J, Davey N, et al. Prevalence and severity of patient harm in a sample of uk-hospitalised children detected by the paediatric trigger tool. *BMJ open.* 2014;4(7).

102. Mueller BU, Neuspiel DR, Fisher ERS. Principles of pediatric patient safety: Reducing harm due to medical care. *Pediatrics.* 2019;143(2).
103. Kirkendall ES, Kloppenborg E, Papp J, et al. Measuring adverse events and levels of harm in pediatric inpatients with the global trigger tool. *Pediatrics.* 2012;130(5):e1206.
104. Walsh KE, Bundy DG, Landrigan CP. Preventing health care–associated harm in children. *JAMA.* 2014;311(17):1731-1732.
105. Assiri GA, Grant L, Aljadhey H, et al. Investigating the epidemiology of medication errors and error-related adverse drug events (ades) in primary care, ambulatory care and home settings: A systematic review protocol. *BMJ Open.* 2016;6(8):e010675.
106. Shah K, Lo C, Babich M, et al. Bar code medication administration technology: A systematic review of impact on patient safety when used with computerized prescriber order entry and automated dispensing devices. *The Canadian Journal of Hospital Pharmacy.* 2016;69(5):394.
107. Bates DW. Using information technology to reduce rates of medication errors in hospitals. *BMJ: British Medical Journal.* 2000;320(7237):788.
108. Aiken LH, Sermeus W, Van den Heede K, et al. Patient safety, satisfaction, and quality of hospital care: Cross sectional surveys of nurses and patients in 12 countries in europe and the united states. *BMJ.* 2012;344:e1717.
109. Starmer AJ, Sectish TC, Simon DW, et al. Rates of medical errors and preventable adverse events among hospitalized children following implementation of a resident handoff bundle. *JAMA.* 2013;310(21):2262-2270.
110. Prin M, Wunsch H. International comparisons of intensive care: Informing outcomes and improving standards. *Curr Opin Crit Care.* 2012;18(6):700-706.
111. Weil MH, Tang W. From intensive care to critical care medicine: A historical perspective. *American Journal of Respiratory and Critical Care Medicine.* 2011;183(11):1451-1453.
112. Reisner-Sénélar L. The birth of intensive care medicine: Björn ibsen's records. *Intensive Care Medicine.* 2011;37(7):1084-1086.
113. Intensive Care National Audit & Research Centre. Key statistics from the case mix programme — adult, general critical care units. https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports/Summary-Statistics. Published 2019. Accessed 17 Nov, 2020.
114. Department of Health and Social Care. Comprehensive critical care: A review of adult critical care services. https://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006585. Published 2000. Accessed 17 Nov, 2020.
115. NHS England and NHS Improvement. Paediatric critical care and surgery in children review. https://www.england.nhs.uk/wp-content/uploads/2019/11/paediatric-critical-care-and-surgery-in-children-review-summary-report-nov-2019.pdf. Published 2019. Accessed 17 NOV, 2020.
116. Straney L, Clements A, Parslow RC, et al. Paediatric index of mortality 3: An updated model for predicting mortality in pediatric intensive care. *Pediatric Critical Care Medicine.* 2013;14(7):673-681.
117. Rothschild JM, Landrigan CP, Cronin JW, et al. The critical care safety study: The incidence and nature of adverse events and serious medical errors in intensive care. *Critical Care Medicine.* 2005;33(8):1694-1700.

118. Çelik S, Taşdemir N, Kurt A, et al. Fatigue in intensive care nurses and related factors. *Int J Occup Environ Med.* 2017;8(4):199-206.
119. Kumar A, Pore P, Gupta S, et al. Level of stress and its determinants among intensive care unit staff. *Indian J Occup Environ Med.* 2016;20(3):129-132.
120. World Health Organization. What is human factors and why is it important to patient safety. https://www.who.int/patientsafety/education/curriculum/who_mc_topic-2.pdf?ua=1. Published 2009. Accessed 18 Nov, 2020.
121. Sutherland A, Ashcroft DM, Phipps DL. Exploring the human factors of prescribing errors in paediatric intensive care units. *Archives of Disease in Childhood.* 2019;104(6):588.
122. Cullen DJ, Sweitzer BJ, Bates DW, et al. Preventable adverse drug events in hospitalized patients: A comparative study of intensive care and general care units. *Critical Care Medicine.* 1997;25(8):1289-1297.
123. Agalu A, Ayele Y, Bedada W, et al. Medication administration errors in an intensive care unit in ethiopia. *International Archives of Medicine.* 2012;5(1):15.
124. Fahimi F, Ariapanah P, Faizi M, et al. Errors in preparation and administration of intravenous medications in the intensive care unit of a teaching hospital: An observational study. *Australian Critical Care.* 2008;21(2):110-116.
125. Poole RL, Carleton BC. Medication errors: Neonates, infants and children are the most vulnerable! *The Journal of Pediatric Pharmacology and Therapeutics.* 2008;13(2):65-67.
126. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. *British journal of clinical pharmacology.* 2015;79(3):357-369.
127. Knutsen A, Butler AS, Vanchieri C. *Addressing the barriers to pediatric drug development: Workshop summary.* National Academies Press; 2008.
128. Orubu ES, Tuleu C. Medicines for children: Flexible solid oral formulations. *Bull World Health Organ.* 2017;95(3):238-240.
129. Tse Y, Vasey N, Dua D, et al. The kidzmed project: Teaching children to swallow tablet medication. *Archives of Disease in Childhood.* 2020;105(11):1105.
130. Rashed AN, Terry D, Fox A, et al. Feasibility of developing children's pill school within a uk hospital. *Archives of Disease in Childhood.* 2020:archdischild-2020-319154.
131. Batchelor HK, Marriott JF. Formulations for children: Problems and solutions. *British Journal of Clinical Pharmacology.* 2015;79(3):405-418.
132. Richey RH, Shah UU, Peak M, et al. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. *BMC Pediatrics.* 2013;13(1):81.
133. Turner S, Longworth A, Nunn AJ, et al. Unlicensed and off label drug use in paediatric wards: Prospective study. *BMJ.* 1998;316(7128):343-345.
134. Dickinson CJ, Wagner DS, Shaw BE, et al. A systematic approach to improving medication safety in a pediatric intensive care unit. *Critical Care Nursing Quarterly.* 2012;35(1):15-26.
135. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: A systematic review and meta-analysis. *JAMA.* 2011;306(12):1359-1369.
136. Budetti PP. Ensuring safe and effective medications for children. *JAMA.* 2003;290(7):950-951.
137. European Parliament and the Council of the European Union. Regulation (ec) no 1901/2006 of the european parliament and of the council of 12 december 2006 on

medicinal products for paediatric use and amending regulation (eec) no 1768/92, directive 2001/20/ec, directive 2001/83/ec and regulation (ec) no 726/2004. *Official Journal of the European Union.* 2006;378:1-19.
138. Bonati M, Jacqz-Aigrain E, Choonara I. Licensed medicines, off-label use or evidence-based. Which is most important? In: BMJ Publishing Group Ltd; 2017.
139. Dresser R, Frader J. Off-label prescribing: A call for heightened professional and government oversight. *J Law Med Ethics.* 2009;37(3):476-396.
140. Niederhauser VP. Prescribing for children: Issues in pediatric pharmacology. *The Nurse Practitioner.* 1997;22(3):16-32.
141. Kozer E. Medication errors in children. *Pediatric Drugs.* 2009;11(1):52-54.
142. Kaushal R, Jaggi T, Walsh K, et al. Pediatric medication errors: What do we know? What gaps remain? *Ambulatory Pediatrics.* 2004;4(1):73-81.
143. Booth R, Sturgess E, Taberner-Stokes A, et al. Zero tolerance prescribing: A strategy to reduce prescribing errors on the paediatric intensive care unit. *Intensive Care Medicine.* 2012;38(11):1858-1867.
144. Machado APC, Tomich CSF, Osme SF, et al. Prescribing errors in a brazilian neonatal intensive care unit. *Cadernos De Saude Publica.* 2015;31(12):2610-2620.
145. Ewig CL, Cheung HM, Kam KH, et al. Occurrence of potential adverse drug events from prescribing errors in a pediatric intensive and high dependency unit in hong kong: An observational study. *Pediatric Drugs.* 2017;19(4):347-355.
146. Campino A, Lopez-Herrera MC, Lopez-de-Heredia I, et al. Medication errors in a neonatal intensive care unit. Influence of observation on the error rate. *Acta Paediatrica.* 2008;97(11):1591-1594.
147. Larose G, Levy A, Bailey B, et al. Decreasing prescribing errors during pediatric emergencies: A randomized simulation trial. *Pediatrics.* 2017;139(3):e20163200.
148. Food & Drug Administration. Important labeling changes to critical care medications. https://www.fda.gov/media/105663/download. Published 2017. Accessed 12 Nov, 2020.
149. Kaushal R, Barker KN, Bates DW. How can information technology improve patient safety and reduce medication errors in children's health care? *Archives of Pediatrics & Adolescent Medicine.* 2001;155(9):1002-1007.
150. Andrade PHS, Lobo IMF, da Silva WB. Risk factors for adverse drug reactions in pediatric inpatients: A cohort study. *PloS One.* 2017;12(8):e0182327.
151. Stebbing C, Wong ICK, Kaushal R, et al. The role of communication in paediatric drug safety. *Archives of Disease in Childhood.* 2007;92(5):440-445.
152. Miller MR, Robinson KA, Lubomski LH, et al. Medication errors in paediatric care: A systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. *Quality and Safety in Health Care.* 2007;16(2):116-126.
153. Wong ICK, Ghaleb MA, Franklin BD, et al. Incidence and nature of dosing errors in paediatric medications. *Drug Safety.* 2004;27(9):661-670.
154. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. *JAMA.* 1997;277(4):312-317.
155. Sakuma M, Ida H, Nakamura T, et al. Adverse drug events and medication errors in japanese paediatric inpatients: A retrospective cohort study. *BMJ Quality and Safety.* 2014;23(10):830-837.
156. Morimoto T, Sakuma M, Matsui K, et al. Incidence of adverse drug events and medication errors in japan: The jade study. *Journal of General Internal Medicine.* 2011;26(2):148-153.

157. Lesar TS. Errors in the use of medication dosage equations. *Archives of Pediatrics & Adolescent Medicine.* 1998;152(4):340-344.
158. Ozkan S, Kocaman G, Ozturk C, et al. Frequency of pediatric medication administration errors and contributing factors. *Journal of Nursing Care Quality.* 2011;26(2):136-143.
159. Ghaleb MA, Barber N, Franklin BD, et al. The incidence and nature of prescribing and medication administration errors in paediatric inpatients. *Archives of Disease in Childhood.* 2010:adc158485.
160. Sutcliffe K, Stokes G, O'Mara A, et al. *Paediatric medication error: A systematic review of the extent and nature of the problem in the uk and international interventions to address it.* EPPI-Centre, Social Science Research Unit, Institute of Education, University of London; 2014.
161. Sterling V. Minimizing medication errors in pediatric patients. *US Pharmacist.* 2018;44(4):20-23.
162. Huynh C, Wong IC, Correa-West J, et al. Paediatric patient safety and the need for aviation black box thinking to learn from and prevent medication errors. *Pediatric Drugs.* 2017;19(2):99-105.
163. Conn RL, Kearney O, Tully MP, et al. What causes prescribing errors in children? Scoping review. *BMJ Open.* 2019;9(8):e028680.
164. Cimino MA, Kirschbaum MS, Brodsky L, et al. Assessing medication prescribing errors in pediatric intensive care units. *Pediatric Critical Care Medicine.* 2004;5(2):124-132.
165. Lesar TS, Mitchell A, Sommo P. Medication safety in critically ill children. *Clinical Pediatric Emergency Medicine.* 2006;7(4):215-225.
166. Holdsworth MT, Fichtl RE, Raisch DW, et al. Impact of computerized prescriber order entry on the incidence of adverse drug events in pediatric inpatients. *Pediatrics.* 2007;120(5):1058-1066.
167. Ross LM, Wallace J, Paton JY. Medication errors in a paediatric teaching hospital in the uk: Five years operational experience. *Archives of Disease in Childhood.* 2000;83(6):492-497.
168. Maaskant JM, Vermeulen H, Apampa B, et al. Interventions for reducing medication errors in children in hospital. *Cochrane Database of Systematic Reviews.* 2015(3).
169. Gates PJ, Meyerson SA, Baysari MT, et al. The prevalence of dose errors among paediatric patients in hospital wards with and without health information technology: A systematic review and meta-analysis. *Drug Safety.* 2019;42(1):13-25.
170. Krzyzaniak N, Bajorek B. Medication safety in neonatal care: A review of medication errors among neonates. *Therapeutic Advances in Drug Safety.* 2016;7(3):102-119.
171. Rashed AN, Wong ICK, Wilton L, et al. Drug utilisation patterns in children admitted to a paediatric general medical ward in five countries. *Drugs - Real World Outcomes.* 2015;2(4):397-410.
172. Stavroudis TA, Shore AD, Morlock L, et al. Nicu medication errors: Identifying a risk profile for medication errors in the neonatal intensive care unit. *Journal of Perinatology.* 2010;30(7):459-468.
173. de Andrade T, Goes A, Santos A, et al. Harm prevalence due to medication errors involving high-alert medications: A systematic review. *Journal of Patient Safety.* 2020.

174. Alanazi M, Tully M, Lewis P. A systematic review of the prevalence and incidence of prescribing errors with high-risk medicines in hospitals. *Journal of Clinical Pharmacy and Therapeutics.* 2016;41(3):239-245.
175. Mooney J. The safer use of intravenous gentamicin for neonates. National Patient Safety Agency. https://www.ukmi.nhs.uk/filestore/ukmiaps/NPSA-2010-PSA01(8).pdf. Published 2010. Accessed 20 Sep, 2020.
176. Williams C, Maddox RR. Implementation of an iv medication safety system. *American Journal of Health-System Pharmacy.* 2005;62(5):530-536.
177. Keers RN, Williams SD, Cooke J, et al. Prevalence and nature of medication administration errors in health care settings: A systematic review of direct observational evidence. *Annals of Pharmacotherapy.* 2013;47(2):237-256.
178. Gaetani M, Frndova H, Seto W, et al. Concurrent intravenous drug administration to critically ill children: Evaluation of frequency and compatibility. *Journal of Critical Care.* 2017;41:198-203.
179. McDonnell C, Hum S, Frndova H, et al. Pharmacotherapy in pediatric critical illness. *Pediatric Drugs.* 2009;11(5):323-331.
180. Paquette V, McGloin R, Northway T, et al. Describing intravenous extravasation in children. *The Canadian Journal of Hospital Pharmacy.* 2011;64(5):340-345.
181. Chappell K, Newman C. Potential tenfold drug overdoses on a neonatal unit. *Archives of Disease in Childhood.* 2004;89(6):F483-F484.
182. Amodeo I, Pesenti N, Raffaeli G, et al. Robotic therapy: Cost, accuracy, and times. New challenges in the neonatal intensive care unit. *Front Pharmacol.* 2019;10:1431-1431.
183. Thyagarajan B, Deshpande SS. Cotrimoxazole and neonatal kernicterus: A review. *Drug Chem Toxicol.* 2014;37(2):121-129.
184. Sammons HM, Choonara I. Learning lessons from adverse drug reactions in children. *Children (Basel).* 2016;3(1):1.
185. Glanzmann C, Frey B, Meier CR, et al. Analysis of medication prescribing errors in critically ill children. *European Journal of Pediatrics.* 2015;174(10):1347-1355.
186. Agarwal S, Classen D, Larsen G, et al. Prevalence of adverse events in pediatric intensive care units in the united states. *Pediatric Critical Care Medicine.* 2010;11(5):568-578.
187. Kaushal R, Bates DW, Abramson EL, et al. Unit-based clinical pharmacists' prevention of serious medication errors in pediatric inpatients. *American Journal of Health-System Pharmacy.* 2008;65(13):1254-1260.
188. Kadmon G, Bron-Harlev E, Nahum E, et al. Computerized order entry with limited decision support to prevent prescription errors in a picu. *Pediatrics.* 2009;124(3):935-940.
189. Nguyen M-NR, Mosel C, Grzeskowiak LE. Interventions to reduce medication errors in neonatal care: A systematic review. *Therapeutic Advances in Drug Safety.* 2018;9(2):123-155.
190. Manias E, Kinney S, Cranswick N, et al. Interventions to reduce medication errors in pediatric intensive care. *Annals of Pharmacotherapy.* 2014;48(10):1313-1331.
191. Naseralallah LM, Hussain TA, Jaam M, et al. Impact of pharmacist interventions on medication errors in hospitalized pediatric patients: A systematic review and meta-analysis. *International Journal of Clinical Pharmacy.* 2020.
192. Prgomet M, Li L, Niazkhani Z, et al. Impact of commercial computerized provider order entry and clinical decision support systems on medication errors, length of stay, and mortality in intensive care units: A systematic review and meta-analysis. *Journal of the American Medical Informatics Association.* 2017;24(2):413-422.

193. Stockwell DC, Slonim AD. Quality and safety in the intensive care unit. *Journal of Intensive Care Medicine.* 2006;21(4):199-210.
194. Paediatric Intensive Care Audit Network. Annual reporting and publications. https://www.picanet.org.uk/annual-reporting-and-publications/. Published 2016. Accessed 17 Nov, 2020.
195. Zimmerman JJ, Anand KJS, Meert KL, et al. Research as a standard of care in the picu. *Pediatric Critical Care Medicine.* 2016;17(1):e13-e21.
196. Koumpagioti D, Varounis C, Kletsiou E, et al. Evaluation of the medication process in pediatric patients: A meta-analysis. *Jornal De Pediatria.* 2014;90(4):344-355.
197. Ghaleb MA, Barber N, Franklin BD, et al. Systematic review of medication errors in pediatric patients. *The Annals of Pharmacotherapy.* 2006;40(10):1766-1776.
198. Assiri GA, Shebl NA, Mahmoud MA, et al. What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature. *BMJ Open.* 2018;8(5):e019101.
199. Gopalakrishnan S, Ganeshkumar P. Systematic reviews and meta-analysis: Understanding the best evidence in primary healthcare. *J Family Med Prim Care.* 2013;2(1):9-14.
200. Formica D, Sultana J, Cutroneo PM, et al. The economic burden of preventable adverse drug reactions: A systematic review of observational studies. *Expert Opinion on Drug Safety.* 2018;17(7):681-695.
201. Oliver S, Dickson K, Bangpan M. Systematic reviews: Making them policy relevant. A briefing for policy makers and systematic reviewers. https://www.who.int/alliance-hpsr/projects/eppibrief15.pdf. Published 2015. Accessed 25 Jan, 2021.
202. Cliff-Eribo KO, Sammons H, Choonara I. Systematic review of paediatric studies of adverse drug reactions from pharmacovigilance databases. *Expert Opinion on Drug Safety.* 2016;15(10):1321-1328.
203. Smyth RL, Peak M, Turner MA, et al. Adric: Adverse drug reactions in children – a programme of research using mixed methods. Chapter 4, systematic review of paediatric adverse drug reactions. https://www.ncbi.nlm.nih.gov/books/NBK262753/. Published 2014. Accessed 3 Aug, 2018.
204. Truter A, Schellack N, Meyer JC. Identifying medication errors in the neonatal intensive care unit and paediatric wards using a medication error checklist at a tertiary academic hospital in gauteng, south africa. *South African Journal of Child Health.* 2017;11(1):5-10.
205. Leung JS, Johnson DW, Sperou AJ, et al. A systematic review of adverse drug events associated with administration of common asthma medications in children. *PloS one.* 2017;12(8):e0182738.
206. Khan LM. Comparative epidemiology of hospital-acquired adverse drug reactions in adults and children and their impact on cost and hospital stay–a systematic review. *European Journal of Clinical Pharmacology.* 2013;69(12):1985-1996.
207. Gates PJ, Meyerson SA, Baysari MT, et al. Preventable adverse drug events among inpatients: A systematic review. *Pediatrics.* 2018;142(3):e20180805.
208. Smyth RMD, Gargon E, Kirkham J, et al. Adverse drug reactions in children - a systematic review. *PloS One.* 2012;7(3):e24061-e24061.

209. Van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: A systematic review. *Pediatrics.* 2009;123(4):1184-1190.
210. Gonzales K. Medication administration errors and the pediatric population: A systematic search of the literature. *Journal of Pediatric Nursing.* 2010;25(6):555-565.
211. Ameer A, Dhillon S, Peters MJ, et al. Systematic literature review of hospital medication administration errors in children. *Integrated pharmacy research & practice.* 2015;4:153-165.
212. Morris S, Rivett C. The development of a quality improvement system to monitor, assess and feedback prescribing errors in paediatric intensive care. *Archives of Disease in Childhood.* 2016;101(9):e2-e2.
213. Fordham T, Green H, Badeaa Q, et al. Reduction in prescription errors in a neonatal intensive care unit: A completed audit cycle. *Archives of Disease in Childhood.* 2015;100:A160.
214. Rees P, Edwards A, Powell C, et al. Patient safety incidents involving sick children in primary care in england and wales: A mixed methods analysis. *PLoS medicine.* 2017;14(1):e1002217.
215. World Health Organization. Reporting and learning systems for medication errors: The role of pharmacovigilance centres https://apps.who.int/iris/bitstream/handle/10665/137036/9789241507943_eng.pdf. Published 2014. Accessed 6 Jan, 2021.
216. World Health Organization. The conceptual framework for the international classification for patient safety (icps). https://www.who.int/patientsafety/implementation/taxonomy/ICPS-report/en/. Published 2010. Accessed 30 Nov, 2020.
217. Baraki Z, Abay M, Tsegay L, et al. Medication administration error and contributing factors among pediatric inpatient in public hospitals of tigray, northern ethiopia. *BMC Pediatrics.* 2018;18(1):321.
218. Rishoej RM, Lai Nielsen H, Strzelec SM, et al. Qualitative exploration of practices to prevent medication errors in neonatal intensive care units: A focus group study. *Therapeutic Advances in Drug Safety.* 2018;9(7):343-353.
219. World Health Organization. World alliance for patient safety: Forward programme 2005. https://apps.who.int/iris/handle/10665/43072. Published 2005. Accessed 2 Dec, 2020.
220. Holden RJ, Carayon P, Gurses AP, et al. Seips 2.0: A human factors framework for studying and improving the work of healthcare professionals and patients. *Ergonomics.* 2013;56(11):1669-1686.
221. Wheeler DS, Dewan M, Maxwell A, et al. Staffing and workforce issues in the pediatric intensive care unit. *Transl Pediatr.* 2018;7(4):275-283.
222. Sutherland A, Phipps DL. The rise of human factors in medication safety research. *Joint Commission Journal on Quality and Patient Safety.* 2020;46(12):664-666.
223. Brunsveld-Reinders AH, Arbous MS, De Vos R, et al. Incident and error reporting systems in intensive care: A systematic review of the literature. *International Journal for Quality in Health Care.* 2015;28(1):2-13.
224. Franklin BD, Panesar SS, Vincent C, et al. Identifying systems failures in the pathway to a catastrophic event: An analysis of national incident report data relating to vinca alkaloids. *BMJ Quality & Safety.* 2014;23(9):765.

225. Williams H, Edwards A, Hibbert P, et al. Harms from discharge to primary care: Mixed methods analysis of incident reports. *British Journal of General Practice.* 2015;65(641):e829-e837.
226. World Health Organization. World alliance for patient safety: Who draft guidelines for adverse event reporting and learning systems: From information to action. https://apps.who.int/iris/bitstream/handle/10665/69797/WHO-EIP-SPO-QPS-05.3-eng.pdf?sequence=1&isAllowed=y. Published 2005. Accessed 24 Jan, 2021.
227. Pronovost PJ, Thompson DA, Holzmueller CG, et al. Toward learning from patient safety reporting systems. *Journal of Critical Care.* 2006;21(4):305-315.
228. Johnson JA, Bootman J. Drug-related morbidity and mortality: A cost-of-illness model. *Archives of Internal Medicine.* 1995;155(18):1949-1956.
229. Organization WH. International drug monitoring: The role of national centres, report of a who meeting [held in geneva from 20 to 25 september 1971]. 1972.
230. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *The Lancet.* 2000;356(9237):1255-1259.
231. Ferner RE, Aronson JK. Clarification of terminology in medication errors. *Drug Safety.* 2006;29(11):1011-1022.
232. American Society of Health-System Pharmacists. Ashp standard definition of a medication error. *Am J Hosp Pharm.* 1982;39(2):321.
233. Dean B, Schachter M, Vincent C, et al. Causes of prescribing errors in hospital inpatients: A prospective study. *The Lancet.* 2002;359(9315):1373-1378.
234. Reason J. *Human error.* Cambridge university press; 1990.
235. Ribeiro GdSR, Silva RCd, Ferreira MdA, et al. Slips, lapses and mistakes inthe use of equipment by nurses in an intensive care unit. *Revista da Escola de Enfermagem da USP.* 2016;50(3):419-426.
236. Kanjanarat P, Winterstein AG, Johns TE, et al. Nature of preventable adverse drug events in hospitals: A literature review. *American Journal of Health-System Pharmacy.* 2003;60(17):1750-1759.
237. Gorini A, Pravettoni G. Nurses' violations of a medication administration protocol in italy: An observational study. *Clinical Nursing Studies.* 2013;1(2):80.
238. Amalberti R, Vincent C, Auroy Y, et al. Violations and migrations in health care: A framework for understanding and management. *BMJ Quality & Safety.* 2006;15(suppl 1):i66-i71.
239. Glavin R. Drug errors: Consequences, mechanisms, and avoidance. *British Journal of Anaesthesia.* 2010;105(1):76-82.
240. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA.* 1999;282(3):267-270.
241. Reason J. Understanding adverse events: Human factors. *BMJ Quality & Safety.* 1995;4(2):80-89.
242. Reason J. Human error: Models and management. *BMJ: British Medical Journal.* 2000;320(7237):768.
243. Pronovost PJ, Thompson DA, Holzmueller CG, et al. Defining and measuring patient safety. *Critical Care Clinics.* 2005;21(1):1-19.
244. Aronson JK. Medication errors: Definitions and classification. *British Journal of Clinical Pharmacology.* 2009;67(6):599-604.
245. Barker KN, Mikeal RL, Pearson R, et al. Medication errors in nursing homes and small hospitals. *American Journal of Health-System Pharmacy.* 1982;39(6):987-991.

246. Hynniman CE, Conrad WF, Parker P. A comparison of medication errors under the university of kentucky unit dose system and traditional drug distribution systems in four hospitals. *American Journal of Hospital Pharmacy.* 1970;27(10):802-814.
247. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: Implications for prevention. *JAMA.* 1995;274(1):29-34.
248. Billstein-Leber M, Carrillo CJD, Cassano AT, et al. Ashp guidelines on preventing medication errors in hospitals. *American Journal of Health-System Pharmacy.* 2018;75(19):1493-1517.
249. National Coordinating Council for Medication Error Reporting and Prevention. Nccmerp index for categorizing medication errors. https://www.nccmerp.org/types-medication-errors. Accessed 12 Feb 2018.
250. Ferner RE, Aronson JK. Errors in prescribing, preparing, and giving medicines: Definition, classification, and prevention. *Side effects of drugs annual.* 1999;22: xxiii-xxxvi.
251. Taylor-Adams S, Vincent C. Systems analysis of clinical incidents: The london protocol. *Clinical Risk.* 2004;10(6):211-220.
252. Khatri N, Brown GD, Hicks LL. From a blame culture to a just culture in health care. *Health Care Manage Rev.* 2009;34(4):312-322.
253. National Coordinating Council for Medication Error Reporting and Prevention. Statement from ncc merp: Use of medication error rates to compare health care organizations is of no value. http://www.nccmerp.org/statement-medication-error-rates. Accessed 12 Feb, 2018.
254. Franklin BD, Birch S, Savage I, et al. Methodological variability in detecting prescribing errors and consequences for the evaluation of interventions. *Pharmacoepidemiology and Drug Safety.* 2009;18(11):992-999.
255. Meyer-Massetti C, Cheng CM, Schwappach DL, et al. Systematic review of medication safety assessment methods. *American Journal of Health-System Pharmacy.* 2011;68(3):227-240.
256. Bagian JP, Gosbee J, Lee CZ, et al. The veterans affairs root cause analysis system in action. *The Joint Commission Journal on Quality Improvement.* 2002;28(10):531-545.
257. Carson-Stevens A, Hibbert P, Avery A, et al. A cross-sectional mixed methods study protocol to generate learning from patient safety incidents reported from general practice. *BMJ Open.* 2015;5(12):e009079.
258. National Health Service (NHS). Patient safety alret - stage three: Directive improving medication error incident reporting supporting information and learning. https://www.england.nhs.uk/wp-content/uploads/2014/03/psa-sup-info-med-error.pdf. Published 2014. Accessed 18 Dec, 2020.
259. Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the national reporting and learning system in england and wales over 6 years (2005-2010). *British Journal of Clinical Pharmacology.* 2012;74(4):597-604.
260. Rozich J, Haraden C, Resar R. Adverse drug event trigger tool: A practical methodology for measuring medication related harm. *BMJ Quality & Safety.* 2003;12(3):194-200.
261. Kilbridge PM, Campbell UC, Cozart HB, et al. Automated surveillance for adverse drug events at a community hospital and an academic medical center. *Journal of the American Medical Informatics Association.* 2006;13(4):372-377.
262. Dovey S, Phillips R. What should we report to medical error reporting systems? *BMJ Quality & Safety.* 2004;13:322-323.

263. National Reporting and Learning System. Organisation patient safety incident reports. Secondary organisation patient safety incident reports. https://improvement.nhs.uk/resources/learning-from-patient-safety-incidents/. Accessed 18 March, 2019.
264. The NHS Specialist Pharmacy Service. Archived patient (medication) safety alerts from the npsa and sps resources to support their implementation. https://www.sps.nhs.uk/articles/patient-medication-safety-alerts-from-the-npsa-and-sps-resources-to-support-their-implementation/. Published 2018. Accessed 30 Nov, 2020.
265. Conn RL, Tully MP, Shields MD, et al. Characteristics of reported pediatric medication errors in northern ireland and use in quality improvement. *Pediatric Drugs.* 2020;22:551-560.
266. National Patient Safety Agency. Safer lithium therapy. https://www.sps.nhs.uk/wp-content/uploads/2018/02/2009-NRLS-0921-Safer-lithium-tmation-2010.01.12-v1.pdf. Published 2009. Accessed 25 Dec, 2020.
267. National Patient Safety Agency. Actions that can make oral anticoagulant therapy safer. https://www.sps.nhs.uk/articles/npsa-alert-actions-that-can-make-oral-anticoagulant-therapy-safer-2007/. Published 2007. Accessed 25 Jan, 2021.
268. Matt V, Matthew H. The retrospective chart review: Important methodological considerations. *Journal of Educational Evaluation for Health Professions.* 2013;10.
269. Flynn EA, Barker KN, Pepper GA, et al. Comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities. *American Journal of Health-System Pharmacy.* 2002;59(5):436-446.
270. Redfern S, Norman I, Calman L, et al. Assessing competence to practise in nursing: A review of the literature. *Research Papers in Education.* 2002;17(1):51-77.
271. Taxis K, Barber N. Ethnographic study of incidence and severity of intravenous drug errors. *BMJ.* 2003;326(7391):684.
272. Takata GS, Mason W, Taketomo C, et al. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in us children's hospitals. *Pediatrics.* 2008;121(4):e927-e935.
273. Handler SM, Hanlon JT. Detecting adverse drug events using a nursing home specific trigger tool. *The Annals of Long-Term Care.* 2010;18(5):17.
274. Sharek PJ, Horbar JD, Mason W, et al. Adverse events in the neonatal intensive care unit: Development, testing, and findings of an nicu-focused trigger tool to identify harm in north american nicus. *Pediatrics.* 2006;118(4):1332-1340.
275. Steinman MA, Handler SM, Gurwitz JH, et al. Beyond the prescription: Medication monitoring and adverse drug events in older adults. *Journal of the American Geriatrics Society.* 2011;59(8):1513-1520.
276. Resar R, Rozich J, Classen D. Methodology and rationale for the measurement of harm with trigger tools. *BMJ Quality & Safety.* 2003;12(suppl 2):ii39-ii45.
277. Rozich J, Resar R. Medication safety: One organization's approach to the challenge. *JCOM-WAYNE PA-.* 2001;8(10):27-34.
278. Resar RK, Rozich JD, Simmonds T, et al. A trigger tool to identify adverse events in the intensive care unit. *Joint Commission Journal on Quality and Patient Safety.* 2006;32(10):585-590.
279. Classen DC, Lloyd RC, Provost L, et al. Development and evaluation of the institute for healthcare improvement global trigger tool. *Journal of Patient Safety.* 2008;4(3):169-177.

280. Tham E, Calmes HM, Poppy A, et al. Sustaining and spreading the reduction of adverse drug events in a multicenter collaborative. *Pediatrics.* 2011;128(2):e438-e445.
281. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients: Results of the harvard medical practice study ii. *New England Journal of Medicine.* 1991;324(6):377-384.
282. Folli HL, Poole RL, Benitz WE, et al. Medication error prevention by clinical pharmacists in two children's hospitals. *Pediatrics.* 1987;79(5):718-722.
283. Raju TK, Thornton J, Kecskes S, et al. Medication errors in neonatal and paediatric intensive-care units. *The Lancet.* 1989;334(8659):374-376.
284. Vincer MJ, Murray JM, Yuill A, et al. Drug errors and incidents in a neonatal intensive care unit: A quality assurance activity. *American Journal of Diseases of Children.* 1989;143(6):737-740.
285. Al-Jeraisy MI, Alanazi MQ, Abolfotouh MA. Medication prescribing errors in a pediatric inpatient tertiary care setting in saudi arabia. *BMC research notes.* 2011;4(1):294.
286. Benkirane RR, Redouane R, Haimeur CC, et al. Incidence of adverse drug events and medication errors in intensive care units: A prospective multicenter study. *Journal of Patient Safety.* 2009;5(1):16-22.
287. Takata GS, Taketomo CK, Waite S. Characteristics of medication errors and adverse drug events in hospitals participating in the california pediatric patient safety initiative. *American Journal of Health-System Pharmacy.* 2008;65(21):2036-2044.
288. Holdsworth MT, Fichtl RE, Behta M, et al. Incidence and impact of adverse drug events in pediatric inpatients. *Archives of Pediatrics & Adolescent Medicine.* 2003;157(1):60-65.
289. de Vries EN, Ramrattan MA, Smorenburg SM, et al. The incidence and nature of in-hospital adverse events: A systematic review. *Quality & Safety in Health Care.* 2008;17(3):216-223.
290. Avery AJ, Rodgers S, Cantrill JA, et al. A pharmacist-led information technology intervention for medication errors (pincer): A multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. *The Lancet.* 2012;379(9823):1310-1319.
291. Paoletti RD, Suess TM, Lesko MG, et al. Using bar-code technology and medication observation methodology for safer medication administration. *American Journal of Health-System Pharmacy* 2007;64(5):536-543.
292. Chapuis C, Bedouch P, Detavernier M, et al. Automated drug dispensing systems in the intensive care unit: A financial analysis. *Critical Care.* 2015;19(1):318-318.
293. Campino A, Lopez-Herrera MC, Lopez-de-Heredia I, et al. Educational strategy to reduce medication errors in a neonatal intensive care unit. *Acta Paediatrica.* 2009;98(5):782-785.
294. Suresh G, Horbar JD, Plsek P, et al. Voluntary anonymous reporting of medical errors for neonatal intensive care. *Pediatrics.* 2004;113(6):1609-1618.
295. Stambouly J, McLaughlin L, Mandel F, et al. Complications of care in a pediatric intensive care unit: A prospective study. *Intensive Care Medicine.* 1996;22(10):1098-1104.
296. der Merwe F, Wallis S, Udy A. Understanding the impact of critical illness on drug pharmacokinetics-scientifically robust study design. *Journal of Clinical Toxicology.* 2012;4:2161-0495.

297. Langerová P, Vrtal J, Urbánek K. Incidence of unlicensed and off-label prescription in children. *Italian Journal of Pediatrics.* 2014;40:12-12.
298. Schroeder L, Stockwell DC. The persistent challenge of understanding preventable adverse drug events. *Pediatrics.* 2018;142(3):e20181841.
299. Panagioti M, Khan MK, Keers R, et al. Preventable patient harm across health care services. https://www.gmc-uk.org/about/what-we-do-and-why/data-and-research/research-and-insight-archive/preventable-patient-harm-across-healthcare-services. Published 2017. Accessed 27 April, 2019.
300. Rees P, Edwards A, Powell C, et al. Pediatric immunization-related safety incidents in primary care: A mixed methods analysis of a national database. *Vaccine.* 2015;33(32):3873-3880.
301. Otero P, Leyton A, Mariani G, et al. Medication errors in pediatric inpatients: Prevalence and results of a prevention program. *Pediatrics.* 2008;122(3):e737-e743.
302. Likhi D, Phatak A, Morgaonkar V, et al. Audit of medication errors in a neonatal intensive care unit of a tertiary care hospital in western india. 6th Congress of the European Academy of Paediatric Societies; 2016; Netherlands.
303. Palmero D, Di Paolo ER, Beauport L, et al. A bundle with a preformatted medical order sheet and an introductory course to reduce prescription errors in neonates. *European Journal of Pediatrics.* 2016;175(1):113-119.
304. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *PLOS Medicine.* 2009;6(7):e1000097.
305. Mateen FJ, Oh J, Tergas AI, et al. Titles versus titles and abstracts for initial screening of articles for systematic reviews. *Clinical Epidemiology.* 2013;5:89-95.
306. Jain S, Basu S, Parmar V. Medication errors in neonates admitted in intensive care unit and emergency department. *Indian Journal of Medical Sciences.* 2009;63(4):145.
307. Larsen GY, Donaldson AE, Parker HB, et al. Preventable harm occurring to critically ill children. *Pediatric Critical Care Medicine.* 2007;8(4):331-336.
308. Kilbridge PM, Noirot LA, Reichley RM, et al. Computerized surveillance for adverse drug events in a pediatric hospital. *Journal of the American Medical Informatics Association.* 2009;16(5):607-612.
309. Allan E, Barker K. Fundamentals of medication error research. *American Journal of Health-System Pharmacy.* 1990;47(3):555-571.
310. Alsulami Z, Conroy S, Choonara I. Medication errors in the middle east countries: A systematic review of the literature. *European journal of clinical pharmacology.* 2013;69(4):995-1008.
311. Alshehri GH, Keers RN, Ashcroft DM. Frequency and nature of medication errors and adverse drug events in mental health hospitals: A systematic review. *Drug Safety.* 2017;40(10):871-886.
312. Kunac DL, Kennedy J, Austin N, et al. Incidence, preventability, and impact of adverse drug events (ades) and potential ades in hospitalized children in new zealand. *Pediatric Drugs.* 2009;11(2):153-160.
313. Kunac DL, Reith DM. Preventable medication-related events in hospitalised children in new zealand. *The New Zealand Medical Journal (Online).* 2008;121(1272).
314. Fortescue EB, Kaushal R, Landrigan CP, et al. Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. *Pediatrics.* 2003;111(4):722-729.

315. Khoo TB, Tan JW, Ng HP, et al. Paediatric in-patient prescribing errors in malaysia: A cross-sectional multicentre study. *International Journal of Clinical Pharmacy.* 2017;39(3):551-559.
316. Potts AL, Barr FE, Gregory DF, et al. Computerized physician order entry and medication errors in a pediatric critical care unit. *Pediatrics.* 2004;113(1):59-63.
317. Buckley MS, Erstad BL, Kopp BJ, et al. Direct observation approach for detecting medication errors and adverse drug events in a pediatric intensive care unit. *Pediatric Critical Care Medicine.* 2007;8(2):145-152.
318. Sutherland A, Barber R, Talken-Sinclair J. Reducing prescribing errors in a british picu. *Pediatric Critical Care Medicine.* 2011;12:A148.
319. Isaac RE, Martin J, Reynolds F. Prevalence and characteristics of prescribing errors in a paediatric intensive care unit (picu). *Pediatric Critical Care Medicine.* 2014;15:206.
320. Warrick C, Naik H, Avis S, et al. A clinical information system reduces medication errors in paediatric intensive care. *Intensive Care Medicine.* 2011;37(4):691-694.
321. Maat B, Bollen C, van Vught A, et al. Errors in medication prescriptions in paediatric intensive care patients. *Archives of Disease in Childhood.* 2012;97(Suppl 2):A62-A62.
322. Alagha HZ, Badary OA, Ibrahim HM, et al. Reducing prescribing errors in the paediatric intensive care unit: An experience from egypt. *Acta Paediatrica.* 2011;100(10).
323. Morriss FH, Abramowitz PW, Nelson SP, et al. Effectiveness of a barcode medication administration system in reducing preventable adverse drug events in a neonatal intensive care unit: A prospective cohort study. *The Journal of Pediatrics.* 2009;154(3):363-368. e361.
324. Jozefczyk KG, Kennedy WK, Lin MJ, et al. Computerized prescriber order entry and opportunities for medication errors: Comparison to tradition paper-based order entry. *Journal of Pharmacy Practice.* 2013;26(4):434-437.
325. Ridges S, Huggins F. Comparison of medication order entry error rates in a neonatal intensive care unit versus an adult intensive care unit in a predominantly adult hospital. https://www.ashp.org/Meetings-and-Events/Meetings-and-Conferences/Midyear-Clinical-Meeting-and-Exhibition/Midyear-Clinical-Meeting-Abstracts-Archive. Published 2009. Accessed 19 Jun, 2019.
326. Chedoe I, Molendijk H, Hospes W, et al. The effect of a multifaceted educational intervention on medication preparation and administration errors in neonatal intensive care. *Archives of Disease in Childhood.* 2012;97(6):F449-F455.
327. Raja Lope R, Boo N, Rohana J, et al. A quality assurance study on the administration of medication by nurses in a neonatal intensive care unit. *Singapore Medical Journal.* 2009;50(1):68.
328. Dean B, Schachter M, Vincent C, et al. Prescribing errors in hospital inpatients: Their incidence and clinical significance. *Quality and Safety Health Care.* 2002;11(4):340-344.
329. Greenberg RG, Smith PB, Bose C, et al. National survey of neonatal intensive care unit medication safety practices. *American Journal of Perinatology.* 2018;35(14):1419-1422.
330. Matti N, Nguyen MR, Mosel C, et al. Utilization of neonatal medication error prevention strategies: A clinical practice survey of australian and new zealand neonatal units. *Therapeutic advances in drug safety.* 2018;9(11):609-617.
331. Murthy S, Wunsch H. Clinical review: International comparisons in critical care - lessons learned. *Critical Care.* 2012;16(2):218.

332. Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across north america and western europe. *Critical Care Medicine.* 2008;36(10).
333. Royal College of Paediatrics and Child Health (RCPCH). High dependency care for children–time to move on. *RCPCH.* 2014.
334. Alghamdi AA, Keers RN, Sutherland A, et al. Prevalence and nature of medication errors and preventable adverse drug events in paediatric and neonatal intensive care settings: A systematic review. *Drug Safety.* 2019;42(12):1423-1436.
335. Child Health Corporation of America. Pediatric trigger toolkit: Measuring adverse drug events in the children's hospital. http://www.ihi.org/resources/Pages/Tools/PediatricADETriggerToolkit.aspx. Accessed 12 Feb, 2018.
336. Silva DCB, Araujo OR, Arduini RG, et al. Adverse drug events in a paediatric intensive care unit: A prospective cohort. *BMJ Open.* 2013;3(2):e001868.
337. Gallagher RM, Kirkham JJ, Mason JR, et al. Development and inter-rater reliability of the liverpool adverse drug reaction causality assessment tool. *PLoS One.* 2011;6(12):e28096.
338. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hospital pharmacy.* 1992;27(6):538.
339. *Stata statistical software: Release 15* [computer program]. TX: StataCorp LLC.2017.
340. Eslami K, Aletayeb F, Aletayeb SMH, et al. Identifying medication errors in neonatal intensive care units: A two-center study. *BMC Pediatrics.* 2019;19(1):365-365.
341. Long AL, Horvath MM, Cozart H, et al. Tailoring adverse drug event surveillance to the paediatric inpatient. *Quality and Safety in Health Care.* 2010;19(5):e40-e40.
342. Gill A, Leach H, Hughes J, et al. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatrica.* 1995;84(4):438-441.
343. White WA, Kennedy K, Belgum HS, et al. The well-defined pediatric icu: Active surveillance using nonmedical personnel to capture less serious safety events. *The Joint Commission Journal on Quality and Patient Safety.* 2015;41(12):550-AP552.
344. Lao KS, Chui CS, Man KK, et al. Medication safety research by observational study design. *International Journal of Clinical Pharmacy.* 2016;38(3):676-684.
345. Abel G, Elliott MN. Identifying and quantifying variation between healthcare organisations and geographical regions: Using mixed-effects models. *BMJ Quality & Safety.* 2019;28(12):1032.
346. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLOS Medicine.* 2008;5(3):e67.
347. Franklin BD, Vincent C, Schachter M, et al. The incidence of prescribing errors in hospital inpatients - an overview of the research methods. *Drug Safety.* 2005;28(10):891-900.
348. Al-Tajir GK, Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. *Annals of Pharmacotherapy.* 2005;39(7-8):1169-1174.
349. NHS Improvement. National patient safety alerts. https://www.england.nhs.uk/patient-safety/patient-safety-alerts/#national-patient-safety-alerts. Published 2020. Accessed 25 Dec, 2020.
350. Thomas A, Taylor R. An analysis of patient safety incidents associated with medications reported from critical care units in the north west of england between 2009 and 2012. *Anaesthesia.* 2014;69(7):735-745.

351. Stuttaford L, Chakraborty M, Carson-Stevens A, et al. Patient safety incidents in neonatology: A 10-year descriptive analysis of reports from nhs england and wales. *Archives of Disease in Childhood.* 2018;103(Suppl 1):A78.
352. Thomas A, Panchagnula U. Medication-related patient safety incidents in critical care: A review of reports to the uk national patient safety agency. *Anaesthesia.* 2008;63(7):726-733.
353. National Reporting and Learning System. National patient safety incident reports: 21 march 2018. https://improvement.nhs.uk/resources/national-patient-safety-incident-reports-21-march-2018/. Accessed 18 March, 2019.
354. National Health Service. Patient safety incidents. https://improvement.nhs.uk/resources/report-patient-safety-incident/. Accessed 25 Feb, 2020.
355. NHS Improvement. Guidance notes on national reporting and learning system official statistics publications. https://improvement.nhs.uk/documents/1728/Guidance_notes_on_NRLS_officia_statistics_Sept_2017.pdf. Published 2017. Accessed 23 June, 2020.
356. Cooper A, Edwards A, Williams H, et al. Sources of unsafe primary care for older adults: A mixed-methods analysis of patient safety incident reports. *Age Ageing.* 2017;46(5):833-839.
357. Gibson R, MacLeod N, Donaldson LJ, et al. A mixed-methods analysis of patient safety incidents involving opioid substitution treatment with methadone or buprenorphine in community-based care in england and wales. *Addiction.* 2020;115:2066-2076.
358. Williams H, Donaldson SL, Noble S, et al. Quality improvement priorities for safer out-of-hours palliative care: Lessons from a mixed-methods analysis of a national incident-reporting database. *Palliative Medicine.* 2019;33(3):346-356.
359. Palmero D, Di Paolo ER, Stadelmann C, et al. Incident reports versus direct observation to identify medication errors and risk factors in hospitalised newborns. *European Journal of Pediatrics.* 2019;178(2):259-266.
360. Nolan TW. System changes to improve patient safety. *BMJ: British Medical Journal.* 2000;320(7237):771.
361. Davis K, Stremikis K, Squires D, et al. Mirror, mirror on the wall. How the performance of the US Health care system compares internationally New York: CommonWealth Fund Web site. https://www.commonwealthfund.org/publications/fund-reports/2010/jun/mirror-mirror-wall-how-performance-us-health-care-system. Published 2014. Accessed 19 Jun, 2019.
362. National Institute for Health and Care Excellence. Medicines optimisation: The safe and effective use of medicines to enable the best possible outcomes. https://www.nice.org.uk/guidance/ng5. Published 2015. Accessed 24 Sep, 2020.
363. Conroy S, Sweis D, Planner C, et al. Interventions to reduce dosing errors in children. *Drug Safety.* 2007;30(12):1111-1125.
364. Neuspiel DR, Taylor MM. Reducing the risk of harm from medication errors in children. *Health Serv Insights.* 2013;6:47-59.
365. Pandolfini C, Bonati M. A literature review on off-label drug use in children. *European Journal of Pediatrics.* 2005;164(9):552-558.
366. Czarniak P, Bint L, Favie L, et al. Clinical setting influences off-label and unlicensed prescribing in a paediatric teaching hospital. *PLoS One.* 2015;10(3):e0120630.

367. Conroy S, McIntyre J, Choonara I, et al. Unlicensed and off label drug use in neonates. *Archives of Disease in Childhood.* 1999;80(2):F142-F145.
368. Bellis JR, Kirkham JJ, Thiesen S, et al. Adverse drug reactions and off-label and unlicensed medicines in children: A nested case?Control study of inpatients in a pediatric hospital. *BMC Medicine.* 2013;11:238-238.
369. Bellis J, Kirkham J, Pirmohamed M. Adverse drug reactions and off-label and unlicensed medicines in children: A nested case-control study of paediatric inpatients. *Archives of Disease in Childhood.* 2013;98(6):e1.
370. Aseeri MA. The impact of a pediatric antibiotic standard dosing table on dosing errors. *J Pediatr Pharmacol Ther.* 2013;18(3):220-226.
371. Izadpanah F, Haddad Kashani H, Sharif MR. Preventing medicine mistakes in pediatric and neonatal patients. *J Med Life.* 2015;8(Spec Iss 3):6-12.
372. Modi A, Germain E, Soma V, et al. Epidemiology of and risk factors for harmful anti-infective medication errors in a pediatric hospital. *The Joint Commission Journal on Quality and Patient Safety.* 2018;44(10):599-604.
373. Grissinger M. Your high-alert medication list is relatively useless without associated risk-reduction strategies. *P T.* 2016;41(10):598-600.
374. Larsen GY, Parker HB, Cash J, et al. Standard drug concentrations and smart-pump technology reduce continuous-medication-infusion errors in pediatric patients. *Pediatrics.* 2005;116(1):e21.
375. Kane-Gill SL, Jacobi J, Rothschild JM. Adverse drug events in intensive care units: Risk factors, impact, and the role of team care. *Critical Care Medicine.* 2010;38:S83-S89.
376. Alcântara TdS, de Araújo Neto FC, Lima HF, et al. Prevalence of medication discrepancies in pediatric patients transferred between hospital wards. *International Journal of Clinical Pharmacy.* 2020.
377. Tariq S, Woodman J. Using mixed methods in health research. *JRSM Short Rep.* 2013;4(6):2042533313479197-2042533313479197.
378. Biban P, Spaggiari S. "Cohabitation" between nicu and picu. *The Journal of Maternal-Fetal & Neonatal Medicine.* 2011;24(sup1):91-93.
379. Blinova E, Lau E, Bitnun A, et al. Point prevalence survey of antimicrobial utilization in the cardiac and pediatric critical care unit. *Pediatric Critical Care Medicine.* 2013;14(6).
380. National Institute for Health and Care Excellence. Neonatal infection (early onset): Antibiotics for prevention and treatment. https://www.nice.org.uk/guidance/cg149. Published 2012. Accessed 12 May, 2020.
381. Pacifici GM. Clinical pharmacokinetics of aminoglycosides in the neonate: A review. *European Journal of Clinical Pharmacology.* 2009;65(4):419-427.
382. Tzialla C, Borghesi A, Perotti GF, et al. Use and misuse of antibiotics in the neonatal intensive care unit. *The Journal of Maternal-Fetal & Neonatal Medicine.* 2012;25(sup4):27-29.
383. National Patient Safety Agency. Safer use of intravenous gentamicin for neonates. London: NPSA; 2010. https://webarchive.nationalarchives.gov.uk/20100811064341/http://www.nrls.npsa.nhs.uk/resources/search-by-audience/junior-doctor/?entryid45=66271. Accessed 19 Feb, 2020.
384. Federico F. Preventing harm from high-alert medications. *The Joint Commission Journal on Quality and Patient Safety.* 2007;33(9):537-542.

385. McCannon CJ, Hackbarth AD, Griffin FA. Miles to go: An introduction to the 5 million lives campaign. *The Joint Commission Journal on Quality and Patient Safety.* 2007;33(8):477-484.
386. Van der Sluijs AF, van Slobbe-Bijlsma ER, Goossens A, et al. Reducing errors in the administration of medication with infusion pumps in the intensive care department: A lean approach. *SAGE Open Medicine.* 2019;7:2050312118822629.
387. Schnock KO, Dykes PC, Albert J, et al. The frequency of intravenous medication administration errors related to smart infusion pumps: A multihospital observational study. *BMJ Quality & Safety.* 2017;26(2):131-140.
388. Porat N, Bitan Y, Shefi D, et al. Use of colour-coded labels for intravenous high-risk medications and lines to improve patient safety. *Quality and Safety in Health Care.* 2009;18(6):505.
389. Mitchell A, Sommo P, Mocerine T, et al. A standardized approach to pediatric parenteral medication delivery. *Hospital pharmacy.* 2004;39(5):433-447.
390. Tubbs-Cooley HL, Mara CA, Carle AC, et al. Association of nurse workload with missed nursing care in the neonatal intensive care unit. *JAMA Pediatrics.* 2019;173(1):44-51.
391. Tubbs-Cooley HL, Pickler RH, Younger JB, et al. A descriptive study of nurse-reported missed care in neonatal intensive care units. *Journal of Advanced Nursing.* 2015;71(4):813-824.
392. Cho S-H, Kim Y-S, Yeon KN, et al. Effects of increasing nurse staffing on missed nursing care. *International Nursing Review.* 2015;62(2):267-274.
393. Paediatric Intensive Care Audit Network. Annual report 2019. https://www.picanet.org.uk/annual-reporting-and-publications/. Accessed 27 Feb, 2020.
394. Lee A, Cheung YSL, Joynt GM, et al. Are high nurse workload/staffing ratios associated with decreased survival in critically ill patients? A cohort study. *Annals of Intensive Care.* 2017;7(1):46.
395. Bray K, Wren I, Baldwin A, et al. Standards for nurse staffing in critical care units determined by: The british association of critical care nurses, the critical care networks national nurse leads, royal college of nursing critical care and in-flight forum. *Nursing in Critical Care.* 2010;15(3):109-111.
396. Johnstone L, Sutherland A, Hawkins K. Do distractions increase the number of prescribing errors in paediatric intensive care? *Archives of Disease in Childhood.* 2014;99(8):e3.
397. Nichols P, Copeland TS, Craib IA, et al. Learning from error: Identifying contributory causes of medication errors in an australian hospital. *Medical Journal of Australia.* 2008;188(5):276-279.
398. Freeman R, McKee S, Lee-Lehner B, et al. Reducing interruptions to improve medication safety. *Journal of nursing care quality.* 2013;28(2):176-185.
399. Tomietto M, Sartor A, Mazzocoli E, et al. Paradoxical effects of a hospital-based, multi-intervention programme aimed at reducing medication round interruptions. *Journal of nursing management.* 2012;20(3):335-343.
400. Yoder M, Schadewald D, Dietrich K. The effect of a safe zone on nurse interruptions, distractions, and medication administration errors. *Journal of Infusion Nursing.* 2015;38(2):140-151.
401. Raban MZ, Westbrook JI. Are interventions to reduce interruptions and errors during medication administration effective?: A systematic review. *BMJ quality & safety.* 2014;23(5):414-421.

402. Xie A, Carayon P. A systematic review of human factors and ergonomics (hfe)-based healthcare system redesign for quality of care and patient safety. *Ergonomics.* 2015;58(1):33-49.
403. Agrawal A. Medication errors: Prevention using information technology systems. *British journal of clinical pharmacology.* 2009;67(6):681-686.
404. Gray J, Goldmann D. Medication errors in the neonatal intensive care unit: Special patients, unique issues. *Archives of Disease in Childhood.* 2004;89(6):F472-F473.
405. The electronic medicines compendium. Diamorphine hydrochloride bp 5 mg lyophilisate for solution for injection. https://www.medicines.org.uk/emc/product/7244/smpc. Published 2020. Accessed 15 Oct, 2020.
406. Allegaert K, Anderson B, Vrancken M, et al. Impact of a paediatric vial on the magnitude of systematic medication errors in neonates. *Paediatric and Perinatal Drug Therapy.* 2006;7:59-63.
407. Wong I, Sweis D, Cope J, et al. Paediatric medicines research in the uk. *Drug Safety.* 2003;26(8):529-537.
408. Department of Health and Social Care. Transforming nhs pharmacy aseptic services in england. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/931195/aseptic-pharmacy.pdf. Published 2020. Accessed 26 Jan, 2021.
409. Shemilt K, Morecroft CW, Ford JL, et al. Inpatient prescribing systems used in nhs acute trusts across england: A managerial perspective. *European Journal of Hospital Pharmacy.* 2017;24(4):213-217.
410. Wilkinson E. 'A blessing and a curse': The struggle to introduce e-prescribing in hospitals. *The Pharmaceutical Journal.* 2019;303:34.
411. National Health Service (NHS). Digital child health transformation programme. https://www.england.nhs.uk/digitaltechnology/child-health/. Published 2016. Accessed 7 Oct, 2020.
412. National Health Service (NHS). Annual progress report for the nhs patient safety strategy: Year one. https://www.england.nhs.uk/wp-content/uploads/2020/09/Patient-safety_Year-one-strategy-progress-report-FINAL-version-.pdf. Published 2020. Accessed 13 Jan, 2021.
413. Derham C. Achieving comprehensive critical care. *Nursing in Critical Care.* 2007;12(3):124-131.
414. Cunningham KJ. Analysis of clinical interventions and the impact of pediatric pharmacists on medication error prevention in a teaching hospital. *J Pediatr Pharmacol Ther.* 2012;17(4):365-373.
415. Pitkälä KH, Juola AL, Kautiainen H, et al. Education to reduce potentially harmful medication use among residents of assisted living facilities: A randomized controlled trial. *J Am Med Dir Assoc.* 2014;15(12):892-898.
416. Forsetlund L, Eike MC, Gjerberg E, et al. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: A systematic review of randomised controlled trials. *BMC geriatrics.* 2011;11(1):16.
417. Likic R, Maxwell SRJ. Prevention of medication errors: Teaching and training. *British journal of clinical pharmacology.* 2009;67(6):656-661.
418. Kowiatek JG, Weber RJ, Skledar SJ, et al. Medication safety manager in an academic medical center. *American journal of health-system pharmacy.* 2004;61(1):58-64.

419. Machen S, Jani Y, Turner S, et al. The role of organizational and professional cultures in medication safety: A scoping review of the literature. *International Journal for Quality in Health Care.* 2019;31(10):G146-G157.
420. Pollack MM, Holubkov R, Reeder R, et al. Picu length of stay: Factors associated with bed utilization and development of a benchmarking model. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.* 2018;19(3):196-203.
421. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev.* 2017;1(1):CD002052-CD002052.
422. Jenkins IA, Playfor SD, Bevan C, et al. Current united kingdom sedation practice in pediatric intensive care. *Pediatric Anesthesia.* 2007;17(7):675-683.
423. Curley MAQ, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: A randomized clinical trial. *JAMA.* 2015;313(4):379-389.
424. Vet NJ, Kleiber N, Ista E, et al. Sedation in critically ill children with respiratory failure. *Front Pediatr.* 2016;4:89-89.
425. Blackwood B, Junk C, Lyons JDM, et al. Role responsibilities in mechanical ventilation and weaning in pediatric intensive care units: A national survey. *American Journal of Critical Care.* 2013;22(3):189-197.
426. Blackwood B, Tume L. The implausibility of 'usual care'in an open system: Sedation and weaning practices in paediatric intensive care units (picus) in the united kingdom (uk). *Trials.* 2015;16(1):325.
427. Blackwood B, Agus A, Boyle R, et al. Sedation and weaning in children (sandwich): Protocol for a cluster randomised stepped wedge trial. *BMJ Open.* 2019;9(11):e031630.
428. Protocol directed sedation by nurses reduced the duration of mechanical ventilation in critically ill patients. *Evidence Based Nursing.* 2000;3(3):82.
429. Blackwood B, Burns KEA, Cardwell CR, et al. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. *Cochrane Database of Systematic Reviews.* 2014;2014(11):CD006904-CD006904.
430. Blackwood B, Murray M, Chisakuta A, et al. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients. *Cochrane Database of Systematic Reviews.* 2013(7).
431. Blackwood B, Burns KEA, Cardwell CR, et al. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. *Cochrane Database of Systematic Reviews.* 2014(11).
432. Department of Health and Social Care. Hospital discharge service: Policy and operating model. https://www.gov.uk/government/publications/hospital-discharge-service-policy-and-operating-model/hospital-discharge-service-policy-and-operating-model. Published 2020. Accessed 13 Jan, 2021.
433. Tandale SR, Dave N, Garasia M, et al. A study of morbidity and cost of peripheral venous cannulation in neonates admitted to paediatric surgical intensive care unit. *J Clin Diagn Res.* 2017;11(3):UC08-UC10.
434. National Institute for Health and Care Excellence. Neonatal parenteral nutrition. https://www.nice.org.uk/guidance/ng154/evidence/b-venous-access-pdf-7083230943. Published 2020. Accessed 8 Oct, 2020.

435. Al Sofyani K, Julia G, Abdulaziz B, et al. Ultrasound guidance for central vascular access in the neonatal and pediatric intensive care unit. *Saudi J Anaesth.* 2012;6(2):120-124.
436. Crenshaw NA, Briones P, Gonzalez JM, et al. A review of central venous access using ultrasound guidance technology. *Advanced Emergency Nursing Journal.* 2020;42(2):119-127.
437. Leibowitz A, Oren-Grinberg A, Matyal R. Ultrasound guidance for central venous access: Current evidence and clinical recommendations. *Journal of Intensive Care Medicine.* 2020;35(3):303-321.
438. National Institute for Health and Care Excellence. Guidance on the use of ultrasound locating devices for placing central venous catheters. https://www.nice.org.uk/guidance/TA49. Published 2002. Accessed 8 Oct, 2020.
439. Woodley N, Teh A, Hewitt I, et al. Paediatric prescribing error – moving towards zero tolerance. *Archives of Disease in Childhood.* 2012;97(Suppl 1):A99.
440. Peters DH, Tran NT, Adam T. *Implementation research in health: A practical guide.* World Health Organization; 2013.
441. Glasgow RE, Emmons KM. How can we increase translation of research into practice? Types of evidence needed. *Annual Review of Public Health.* 2007;28(1):413-433.
442. Eccles MP, Mittman BS. Welcome to implementation science. *Implementation Science.* 2006;1(1):1.
443. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: Following considerable development in the field since 2006, mrc and nihr have jointly commissioned an update of this guidance to be published in 2019, 2006. *UK: Medical Research Council.* 2008.
444. Peters DH, Paina L, Bennett S. Expecting the unexpected: Applying the develop-distort dilemma to maximize positive market impacts in health. *Health policy and planning.* 2012;27(suppl_4):iv44-iv53.
445. Birken SA, Haines ER, Hwang S, et al. Advancing understanding and identifying strategies for sustaining evidence-based practices: A review of reviews. *Implementation Science.* 2020;15(1):1-13.
446. Zheng K, Abraham J, Novak LL, et al. A survey of the literature on unintended consequences associated with health information technology: 2014-2015. *Yearb Med Inform.* 2016(1):13-29.
447. Brown CL, Mulcaster HL, Triffitt KL, et al. A systematic review of the types and causes of prescribing errors generated from using computerized provider order entry systems in primary and secondary care. *Journal of the American Medical Informatics Association.* 2016;24(2):432-440.
448. Van Der Sijs H, Aarts J, Vulto A, et al. Overriding of drug safety alerts in computerized physician order entry. *Journal of the American Medical Informatics Association.* 2006;13(2):138-147.
449. Ward MM, Baloh J, Zhu X, et al. Promoting action on research implementation in health services framework applied to teamstepps implementation in small rural hospitals. *Health Care Manage Rev.* 2017;42(1):2-13.
450. Greenhalgh T, Robert G, Macfarlane F, et al. Diffusion of innovations in service organizations: Systematic review and recommendations. *Milbank Q.* 2004;82(4):581-629.
451. Cochrane LJ, Olson CA, Murray S, et al. Gaps between knowing and doing: Understanding and assessing the barriers to optimal health care. *J Contin Educ Health Prof.* 2007;27(2):94-102.

452. Damschroder LJ, Aron DC, Keith RE, et al. Fostering implementation of health services research findings into practice: A consolidated framework for advancing implementation science. *Implementation Science.* 2009;4:50.
453. Nilsen P. Making sense of implementation theories, models and frameworks. *Implementation science.* 2015;10(1):53.
454. Bonell C, Oakley A, Hargreaves J, et al. Assessment of generalisability in trials of health interventions: Suggested framework and systematic review. *BMJ.* 2006;333(7563):346.
455. Davis L, Ware R, McCann D, et al. Evaluation of contextual influences on the medication administration practice of paediatric nurses. *Journal of advanced nursing.* 2009;65(6):1293-1299.
456. Wallin L, Estabrooks CA, Midodzi WK, et al. Development and validation of a derived measure of research utilization by nurses. *Nursing Research.* 2006;55(3):149-160.
457. Adewale AJ, Hayduk L, Estabrooks CA, et al. Understanding hierarchical linear models: Applications in nursing research. *Nursing Research.* 2007;56(4):S40-S46.
458. Cummings GG, Estabrooks CA, Midodzi WK, et al. Influence of organizational characteristics and context on research utilization. *Nursing Research.* 2007;56(4):S24-S39.
459. Johnson MJ, May CR. Promoting professional behaviour change in healthcare: What interventions work, and why? A theory-led overview of systematic reviews. *BMJ Open.* 2015;5(9):e008592.
460. Campbell M, Fitzpatrick R, Haines A, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ.* 2000;321(7262):694-696.
461. Lakshman R, Griffin S, Hardeman W, et al. Using the medical research council framework for the development and evaluation of complex interventions in a theory-based infant feeding intervention to prevent childhood obesity: The baby milk intervention and trial. *Journal of Obesity.* 2014;2014:646504.
462. Bobrow K, Farmer A, Cishe N, et al. Using the medical research council framework for development and evaluation of complex interventions in a low resource setting to develop a theory-based treatment support intervention delivered via sms text message to improve blood pressure control. *BMC Health Services Research.* 2018;18(1):33.
463. Paul G, Smith SM, Whitford D, et al. Development of a complex intervention to test the effectiveness of peer support in type 2 diabetes. *BMC Health Services Research.* 2007;7(1):136.
464. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: The new medical research council guidance. *Bmj.* 2008;337.
465. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: The what, why and how. *BMC medical research methodology.* 2010;10(1):1.
466. Rinke ML, Bundy DG, Velasquez CA, et al. Interventions to reduce pediatric medication errors: A systematic review. *Pediatrics.* 2014;134(2):338-360.
467. Simpson JH, Lynch R, Grant J, et al. Reducing medication errors in the neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed.* 2004;89:F480-F482.
468. Peek N, Gude WT, Keers RN, et al. Evaluation of a pharmacist-led actionable audit and feedback intervention for improving medication safety in uk primary care: An interrupted time series analysis. *PLOS Medicine.* 2020;17(10):e1003286.
469. Medical Research Council. A framework for the development and evaluation of rcts for complex interventions to improve health.

https://mrc.ukri.org/documents/pdf/rcts-for-complex-interventions-to-improve-health/. Published 2000. Accessed 30 Dec, 2020.
470. Fox A, Pontefract S, Brown D, et al. Developing consensus on hospital prescribing indicators of potential harm for infants and children. *British journal of clinical pharmacology.* 2016;82(2):451-460.
471. Mekonnen AB, McLachlan AJ, Brien J-AE. Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: A systematic review and meta-analysis. *BMJ Open.* 2016;6(2):e010003-e010003.
472. Cheema E, Alhomoud FK, Kinsara ASA-D, et al. The impact of pharmacists-led medicines reconciliation on healthcare outcomes in secondary care: A systematic review and meta-analysis of randomized controlled trials. *Plos One.* 2018;13(3):e0193510-e0193510.
473. Cheema E, Sutcliffe P, Singer DRJ. The impact of interventions by pharmacists in community pharmacies on control of hypertension: A systematic review and meta-analysis of randomized controlled trials. *British Journal of Clinical Pharmacology.* 2014;78(6):1238-1247.
474. International Pharmaceutical Federation (FIP). *Patient safety. Pharmacists' role in medication without harm.* The Hague: International Pharmaceutical Federation (FIP); 2020.
475. Wang T, Benedict N, Olsen KM, et al. Effect of critical care pharmacist's intervention on medication errors: A systematic review and meta-analysis of observational studies. *Journal of Critical Care.* 2015;30(5):1101-1106.
476. Alenezi S, Abramson J, Smith C, et al. Interventions made by uk pharmacists to minimise risk from paediatric prescribing errors. *Archives of Disease in Childhood.* 2016;101(9):e2.
477. Tripathi S, Crabtree HM, Fryer KR, et al. Impact of clinical pharmacist on the pediatric intensive care practice: An 11-year tertiary center experience. *J Pediatr Pharmacol Ther.* 2015;20(4):290-298.
478. Crowson K, Collette D, Dang M, et al. Transformation of a pharmacy department: Impact on pharmacist interventions, error prevention, and cost. *The Joint Commission Journal on Quality Improvement.* 2002;28(6):324-330.
479. Malfará M, Pernassi M, Aragon D, et al. Impact of the clinical pharmacist interventions on prevention of pharmacotherapy related problems in the paediatric intensive care unit. *International Journal of Clinical Pharmacy.* 2018;40(3):513-519.
480. Healthcare Safety Investigation Branch. The role of clinical pharmacy services in helping to identify and reduce high-risk prescribing errors in hospital. https://www.hsib.org.uk/investigations-cases/high-risk-prescribing-errors-hospital/final-report/. Published 2020. Accessed 15 Oct, 2020.
481. Manias E. Detection of medication-related problems in hospital practice: A review. *British Journal of Clinical Pharmacology.* 2013;76(1):7-20.
482. Henriksen K, Battles J, Marks E, et al. Methodological challenges in describing medication dosing errors in children - advances in patient safety: From research to implementation (volume 2: Concepts and methodology). https://www.ncbi.nlm.nih.gov/books/NBK20505/. Published 2005. Accessed 28 Jan, 2021.
483. Jung M, Park H, Kang D, et al. The effect of bed-to-nurse ratio on hospital mortality of critically ill children on mechanical ventilation: A nationwide population-based study. *Annals of Intensive Care.* 2020;10(1):159.

484. Kadmon G, Pinchover M, Weissbach A, et al. Case not closed: Prescription errors 12 years after computerized physician order entry implementation. *The Journal of Pediatrics.* 2017;190:236-240. e232.
485. Rishoej RM, Almarsdóttir AB, Thybo Christesen H, et al. Identifying and assessing potential harm of medication errors and potentially unsafe medication practices in paediatric hospital settings: A field study. *Therapeutic Advances in Drug Safety.* 2018;9(9):509-522.

Appendices

Appendix 1: Search strategy for the systematic literature review. *(presented in multiple pages)*

#	Searches	Results
1	exp error/	314309
2	exp medication error/ or medication error*.mp.	18217
3	medical error*.mp.	18699
4	drug error*.mp.	543
5	treatment error*.mp.	507
6	therapeutic error*.mp.	1503
7	exp drug safety/ or medication safety.mp.	303807
8	exp patient safety/	89070
9	exp side effect/	457343
10	drug related problem*.mp.	2419
11	drug related harm*.mp.	272
12	medication related harm*.mp.	28
13	drug related adverse event*.mp.	2924
14	potential adverse drug event*.mp.	151
15	((adverse drug or adverse medication) adj1 (event or events or incident* or reaction* or effect or effects or outcome*)).mp.	1405638
16	near miss.mp.	1851
17	medication incident*.mp.	205
18	clinical incident*.mp.	321
19	drug incident*.mp.	22
20	incident report*.mp.	3137
21	prescribing error*.mp.	1124
22	prescription error*.mp.	665
23	exp inappropriate prescribing/	3190
24	administration error*.mp.	928
25	dispensing error*.mp.	454
26	transcription error*.mp.	419
27	omission.mp.	11558
28	discrepancy.mp.	47787

29	epidemiol*.mp.	1420479
30	rate*.mp.	3427724
31	exp prevalence/ or prevalen*.mp.	961569
32	exp incidence/ or inciden*.mp.	1128246
33	frequenc*.mp. or exp frequency/	1061690
34	29 or 30 or 31 or 32 or 33	6364514
35	adolescent*.mp.	1495825
36	child*.mp.	2433877
37	neonat*.mp.	309704
38	paediatric*.mp.	90444
39	pediatric.mp. or exp pediatrics/	416124
40	infant*.mp.	831807
41	newborn/	526543
42	hospitalization/ or hospitalisation.mp.	297338
43	exp hospital admission/	153308
44	patient admission.mp.	1324
45	exp hospital patient/	130529
46	CCU.mp.	2720
47	ICU.mp.	83063
48	high dependency unit*.mp.	1017
49	life support.mp.	14800
50	critical care unit*.mp.	4331
51	exp intensive care unit/	138035
52	exp pediatric intensive care unit/ or paediatric intensive care unit*.mp.	3076
53	PICU.mp.	7206
54	child* intensive care unit*.mp.	37
55	exp neonatal intensive care unit/ or neonat* intensive care unit*.mp.	18228
56	exp newborn intensive care/	25659
57	NICU.mp.	12910
58	neonat* high dependency unit*.mp.	2
59	special care baby unit*.mp.	467
60	SCBU.mp.	253
61	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	2057948

62	34 and 61	562114
63	35 or 36 or 37 or 38 or 39 or 40 or 41	3839663
64	62 and 63	99616
65	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	717013
66	64 and 65	8111
67	limit 66 to yr="2000 -Current"	7527

End of Appendix 1 (search strategy for the systematic literature review).

Appendix 2: Data extraction form for the systematic literature review. *(presented in multiple pages)*

Name of reviewer: **Date of data extraction:**	
Study Basic Information	
Title	
First Author	
Year of Publication	
The Aim of The Study	
Country of Origin	
Publication Details	
Type (E.g. journal article, conference abstract)	
Name (If journal)	

Study Design
Setting (E.g. ICU,PICU, NICU, hospitalised patients)
The Age Limit Indicated in The Study for Critically Ill Children

Study Duration (If it's an intervention study, use the duration before the intervention)	Study Type (E.g. RCT, observational study)

Study Main Focus (ME/ADE study or both)

Type of ME (If it is ME study)
□ Prescribing error □ Administration error □ Dispensing error □ Transcription error

Route of Administration Error Studied **(**E.g. All, intravenous, oral)

Definition of ME/ADE Used

Method of Detection	How ME/ADE confirmed? (E.g. group discussion, specialist review, definitions, training given checklist etc.)	Reliability measures

Person Involved in Data Collection (E.g. pharmacist, nurse, pharmacy technician)	Was the detected ME intercepted in observational studies?
	□No □ Yes If yes, was the observer trained for this process? □No □ Yes

Further Information About the Study Design

Study Results	
Type of denominators used for ME	Type of denominators used for ADE
Number of ME Reported	
Total Number Prescription/Patient Checked for Error	
Types of MEs Reported (e.g. prescribing errors)	
Number of Errors Detected	
Rate of Error Reported	
Common Subtypes of Errors Detected (e.g. dosing errors)	
Number of Potential ADE/ADE Reported	
Rate of Potential ADE/ADE Reported	

Other Significant outcomes
Factors Associated with Reported ME/ADE (e.g. medications involved, rout of administration or stage of medication use process mostly involved with ME/ADE detected)
Information Related to Severity of Harm Associated With ME/ADE
Who assessed the severity?

Which method utilised to assess the severity?	
Severity of ME/ADE Reported	
Study Strength (based on criteria adapted from previous published studies as mentioned by review protocol)	Study Limitations
Extra Information Captured from the Author	

End of Appendix 2 (data extraction form for the systematic literature review).

Appendix 3: Identified studies in the updated databases search for the systematic review (July 2017 – March 2019).

	Database	**Screened titles and abstracts**	**Identified studies** (relevant setting examined, country of origin and publication year)	**Exclusion reason**
1	IPA	10	None	None
2	Medline	250	• Palmero et al.[359] (NICU - Switzerland - Nov 2018)	The baseline medication error rate was extracted from previous study (2016) that is included in this systematic review.[303]
3	Embase	1722	• Kadmon et al.[484] (PICU - Israel - Nov 2017) • Malfará et al.[479] (PICU - Brazil - Mar 2018)	• Kadmon et al. - the baseline medication error rate was extracted from previous study (2009) that is included in this systematic review.[188] • Malfará et al. - events reported were not medication errors or adverse drug events according to the definition used.
4	MIDIRS	33	None	None
5	Web Of Science	489	None	None
6	Scopus	716	• Rishoej et al.[485] (PICU&NICU - Denmark - Jun 2018)	Examined several paediatric hospital wards and data for NICU and PICU could not be extracted.
7	CINAHL	156	None	None
Total		**3,376**	**4 Full texts screened**	**None included**

Abbreviations: IPA: International Pharmaceutical Abstracts; MIDIRS: Maternity & Infant Care Database; CINAHL: Cumulative Index to Nursing and Allied Health Literature; PICU: paediatric intensive care unit; NICU: neonatal intensive care unit(s).

Appendix 4: Studies on the prevalence and types of MEs and preventable ADEs in PICUs. *(presented in multiple pages)*

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/preventable ADEs
Prescribing stage								
Ewig et al. [145]	Hong Kong (2017)	Prospective: medication orders review (3 months)	PICU (paper charts)	Patients ≥29 days old	41 patients, 217 medication orders	129 PEs	59.4% of orders[a]	78% of 127 MEs were clinically significant/serious; 46.3% of patients having a minimum of one potential ADE
Warrick et al. [320]	UK (2011)	(Intervention study)* Prospective: audit of medication orders (2 weeks)	PICU (paper charts)	Not specified	159 medication orders	14 PEs	8.8% of orders	Severity not addressed
Potts et al. [316]	USA (2004)	(Intervention study)* Prospective: medication orders review (2 months)	20-bed PICU (paper charts)	Not specified	268 patients, 6803 medication orders	2049 PEs	30.1% of orders	147 (7.8%)[a] of total PEs considered potential ADEs (2.2 per 100 orders)
Glanzmann et al. [185]	Switzerland (2015)	Prospective: medication orders review (10 months)	PICU (paper charts)	Not specified, 31% of patients were neonates	153 patients; 1129 medication orders	159 PEs; 23 preventable ADEs	14% of orders	104 errors (70% of total errors; 9% of orders) required intervention and/or caused harm 81 (54%) potential ADEs; 15.2%[a] preventable ADEs
Cimino et al. [164]	USA (2004)	(Intervention study)* Prospective: medication orders review (2 weeks)	(Multicentre) 6 to 24-bed PICUs (electronic charts)	Not specified	12,026 medication orders	3259 PEs;16 preventable ADEs	27.1% of orders	0.13% preventable ADEs; considered at low level of severity
Kadmon et al. [188]	Israel (2009)	(Intervention study)* Retrospective: medication orders review (1 month)	12-bed PICU (electronic charts)	Not specified	1250 medication orders	103 PEs	8.24 % of orders[a]	31 (30%) [a] potential ADEs
Maat et al. [321]	Netherlands (2012)	Prospective: medication orders review (35 months)	14-bed PICU (system not described)	0–18 years	23,207 medication orders; 659 patients	13,924 PEs	60% of orders[a]	Severity not assessed

Appendix 4: Continued.

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/ preventable ADEs
Prescribing stage								
Morris et al. [212]	UK (2016)	(Intervention study)* Retrospective: medication orders review (2 weeks)	PICU (system not described)	Not specified	376 medication orders	47 PEs	12.5% of orders	Severity not addressed
Sutherland et al. [318]	UK (2011)	Prospective: medication orders review (duration not specified)	17 bed PICU (paper charts)	Not specified	815 medication orders	99 PEs	12% of orders	One serious error; no life-threatening errors. 81% of errors had no clinical significance
Isaac et al. [319]	UK (2014)	Retrospective: medication orders review (duration not specified)	PICU (system not described)	Not specified	81 patients, 1152 medicines prescribed on MARs and 744 on the infusion chart	MAR: 521 errors; Infusion chart: 488 errors	12.4 errors per patient [a]	Severity not addressed
Booth et al. [143]	UK (2012)	(Intervention study)* Prospective: medication orders review (36 weeks)	12-bed PICU (paper charts)	Not specified	403 observed patients, 1,111 observed OBDs	NR	892 errors per 1,000 PICU OBDs	Severity not addressed
Alagha et al. [322]	Egypt (2011)	(Intervention study)* Retrospective: medication orders review (5 months)	12-bed PICU (paper charts)	Not specified	1107 medication orders with at least one error for 139 patients	1107 PEs	78.1% of total OEs	Majority of errors (39.8%) were classified as potentially of moderate severity
All medication use process								
Buckley et al. [317]	USA (2007)	Prospective: direct observation (6 months)	6-bed paediatric medical/surgical ICU (paper charts)	Non-neonates patients <18 years old	38 patients; 357 medication orders; 263 observed doses	13 PEs; 9 DEs; 5 TEs; 15 MAEs. 7 preventable ADEs	MEs: 19.8% of doses; 14.6% of orders.	35 (9.8 per 100 orders; 13.3 per 100 doses) potential ADEs. preventable ADEs: 2 per 100 orders; 2.7 per 100 doses. Mostly, both preventable ADEs and potential ADEs were serious/significant
Haghbin et al. [91]	Iran (2016)	Prospective: direct observation (6 months)	10-bed medical PICU (system not described)	1 month - 14 years	41 patients; 512 doses observed	250 MEs	14.2 PEs; 0.78 DEs; 4.88 TEs; 28.9 MAEs (per 100 orders); MEs: 48.8 per100 orders	72.4% of all errors did not cause any harm. TEs (24%) most frequent type of errors caused patient harm

Appendix 4: Continued.

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/ preventable ADEs
Studies assessed preventable ADEs								
Agarwal et al. [186]	USA (2010)	Retrospective cross-sectional: medication orders review (4 months)	(Multicentre) PICUs (system not described)	(0–29 days; up to/>=13 years). 0-29 days= 24 patients	734 medical records	NR	21 preventable ADEs per 1000 patient-days.[a] Preventable ADEs rate for patients aged from 0 - 29 days was: 0.0 per 100 patient-days	Majority of preventable ADEs were of low severity
Kaushal et al. [187]	USA (2008)	(Intervention study)* Prospective: medication orders review (6 months)	PICU and general medical and surgical wards (paper charts)	Not specified, but reported data for both adults and paediatrics	209 patients; 311 patient-days	9 serious MEs	29 serious MEs per 1000 patient-days (2.9%)	Only serious MEs examined
Larsen et al. [307]	USA (2007)	Retrospective: medication orders review (12 months)	26-bed PICU (system not described)	Not specified	259 patients	6 preventable ADEs	2.3 preventable ADEs per 100 patients [a]; 3% preventable ADEs of AEs detected	All preventable ADEs caused minor harm

* Pre-intervention (baseline) data were extracted.

[a] Self-calculated.

Abbreviations: NR: not reported; PICU(s): paediatric intensive care unit(s); OBD(s): observed occupied bed day(s); ME(s): medication error(s); OE(s): opportunities for error(s); ADE(s): adverse drug event(s); AE(s): adverse event(s); MAR(s): medication administration record(s); PE(s): prescribing error(s); DE(s): dispensing error(s); TE(s): transcription error(s); MAE(s): medication administration error(s).

End of Appendix 4 (studies on the prevalence and types of MEs and preventable ADEs in PICUs).

Appendix 5: Studies on the prevalence and types of MEs and preventable ADEs in NICUs. *(presented in multiple pages)*

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/preventable ADEs
Prescribing stage								
Campino et al. [146]	Spain (2008)	(Intervention study)* Prospective: medication orders review (10 days)	42-bed NICU (paper charts)	Not specified	122 medication orders	40 PEs	32.8% of orders	Severity not assessed
Palmero et al. [303]	Switzerland (2016)	(Intervention study)* Prospective: medication orders review (4 months)	11-bed NICU (paper charts)	Not specified	83 patients; 505 medication orders	146 PEs	28.9% of orders; 2.1 per100 OEs	Severity not addressed
Ridges et al. [325]	USA (2009)	Retrospective cross-sectional: medication orders review (4 months)	NICU and adult ICU in an adult hospital (system not described)	Not specified	2500 medication orders	13 PEs [a]	0.5% of orders	Severity not addressed
Fordham et al. [213]	UK (2015)	(Intervention study)* Prospective: medication orders review (7 weeks)	NICU (system not described)	Not specified	292 medication orders	16 PEs	5.5% of orders	Severity not addressed
Jozefczyk et al. [324]	USA (2013)	(Intervention study)* Retrospective: medication orders review (2 months)	44-bed NICU (paper charts)	Not specified	500 medication orders; 8036 possible OEs	683 OEs	8.5% of total OEs	Severity not addressed
Machado et al. [144]	Brazil (2015)	Retrospective: medication orders review (9 months)	NICU (paper charts)	Not specified (new-born only)	150 patients; 478 medication orders, 1491 prescribed drugs	648 PEs in prescribed drugs	43.5% of total prescribed drugs	Severity not addressed

Appendix 5: Continued.

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/preventable ADEs
Prescribing and dispensing stages								
Jain S. et al. [306]	India (2009)	Retrospective: medication orders review (4 months)	6-bed NICU and emergency department (paper charts)	Not specified	38 patients; 494 medication orders	27 PEs and DEs	0.7 per patient	None of the errors caused any significant harm
Administration stage								
Raja Lope et al. [327]	Malaysia (2009)	(Intervention study)* Prospective: direct observations (2 weeks)	34-bed NICU (paper charts)	Not specified	188 observed doses	59 MAEs	31.4% of observed doses	Severity not addressed
Chedoe et al. [326]	Netherlands (2012)	(Intervention study)* Prospective: direct observations (20 days)	14-bed NICU (paper charts)	25 weeks to > 35 weeks	311 observed doses	(31 preparation errors, 128 administration errors) in 151 doses	20.5% in preparation; 84.8% of administration [a]	1% severe errors; mostly, 57% of errors caused moderate severity
All medication use process								
Morriss et al. [323]	USA (2009)	(Intervention study)* Prospective: audit of medical records and incident reports (19 weeks)	36-bed NICU (paper charts)	Not specified	475 patients	NR	69.5 MEs per1000 doses	Severity of MEs addressed through preventable ADEs: 15.1 potential ADEs per1000 doses (1.51%); 0.86 preventable ADEs per1000 doses (0.086%)
Likhi et al. [302]	India (2016)	Retrospective: medication orders review (8 months)	NICU (system not described)	< 7 days old	110 case records	29 MEs	26.4% of records [a]	Severity not addressed
Truter et al. [204]	South Africa (2017)	Prospective: medication orders review and direct observations (16 weeks)	55-bed NICU; 40-bed orthopaedics ward; 40-bed surgical ward; 20-bed oncology ward (paper charts)	Not specified	136 medications observ	106 MEs	77.9% of orders [a]	Severity not reported for NICU

Appendix 5: Continued.

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/preventable ADEs
Studies assessed preventable ADEs								
Kunac et al. [312,313] [b]	New Zealand (2009)	Prospective: medication orders review, attending ward meetings, voluntary incident reports and interviewing parents and children. (12 weeks)	NICU, postnatal ward and paediatric ward (paper charts)	Not specified	16 patient days	41 potential ADEs; 21 preventable ADEs	27.4 per 1000 patient-days potential ADEs; 14.38 per 1000 patient-days preventable ADEs	3 preventable ADEs (14.3%)[a] caused preventable persistent disability

* Pre-intervention (baseline) data were extracted.

[a] Self-calculated.

[b] Data were used in two published studies.

Abbreviations: NICU(s): neonatal intensive care unit(s); OE(s): opportunities for error(s); PE(s): prescribing error(s); NR: not reported; ME(s): medication error(s); ADE(s): adverse drug event(s); DE(s): dispensing error(s); MAE(s): medication administration error(s).

End of Appendix 5 (studies on the prevalence and types of MEs and preventable ADEs in NICUs).

Appendix 6: Studies on the prevalence and types of MEs and preventable ADEs included both NICUs and PICUs. *(presented in multiple pages)*

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/preventable ADEs
Prescribing and administration stages								
Khoo et al. [315]	Malaysia (2017)	Prospective: medication orders review (6 months)	(Multicentre) General paediatric wards, 14 NICUs and 8 PICUs in 17 hospitals (electronic charts)	Not specified	PICU: 2931 medication orders; NICU: 5896 medication orders	PICU: 243 PEs NICU: 431 PEs	PICU: 8.3% of orders NICU: 7.3% of orders	PICU: 74 (30.5%) of errors were potentially not significant; 2 errors were potentially serious NICU: 86 (20%) of errors were potentially not significant; 2 errors were potentially serious
Otero et al. [301]	Argentina (2008)	(Intervention study)* Retrospective cross-sectional: medication orders and nurses' records review (1 month)	General paediatric ward, PICU and NICU (paper charts)	0 –18 years	PICU: 23 patients, 169 medication orders, 364 administrations; NICU: 37 patients, 181 medication orders, 367 administrations	PICU: 38 PEs; 30 MAEs NICU: 21 PEs; 31 MAEs	PICU PEs: 11.6% of orders; MAEs: 8.2% of administrations NICU PEs: 22.5% of orders; MAEs: 8.2% of administrations	Severity not addressed
All medication use process								
Benkirane et al. [286]	Morocco (2009)	Prospective: direct observations and incident reports (3 months)	(Multicentre) 7 intensive care units in academic and military hospital including PICU and NICU (paper charts)	Not specified	PICU: 155 patients, 1212 patient days; NICU: *114 patients *2550 patient days	PICU: 11 MEs NICU: 10 MEs	PICU MEs: 9.1 per 1000 patient-days NICU MEs: 4 per 1000 patient-days	Reported for both PICU & NICU: 17 (6.3%) potential ADEs 4 (1.5 %) preventable ADEs
Sakuma et al. [155]	Japan (2014)	Retrospective: medication orders review and incident reports (3 months)	(Multicentre) Paediatric wards in 2 children's hospitals including PICU and NICU (electronic charts)	Not specified	PICU: 18 patients, 157 Patient-days; NICU: 169 patients, 4214 Patient-days	PICU: 1 MEs NICU: 148 MEs	PICU MEs: 6.4 Per 1000 patient-days (95% CI, 0.16 to 35.5) NICU MEs: 35.1 per 1000 patient-days (95% CI, 29.5 to 40.8)	PICU: Error did not cause harm NICU: 2 preventable ADEs in 2 patients, one event per patient (0.47 per 1000 patient-days); both events at ordering stage and caused serious harms [c]

Appendix 6: Continued.

Reference	Country (year)	Study method (duration)	Setting (prescribing system)	Age range	Denominator	Numerator	Rate	Severity of MEs/preventable ADEs
All medication use process								
Kaushal et al. [35,314 b]	USA (2001)	Prospective: incident reports, medication order review, MAR and patient charts (6 weeks)	(Multicentre) Paediatric wards at 2 academic institutions including paediatric medical/surgical ICU and NICU (paper charts)	Not specified	NR	PICU: NR NICU: 49 MEs	PICU MEs: 5.7 per 100 orders NICU MEs: 5.5 per 100 orders	PICU: Rate of potential ADEs/ preventable ADEs 1.3 per 100 orders NICU: 25 potential ADEs (46 per 100 admissions)

* Pre-intervention (baseline) data were extracted.
[b] Data were used in two published studies.
[c] Authors provided data by email.
Abbreviations: PICU(s): paediatric intensive care unit(s); NICU(s): neonatal intensive care unit(s); PE(s): prescribing error(s); MAE(s): medication administration error(s); MAR(s): medication administration record(s); ME(s): medication error(s); ADE(s): adverse drug event(s); NR: not reported.

End of Appendix 6 (studies on the prevalence and types of MEs and preventable ADEs included both NICUs and PICUs).

Appendix 7: Definitions, subtypes and rates of MEs in studies examining PICUs and NICUs. *(presented in multiple pages)*

Studies Examining PICUs			
Reference	Definition	Included event subtypes	Rate
Prescribing error			
Ewig et al. [145]	Errors were defined based on the Institute of Medicine definition, wherein the error occurred during the order writing or transcribing phase.	All pharmacological (such as medications) and non-pharmacological (such as nutritional supplements or milk formulas). Error subtypes were categorised as wrong rate of administration, drug, dose, unit, dosage interval (frequency), dosage form, body weight, diluent, strength (or strength unavailable) and route.	59.4% of orders.
Warrick et al. [320]	NR	Incomplete prescriptions (no signature, no start date, no dose, no frequency, no route), insufficient information (no patient name, no hospital number, drug sensitivity box not completed), illegible prescriptions, and errors in the prescribing decision (need for drug, inappropriate choice of drug, duplication of therapy, inappropriate dose, inappropriate frequency, inappropriate route).	8.8% of orders.
Potts et al. [316]	Errors in which inadequate information was provided or further interpretation (e.g. illegibility) was required for the order to be processed.	Weight not available, missing information and illegible prescriptions.	30.1% of orders.
Glanzmann et al. [185]	A prescribing decision or prescribing writing process that resulted in an unintentional, significant reduction in the probability of treatment being timely and effective or increase in risk of harm, when compared with generally accepted practice.	Drug selection (pharmacodynamic or pharmacokinetic interaction), dose selection (dose too high or too low), drug formulation, treatment duration, drug use process, missing information (missing drug formulation).	14 % of orders.
Cimino et al. [164]	Any error, large or small, at any point in the medication system from the time the drug is ordered until the patient receives it.	Missing drug, dose, route, dosage form, or dosage interval.	27.1% of orders.
Kadmon et al. [188]	Incomplete or illegible prescription that required additional clarification to be executed.	Missing rate of administration, missing units, and illegible handwriting.	8.24 % of orders.
Maat et al. [321]	NR	NR	60% of orders.
Sutherland et al. [318]	NR	NR	12% of orders.
Morris et al. [212]	NR	NR	12.5% of orders.
Alagha et al. [322]	Error that occurs at the stage of prescribing.	Wrong drug selection (contraindications, contraindicated drug interactions, known allergies), wrong dose (deviation of ≥ 10% of the recommended dose in paediatric references), wrong frequency, wrong concentration for administration of intravenous drugs, wrong or missed rate of administration, wrong or missed instructions for proper drug administration by the nurse (wrong diluents, failure to appropriately space in times of administration of interacting drugs, failure to give information for the administration of drugs that should be given at specific times in relation to meals and any other needed information), unclear order and incomplete order (missing drug name, strength, dose).	78.1% of total OEs.
Isaac et al. [319]	NR	Documentation errors (e.g. prohibited abbreviations, failure to use generic drug names and missing patient details) and therapeutic errors (e.g. wrong dose, frequency or incorrect rate).	12.4 errors per patient.

Appendix 7: Continued.

Studies Examining PICUs			
Reference	Definition	Included event subtypes	Rate
Prescribing error			
Booth et al. [143]	A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in either the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice.	Clinical errors (errors in drug dosage, dosage units, strength, dose frequency, incorrect drug or incorrect route). Non-clinical errors (errors of legibility, legality, incomplete patient details or allergy status, or failure to prescribe using the recommended international nonproprietary name. Infusion prescription errors (errors in continuous intravenous infusions, which are prescribed on a separate dedicated infusion prescription, including errors in concentration, rate, incompatible diluent and calculation errors).	892 errors per 1,000 PICU OBDs.
Error in all medication use process			
Buckley et al. [317]	Errors occurring at any stage in the process of ordering or delivering a medication.	Errors in prescribing, transcription, dispensing and administration stages. Error subtypes include wrong dose, omission, wrong time, wrong technique, wrong drug, extra dose, maintenance intravenous fluid/total parenteral nutrition, wrong form, wrong route and drug-drug interaction.	19.8% of doses; 14.6% of orders.
Haghbin et al. [91]	Any avoidable event that harms or has the potential to harm a patient.	Errors in prescribing (wrong dose, drug, route, drug interaction, wrong time and monitoring errors), transcription (omission, wrong time, wrong drug form, wrong dose and un-ordered drug), dispensing and administration (omission, wrong time, wrong dosage form, wrong dose, wrong preparation, wrong technique, un-ordered drug and inappropriate drug) stages.	14.2 PEs; 0.78 DEs; 4.88 TEs; 28.9 MAEs (per 100 medication orders); MEs: 48.8 per100 medication orders.
Studies assessed preventable ADEs			
Agarwal et al. [186]	An injury, large or small, caused by the use (including non-use) of a drug identified during the PICU stay. The definition of "preventability definition of adverse event was determined by individual sites based on local interpretations of each event but in general was based on the premise that the adverse event may have been avoidable, given the appropriate implementation of evidence-based medicine and/or appropriate use of available resources.	All adverse event including preventable ADEs.	2.1 preventable ADEs per 100 patient-days.
Kaushal et al. [187]	Preventable ADEs and non-intercepted near misses.	Preventable ADEs (serious MEs) in ordering, transcribing, dispensing, administering, or monitoring stages.	29 serious MEs per 1000 patient-days (2.9%).
Larsen et al. [307]	NR	NR	2.3 preventable ADEs per 100 patients; 3% preventable ADEs of AEs detected.

Appendix 7: Continued.

Studies Examining NICUs			
Reference	Definition	Included event subtypes	Rate
Prescribing error			
Campino et al. [146]	A medication error was assigned if any of dosage, units, route and administration interval were illegible, incorrect or not specifically written.	Dosage, units, route and administration interval.	32.8% of orders.
Palmero et al. [303]	A result of prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice.	Improper dose (under/over dosage), miscalculation of dosage or infusion rate, wrong route of administration, dose omission, wrong drug, name confusion, extra dose, wrong time/frequency, wrong patient, wrong strength/concentration wrong diluent, wrong rate, (too fast/too slow) and wrong duration treatment.	28.9% of orders; 2.1 per100 OEs.
Ridges et al. [325]	NR	NR	0.5% of orders.
Fordham et al. [213]	NR	NR	5.5% of orders.
Jozefczyk et al. [324]	The increased likelihood of a medication error based on adherence to the listed criteria; in other words, a medication order has the greatest opportunity for correct medication-use when all 18 of the listed criteria are present or performed.	1 - Patient identification parameters are present and legible (name, room number, medical record number) 2 - Order is legible 3 - Order is for a formulary medication 4 - Dose is appropriate for specific patient 5 - Frequency is appropriate 6 - Patient's height is present on profile 7 - Patient's weight is present on profile 8 - Patient's serum creatinine is present on profile 9 - Patient's allergy information is present on profile 10 - Dosage form is appropriate for patient 11 - Drug name is spelled correctly 12 - Order is not vague (''d/c all ABX,'' ''continue home meds'') 13 - Dose is present 14 - Route is present 15 - Frequency is present 16 - Abbreviations used are approved (including appropriate use of trailing and leading zeros) 17 - Date and time are present on the order 18 - Physician can be identified by name or pager number	8.5% of total OEs.
Machado et al. [144]	An error that occurs at the stage of prescribing.	Wrong doses, administration route, interval, diluent and infusion rate.	43.5% of total prescribed drugs.
Prescribing and dispensing error			
Jain S. et al. [306]	Any preventable event that occurs in the process of ordering, transcribing, dispensing, administering or monitoring a drug irrespective of whether the injury occurred or potential for injury was present.	Wrong dose, time, rate and administration.	0.7 per patient.

Appendix 7: Continued.

Studies Examining NICUs			
Reference	Definition	Included event subtypes	Rate
Administration error			
Raja Lope et al. [327]	Errors were defined to be present whenever there was any of the 9 listed criteria are present or performed.	Omission, an extra dose given, wrong preparation of a medication, incorrect dose given, incorrect drug given, deteriorated drug given or if a drug was given via the wrong route, wrong rate or at the wrong time.	31.4% of observed doses.
Chedoe et al. [326]	Any deviation in preparation or administration of the medication or both from the doctor's prescription, the hospital's intravenous policy or the manufacturer's instructions.	Wrong drug, dose, choice and volume of solvent/diluent, administration time, technique, route, rate of administration, and physical and chemical compatibilities.	20.5% in preparation; 84.8% of administration.
Error in all medication use process			
Morriss et al. [323]	Error in ordering, transcribing, dispensing, administering, or monitoring a medication.	Omitted dose, wrong dose ordered, wrong dose given, unordered drug, wrong time, wrong administration rate, faulty administration technique, reconciliation error, transcription error and duplication order.	69.5 MEs per1000 doses.
Likhi et al. [302]	NR	NR	26.4% of records.
Truter et al. [204]	NR	- Inadequate preparation of medication: when medication was prepared or manipulated incorrectly. This includes incorrect method of reconstitution or dilution, not shaking the suspension thoroughly and crushing of specially coated tablets. - Incorrect dose: dose that was prescribed or administered was >10% above or below the correct dose based on the patient's weight. - Incorrect duration: medication administered for a longer period of time than was prescribed, or prescribed medication that was not discontinued when indicated. - Incorrect frequency: medication administered at incorrect intervals (e.g. 8-hourly instead of 6-hourly). - Incorrect medication: administration of medication that was not prescribed, misread prescription, or medication administered to the wrong patient. - Incorrect time: there was >1 h difference between the scheduled time and time of administration. - Mislabelling: when reconstituted medication was kept in storage and had no label indicating the time of reconstitution and volume of diluent used. Infusion not labelled with the name or dose of medication that was being administered. - Omission: failure to administer a prescribed medication, or medication that was being administered without noting that it had been dispensed. - Prescribing error (e.g. no route): elements of good prescribing practice were observed and each medication prescribed was evaluated for compliance with pharmacy legislation as stipulated in good pharmacy practice, i.e. the correct name, dosage, units, route, frequency and duration of treatment.	77.9% of orders.
Studies assessed preventable ADEs			
Kunac et al. [312,313a]	Preventable ADEs: actual injuries resulting from the use of medication in error. Potential ADE: Events that have a significant potential for injuring a patien but do not actually cause harm.	Potential and preventable ADEs.	27.4 per 1000 patient-days potential ADEs; 14.38 per 1000 patient-days preventable ADEs.

Appendix 7: Continued.

Studies Examining Both NICUs and PICUs			
Reference	Definition	Included event subtypes	Rate
Prescribing and administration error			
Khoo et al. [315]	A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice.	NR	PICU: 8.3% of orders. NICU: 7.3% of orders.
Otero et al. [301]	The American Society of Health-System Pharmacists standard definition of medication errors.	Lists of prescription and administration-error classifications that were based on the American Society of Health-System Pharmacists standard definition of medication errors.	PICU PEs: 11.6% of orders; MAEs: 8.2% of administrations. NICU PEs: 22.5% of orders; MAEs: 8.2% of administrations.
Error in all medication use process			
Benkirane et al. [286]	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is under the control of the health care professional, patient, or consumer.	Wrong/improper drug, medication not indicated/inappropriate for the condition being treated, inappropriate medication, medication contraindicated, therapeutic duplicity, drug omission, improper dose, wrong duration of treatment, wrong administration timing, wrong dosage form, wrong administration technique, wrong rate of administration, wrong preparation, manipulation, and/or mixing.	PICU MEs: 9.1 per 1000 patient-days. NICU MEs: 4 per 1000 patient-days.
Sakuma et al. [155]	Any deviation from appropriate use of medication in any step of the medication use process including ordering, transcribing, dispensing, administering or monitoring.	NR	PICU MEs: 6.4 Per 1000 patient-days. NICU MEs: 35.1 per 1000 patient-days.
Kaushal et al. [35,314a]	Errors in drug ordering, transcribing, dispensing, administering, or monitoring.	Wrong dose, wrong frequency, wrong route, wrong medication administration record transcription or documentation, wrong drug, wrong patient, known allergy, illegible order, missing or wrong weight and no or wrong date.	PICU MEs: 5.7 per 100 orders. NICU MEs: 5.5 per 100 orders.

[a] Data were used in two published studies.

Abbreviations: PICU(s): paediatric intensive care unit(s); NICU(s): neonatal intensive care unit(s); PE(s): prescribing error(s); MAE(s): medication administration error(s); ME(s): medication error(s); NR: not reported; OE(s): opportunities for error(s); ADE(s): adverse drug event(s); OBD(s): observed occupied bed day(s); DE(s): dispensing error(s); TE(s): transcription error(s).

End of Appendix 7 (definitions, Subtypes and Rates of MEs in Studies Examining PICUs and NICUs).

Appendix 8: Quality assessment criteria applied to the included studies.

Study	Aims/ objectives	ME/ADE definition	ME/ADE categories specified	ME/ADE categories defined	Denominator clearly defined	Data collection method described clearly	Study setting described	Validity measure in place to confirm the occurrence of ME/ADE	Reliability measures (Inter-rater reliability)	Limitations of study listed	Total score of criteria achieved (out of 10)
Ewig et al. [145]	1	1	1	0	1	1	1	0	0	1	7
Warrick et al. [320]	1	1	1	1	1	1	0	0	0	1	7
Potts et al. [316]	1	1	1	1	1	1	1	1	1	1	10
Glanzmann et al. [185]	1	1	1	1	1	1	1	0	0	1	8
Cimino et al. [164]	1	1	1	1	1	1	1	1	1	1	10
Kadmon et al. [188]	1	1	0	0	1	1	1	1	1	1	8
Maat et al. [321]	1	0	1	0	1	1	1	0	0	0	5
Sutherland et al. [318]	1	0	1	0	1	1	1	0	0	0	5
Morris et al. [212]	1	0	0	0	1	1	0	0	0	0	3
Alagha et al. [322]	1	1	1	0	1	1	1	0	0	1	7
Isaac et al. [319]	1	0	1	0	1	1	1	1	0	0	6
Booth et al. [143]	1	1	1	1	1	1	1	0	0	1	8
Buckley et al. [317]	1	1	1	0	1	1	1	1	1	1	9
Haghbin et al. [91]	1	1	1	0	1	1	1	1	0	1	8
Agarwal et al. [186]	1	1	1	1	1	1	1	1	1	1	10
Kaushal et al. [187]	1	1	1	1	1	1	1	1	1	1	10
Larsen et al. [307]	1	0	0	0	1	1	1	0	0	0	4
Campino et al. [146]	1	0	1	0	1	1	1	0	0	1	6
Palmero et al. [303]	1	1	1	1	1	1	1	0	0	1	8
Ridges et al. [325]	1	0	0	0	1	1	1	0	0	0	4
Fordham et al. [213]	1	0	0	0	1	1	1	1	0	0	5
Jozefczyk et al. [324]	1	1	1	1	1	1	1	0	0	1	8
Machado et al. [144]	1	1	1	1	1	1	1	0	0	1	8
Jain S. et al. [306]	1	1	1	0	1	1	1	1	0	1	8
Raja Lope et al. [327]	1	1	1	0	1	1	1	0	0	1	7
Chedoe et al. [326]	1	1	1	1	1	1	1	1	0	1	9
Morriss et al. [323]	1	1	1	1	1	1	1	1	1	1	10
Likhi et al. [302]	1	0	0	0	1	1	1	0	0	0	4
Truter et al. [204]	1	1	1	1	1	1	1	0	0	1	8
Kunac et al. [312]	1	1	1	1	1	1	1	1	0	1	9
Khoo et al. [315]	1	1	1	1	1	1	1	1	0	1	9
Otero et al. [301]	1	1	1	1	1	1	1	0	0	1	8
Benkirane et al. [286]	1	1	1	1	1	1	1	1	1	1	10
Sakuma et al. [155]	1	1	1	0	1	1	1	1	1	1	9
Kaushal et al. [35]	1	1	1	0	1	1	1	1	1	1	9

Appendix 9: Study manual for data collection and data collector training plan. *(presented in multiple pages)*

Incidence and nature of adverse drug events in paediatric intensive care units: A prospective multicentre study

Background

The use of medication is a principal component of patients' care and among the most common causes of adverse events in hospital settings. Some adverse drug events (ADEs) are preventable, which are complications resulting from MEs, while some are non-preventable and are called adverse drug reactions (ADRs).

ADEs vary in severity ranging from a non-significant drug rash to permanent disability or death. Medication safety research in hospitalised children generally focuses on MEs. However, limited data are available regarding ADEs in this population. Critically ill paediatric patients admitted to intensive care units (ICUs) are more vulnerable to development of ADEs than other hospitalised paediatric and adults. They are more likely to experience ADEs due to factors such as the frequent use of intravenous (IV) medications and high-risk drugs with a narrow therapeutic range.

Based on the findings of our systematic review, limited number of studies examined the epidemiology of ADEs in this patient population. None of these studies were conducted in the UK hospitals, which represents a significant knowledge gap and barrier to improvement efforts. Therefore, we are hoping to identify the incidence and nature of ADEs occurring in critically ill children admitted to paediatric intensive care units (PICUs) at UK hospitals.

Definition

ADEs are defined as "injuries that result from the use of a drug". ADE is a broader term that encompasses injury that is a result of ME or not. Harm associated with an ME is considered preventable. An example of this type of ADE is the development of rash after the administration of penicillin to known penicillin-allergic patient. In contrast, when the patient is not previously known to be allergic to penicillin, the event is considered a non-preventable ADR.

Eligible patients

Eligible patients for inclusion will be children who are admitted to the PICUs and stay for a minimum of 24 hours during the study period. High dependency unit patients who might be admitted to PICUs will be excluded.

Eligible patients' dataset

A pseudonymised patients' dataset must be created before collecting any data for this study using ***Master Patient Link Code Sheet*** (Table 1). It is designed to ensure confidentiality and anonymity of patient information. In this sheet, each included patient should be assigned a unique number (e.g. 001, 002,003…) that correspond to the patient NHS number. This unique number (***patient study number***) will enable patient record tracking whilst also keeping NHS numbers confidential. Please store the Master Patient Link Code Sheet form in a locked filing cabinet at your trust and ensure only the pharmacy team collaborating in this study can access it. Please refer to the Master Patient Link Code Sheet to find the patient study number to be recorded on the data collection forms (A and B) during data collection stages.

Table 1. Master Patient Link Code Sheet.

NHS hospital:		Data collector:	
Date:			
Patient NHS number	Patient link code (study number)	Patient NHS number	Patient link code (study number)

Data collection

The identification of suspected ADEs will rely mainly on your professional experience and judgement as a PICU pharmacist, which you perform by virtue of your routine clinical roles. However, this study provides ***supporting guide (table 2)***, which was adapted from the literature to help you identify potential ADEs. This guide contains useful clues to identify and detect ADEs, but is designed to not replace professional judgment regarding any suspected events due to use of medications.

Stage 1 (screening)

Please record information about each included patient screened as part of stage 1 of data collection by completing ***Data collection form (A)*** (appendix 10). This will include age (months/years) at admission, date of admission to the PICU, history of drug allergies and number of medications on the admission date after the medication reconciliation has been completed. Please remember to ***double check*** if each included patient has left the study or not, so you fill in the ***end of study point*** data on form A.

Initially, we advise you to start identifying suspected ADEs through daily screening of medication charts of all patients who met the study inclusion criteria, along with identification and investigation for any alerts to the occurrence of ADEs.

Stage 2 (investigation)

Please perform further inspection of any suspected ADEs. This includes examination of all relevant patient records such as prescription orders or drug administration records, case note entries, laboratory reports, discharge/admission summaries and attending multidisciplinary unit rounds. Please record the data of detected events on ***ADE data collection form B*** (appendix 11). Please report any suspected ADE, even if you are uncertain of its eligibility. As part of completing data collection B, please provide data on the causes, severity and preventability of the event in the provided questions.

Table 2: Data collection guide adapted from the literature to facilitate adverse drug event(s) detection

#	Trigger	Instruction
(T_1)	**Electrolyte derangement**	Consider if any electrolyte abnormality could have been related to medication use (e.g. hyponatraemia and hypotonic fluids; hyperkalaemia following initiation of ACE inhibitor; hypoglycaemia following cessation of TPN; raised ammonia following valproic acid).
(T_2)	**Antihistamines (e.g. Alimemazine, Chlorphenamine, and Promethazine)**	They are frequently used for allergic reactions to drugs but can also be ordered as a sleep aid, a pre-op/pre-procedure medication, or for seasonal allergies. If the drug has been administered, review the chart to determine if it was ordered for symptoms of an allergic reaction to a drug administered either during the hospitalization or prior to admission.
(T_3)	**Antidote prescription (e.g. naloxone, flumazenil, N-acetylcysteine etc.)**	May be related to inadvertent overdose (note NAC may be used to support hepatic function in non-drug-related hepatic impairment) For example: flumazenil reverses benzodiazepine drugs. Determine why the drug was used. If hypotension or marked, prolonged sedation occurred following benzodiazepine administration, an ADE has occurred.
(T_4)	**Drug interactions**	Examples: Meropenem: valproate; fluroquinolones: epilepsy; phenytoin: enteral feeding tubes; fluconazole: jejunal administration.
(T_5)	**Hepatic function derangement**	Consider if liver function is affected by medication (e.g. carbamazepine, phenobarbital, meropenem, fluconazole and rises in ALT >3x ULN).
(T_6)	**Haematological derangement**	Changes in PT related to hepatic dysfunction (above) or inappropriate anticoagulant use; Anti-Factor Xa levels erratic following LMWH administration.
(T_7)	**Haemodynamic changes**	Bradycardia/hypotension with sedation (e.g. benzodiazepine drugs or alpha-blockers).
(T_8)	**Seizures**	Carbapenems in epilepsy and beta-lactam accumulation in acute kidney injury have seizure-inducing potential.
(T_9)	**Rising creatinine/reduced urine output**	Previous aminoglycoside/glycopeptide therapy could be a reason for elevated serum creatinine.
(T_{10})	**Oversedation, sedation withdrawal/delirium, reduced conscious level**	(Check duration of sedation, doses) look in the physician progress notes, nursing or multidisciplinary notes for evidence of oversedation. If found, look for a relationship between the event and administration of a sedative, analgesic, or muscle relaxant.
(T_{11})	**Rash**	There are many causes for a rash. Look for evidence that the rash is related to drug administration, including overuse of antibiotics resulting in yeast infections.
(T_{12})	**Abrupt medication stops**	In the order sets, whenever "hold" or "stop" medication orders appear, look for the reason this was done. Frequently it indicates an event of some kind.
(T_{13})	**Unplanned extubation/intubation**	Associated with changes in conscious level – inadequate/excessive sedation.
(T_{14})	**Laxative or stool softeners**	Look for evidence referring to the use of stool softener or laxatives. Sedation/anticholinergic burden resulting in constipation (not important if started prophylactically)
(T_{15})	**Change of ventilation**	An unexpected change in ventilation requirements that is related to a change in medication.
(T_{16})	**Therapeutic drug monitoring (TDM)**	Unexpected increased/decreased drug level or additional monitoring that would not be necessary through normal use.

Please remember to investigate and report (using your local incident reporting system, manager and medical team) any patient harm events as per local policy and professional accountability. Local study coordinators at your hospital (details provided in table 3) will facilitate and support your daily activities as a data collector. Please report immediately details of any cases of malpractice/negligence that you may identify during the data collection for this study to the local site coordinator.

Table 3. Research sites and local coordinators

Site number	Research site	Address	Local coordinators
1	PICU-C	Address and contact details were provided to the involved clinical pharmacists.	Lead Clinical Pharmacist
2	PICU-B	Address and contact details were provided to the involved clinical pharmacists.	Consultant Pharmacist PICU
3	PICU-A	Address and contact details were provided to the involved clinical pharmacists.	Lead Clinical Pharmacist

Transferring data:

All completed anonymised data collection forms will be securely stored in filing cabinets at each participating NHS hospital during data collection period and will be sent to the University of Manchester for analysis using recorded postal mail that can be tracked. At the end of each month during the data collection period, completed data collection forms for ***patients who reached the study endpoint due to death or discharge*** from PICU will be sent to the University of Manchester. All remaining data collection forms (for ***patients who remain admitted to PICU until the study's endpoint***) will be sent to the University of Manchester at the end of data collection period.

Emotional distress

In line with professional standards, you need to collect all adverse drug events as a collaborator in the study. However, you will be advised to stop collecting data and to go to quiet and comfortable space to disengage from the study in case you experienced any emotional distress due to tragic medication related incident that you might observe on patients during data collection. In addition, we recommend engaging with your local well-being service (occupational health service) or using any of the following Local Occupational Health Services details for professional counselling if needed:

1. Royal College of Nursing
Tel: 0345 4084391 (member support services)
Web: http://www.rcn.org.uk/support/services
2. Cavell nurses' trust
Tel: 01527 595 999 (free support services)
Web: https://www.cavellnursestrust.org/get-help
3. British Medical Association
Tel: 08459 200 169 (member counselling)
http://bma.org.uk/practical-support-at-work/
4. Royal Pharmaceutical Society
Tel: 0845 257 2570 (member support services)
Web: http://www.rpharms.com/support/enquiry-service.asp
5. Pharmacist Support
Tel: 0808 168 2233 (free support services)
Web: http://www.pharmacistsupport.org/
6. Practitioner Help Programme and Support for Doctors
Web: http://www.support4doctors.org/index.php or http://php.nhs.uk/

Please report any distress instances to the NHS site coordinator, sponsor and principal investigator (address and contact details of sponsor and principal investigator were provided to the involved clinical pharmacists).

Data Collector Training Session Plan

Overview

The training session will be undertaken on either NHS hospital premises (following an arrangement with each NHS trust coordinator regarding appropriate dates and locations for the training to take place) or at the University of Manchester. The training session will need to be conducted in a convenient and appropriate room, which could accommodate up to 10 persons. The room should also have necessary equipment for visual materials such as projector and screen. A lunch will be provided for pharmacists during the session.

Pharmacist data collectors will receive a face –to –face training session by the lead study investigator AAA, supported by AS. The training session will cover a general overview of the study's aim, examples of medication related harm and adverse drug events (ADEs) definition, case scenarios, discussion of the ADE data collection guide (a list of triggers) and step wise instructions for how collect the data.

Attendees will have ample opportunity to explore and clarify their own understanding of the topics with the researcher and their peers. In addition, ADE case scenarios will be

provided to the reviewers in order to establish and clarify their understanding of the data collection process before starting the data collection period following the training session.

During training, the fictional patient medical records (case scenarios) will be independently reviewed by the trainee data collectors. They will then discuss their completed data collection forms for these patients in groups, and the data collectors' questions will be answered to ensure that reviewers are ready for data collection.

All NHS sites will receive in advance a study manual containing all information covered in the training session including descriptions of ADE definition, a step-by-step instruction on the method of data collection, and ADE data collection guide that will guide them to identify ADEs. All study materials (e.g. study manual, data collection forms, ADE data collection guide and the training PowerPoint presentation) will be available to data collectors in their trust via pharmacy shared drive. Data collectors will also be invited to contact the research team at any point anytime if they have any queries.

1. Instructor's name: Anwar Alghamdi, study investigator
2. Study supervisors: Richard Keers, Mark Hann and Darren Ashcroft
3. Topic: Adverse drug events in paediatric intensive care units' study
4. Attendee: PICU Clinical pharmacists
5. Date: Not confirmed yet
6. Duration: around 3 hours (10:00 – 13:00)
7. Location: Not confirmed
8. Aim of the training session:

    8.1. To understand why the project is taking place and what we are aiming to achieve

    8.2. To understand what we are trying to measure

    8.3. To collect data and to fill the required information using ADE data collection guide

    8.4. To describe the procedure for communicating any enquiries/issues arising during data collection.

9. Resources

The study manual including data collection forms, ADE data collection guide will be sent in advance to the data collectors. The training presentation will also be made available to data collectors after their training session. This will all be uploaded to their local hospital NHS shared pharmacy team drive.

10. Session Evaluation

Participant will receive an evaluation form to ensure whether the outcomes have been achieved.

Case scenarios

Case scenario 1

Jack is a 5-month-old boy weighing 3.7kg who has been admitted to the PICU from NICU for ongoing management of chronic lung disease and assessment for long term ventilation. He has been with you for 21 days. He is currently sedated with chloral hydrate and promethazine. He is ventilated on continuous positive airway pressure ventilation (CPAP). His medication list is lengthy, including standard neonatal nutritional support (multivitamins, folic acid and iron). He has been on diuretics (furosemide 1mg/kg TDS and spironolactone 1mg/kg BD) for four months. Over the last few days his urine output has been tailing off and his ventilation has been worsening.

His respiratory secretions are clear with no bacterial or viral growth and his inflammatory markers are unremarkable. A renal ultrasound is requested and shows highly echogenic areas consistent with nephrocalcinosis.

His blood gases are as follows:
HCO3: 34 mMol/L. PaO2: 82 mmHg. PaCO2: 43 mmHg. Arterial blood pH: 7.35 SaO2: 94%. GFR: 75 mL/min/1.73 m(2)

Case scenario 2

Madison is a 2-month-old patient with RSV+ bronchiolitis who has been admitted just over a week. She is on chloral hydrate, alimemazine, clonidine and 3% sodium chloride

nebulisers around physio. Furosemide 1mg/kg QDS and spironolaction 1mg/kg BD have also been used to manage her fluid balance.

On review of Madison on Monday morning after the weekend, you noticed that the spironolactone was abruptly discontinued on Friday evening when she was made "Nil-by-Mouth" for an ET tube change. It has not been restarted.

Prior to you leaving on Friday evening her potassium was 3.8mmol/L but over the weekend it has dropped to 2.5mmol/L. She has been prescribed a number of oral and IV potassium corrections and is now on supplementation.

Case scenarios 3

Vijay is a patient with traumatic brain injury (TBI) following a bicycle accident. He has been on PICU for ten days. He is sedated on fentanyl 2microgram/kg/hr and midaozolam 180microgram/kg/hr. He is paralysed with rocuronium and is being cooled to 35°C.

There is a clinical concern regarding seizures as his Intracranial Pressure has been fluctuating since admission. He received three 20mg/kg loading doses of phenytoin over 36hrs day two and three and has been on 2.5mg/kg BD maintenance since.

His phenytoin levels have been in the normal range (5-10mg/L) during his stay. However, his albumin has been low (mean 16g/L, range 12-19g/L). You are asked to review for any medication that may cause neutropenia as this morning his WCC is low (WBC 2000 cells/mm3; Neuts 0.4 cells/mm3). You go back and realise that his adjusted phenytoin level has been ~20mg/L since admission.

Case scenario 4

Jaxon is 4 years old with a complex history of epilepsy who is managed on sodium valproate. He was admitted through the emergency department after an aspiration event at home.

He's been on PICU for five days and has a positive respiratory culture for Enterobacter (R: co-amoxiclav; S: meropenem, piperacillin/tazobactam) so his antibiotics were changed to meropenem three days ago.

In the last 48 hours his mother reports that his seizure frequency has increased. You note that he has required a dose of buccal midazolam overnight.

Case scenario 5

Mohammad is a renal transplant patient who is experiencing acute rejection and has been admitted to PICU for high-dependency care. He weighs 24kg and has a body surface area of 0.9m2. He has a GFR of 28ml/min/1.73m2 (baseline 88ml/min/1.73m2).

His usual medication is as follows:

- Tacrolimus 2mg BD (previous level 3.2ng/ml)

- Mycophenolate 450mg BD

- Co-trimoxazole 240mg daily

- Valganciclovir 175mg daily (reduced from 450mg daily)

He has a urinary tract infection, with positive urine cultures for E.coli. He has been prescribed piperacillin/tazobactam 1.9g TDS and gentamicin 160mg OD.

24 hours after the first dose of gentamicin, the trough level for gentamicin was 3.6mg/L and his GFR had deteriorated to 18ml/min/1.73m2.

Case scenario 6

Amrit is a 2-year-old girl with a metabolic disorder who has been admitted with hyperammonaemia (NH4 = 360micromol/ml). She has been intubated and ventilated because she was showing signs of encephalopathy. She is currently on Continuous Veno-Venous Haemodiafiltration (CVVHDF) but also receiving infusions of sodium benzoate 250mg/kg/day and sodium phenylbutryate 250mg/kg/day. Both infusions are made up in 10% glucose per local guidelines. They are being administered peripherally via a cannula that was sited in the emergency department prior to admission.

She currently has a triple lumen central line through which sedation and drugs are being infused. There is a spare lumen which is being used to transduce central venous pressure.

18 hours into Amrit's admission the peripheral line tissues and sodium benzoate and sodium phenylbutyrate extravasates requiring plastic surgery intervention.

Case scenario 7

Hermione is 4 years old and is 12 hours post-op after a Fontan completion. She's cardiovascularly stable and weaning ventilation and sedation. Fentanyl is currently 1.5microgram/kg/hr and midazolam 120microgram/kg/hr. She's getting regular IV paracetamol for additional pain management. Her adrenaline has been weaned from 0.4microgram/kg/minute and 0.2microgram/kg/minute and her milrinone is 0.5microgram/kg/minute.

To maintain patency of her total cavo-pulmonary circulation (TCPC)_she is on a heparin infusion at 24units/kg/hr. Local guidance recommends an APTT of 100-150 seconds. Her most recent APTT was 40seconds.

Her heparin dose was increased to 28 units/kg/hr and after two hours the APTT was still just 45 seconds. Her heparin dose was increased to the maximum (40units/kg/hr) and her APTT did not increment above 60 seconds.

The consultant ordered the heparin to be re-prepared. After starting at the last dose (40 units/kg/hr) her APTT was reported as being >200 seconds. Her heparin infusion was immediately stopped and solvent-detergent Fresh Frozen Plasma (Octaplas) was administered.

Training session evaluation form

What is your overall evaluation of this training session? (1 = inadequate - 5 = outstanding)

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Which topics or aspects of the training did you find most interesting or useful?

……
……
……
……
……
……

Did the workshop achieve the programme objectives?

☐ Yes ☐ No

If no, why?

……
……
……
……
……
……

Did this training session meet your expectations in terms of the knowledge and information gained?

☐ Yes ☐ No ☐ Somehow

How do you think the training session could have been made more effective?

……
……
……
……
……

Do you have any further comments or suggestions?

……
……
……
……
……

End of Appendix 9 (Study manual for data collection and data collector training plan).

Appendix 10: Data collection form (A): Patient information form.

Please fill the patient details in the following table			
Patient study number (Can be found on the Master Patient Link Code Sheet)		NHS Hospital	□ PICU-A □ PICU-B □ PICU-C
Date of admission to PICU (dd/mm/yy)	…. ./..…/……...	Age at time of PICU admission	……months or ……years
How and when the patient reached the study endpoint (Please check the reason)	□ Discharged/transferred □ Died □ Reached the end of the study period and still an inpatient on the PICU Date: …. /…/…….		
History of drug allergies or drug intolerances	□ Yes □ No If yes, please list: …… …… …… …… …… …… …… ……	Number of medications on the PICU admission date after the medication reconciliation has been completed	
Data collector (Date: dd/mm/yy)			

Appendix 11: Data collection form (B): Adverse drug event information form. *(presented in multiple pages)*

Please complete one form for each suspected ADE			
Patient study number	**Case number** (e.g. 1st or 2nd ADE for this patient)	**Harm Detected** (what happened to the patient e.g. rash)	**Date of ADE Detection** (dd/mm/yy)
			…. /…/…….

Please check if any potential trigger(s) of suspected harm from the list below: (check all that apply)	
☐ **T_1 Electrolyte derangement**	☐ **T_9 Rising creatinine/reduced urine output**
☐ **T_2 Antihistamines (e.g. Alimemazine or Chlorphenamine)**	☐ **T_{10} Oversedation, sedation withdrawal/delirium**
☐ **T_3 Antidote prescription (e.g. naloxone or flumazenil)**	☐ **T_{11} Rash**
☐ **T_4 Drug interactions**	☐ **T_{12} Abrupt medication stop**
☐ **T_5 Hepatic function derangement**	☐ **T_{13} Unplanned extubation/intubation**
☐ **T_6 Haematological derangement**	☐ **T_{14} Laxative or stool softeners**
☐ **T_7 Haemodynamic changes (e.g. bradycardia/hypotension)**	☐ **T_{15} Change of ventilation**
☐ **T_8 Seizures**	☐ **T_{16} Therapeutic drug monitoring (TDM)**

Medication involved	
Name of drug	
Route of administration	
Dose & frequency	
Total doses this patient received	

Please provide a full description of the event:

What happened?

……

……

……

……

……

How was the event detected? (*If not associated with the one of the triggers listed above****)***

……

……

……

What was the outcome for patient?

……

……

……

What was the corrective action?

……

……

……

……

Please turn the page for the remaining data collection sections

Why do you think the drug is the cause of the event? *For example:* ** Drug initiated/removed/changed shortly before harm was occurred* ** Removal of the drug improve the patient's condition*	…… …… …… …… ……

Please Categorise the ADE

☐ **Preventable** Please explain:…… …… …… ……	☐ **Non-preventable** Please explain:…… …… …… ……

What was the severity of the ADE *(Please check only one of the NCC MERP index provided below)*

☐ **E. An error occurred that resulted in the need for treatment or intervention and caused temporary patient harm.** Description:…… …… ……	☐ **F. An error occurred that resulted in initial or prolonged hospitalisation and caused temporary harm.** Description:…… …… …… ……	
☐ **G. An error occurred that resulted in permanent patient harm.** Description:…… …… …… …… …… ……	☐ **H. An error occurred that resulted in near-death event** (e.g. anaphylaxis, cardiac arrest) Description:…… …… …… …… …… ……	☐ **I. An error occurred that resulted in patient death.** Description:…… …… …… …… …… …… ……

Process problem (Please check stage that apply, if more than one circle the primary process problem)

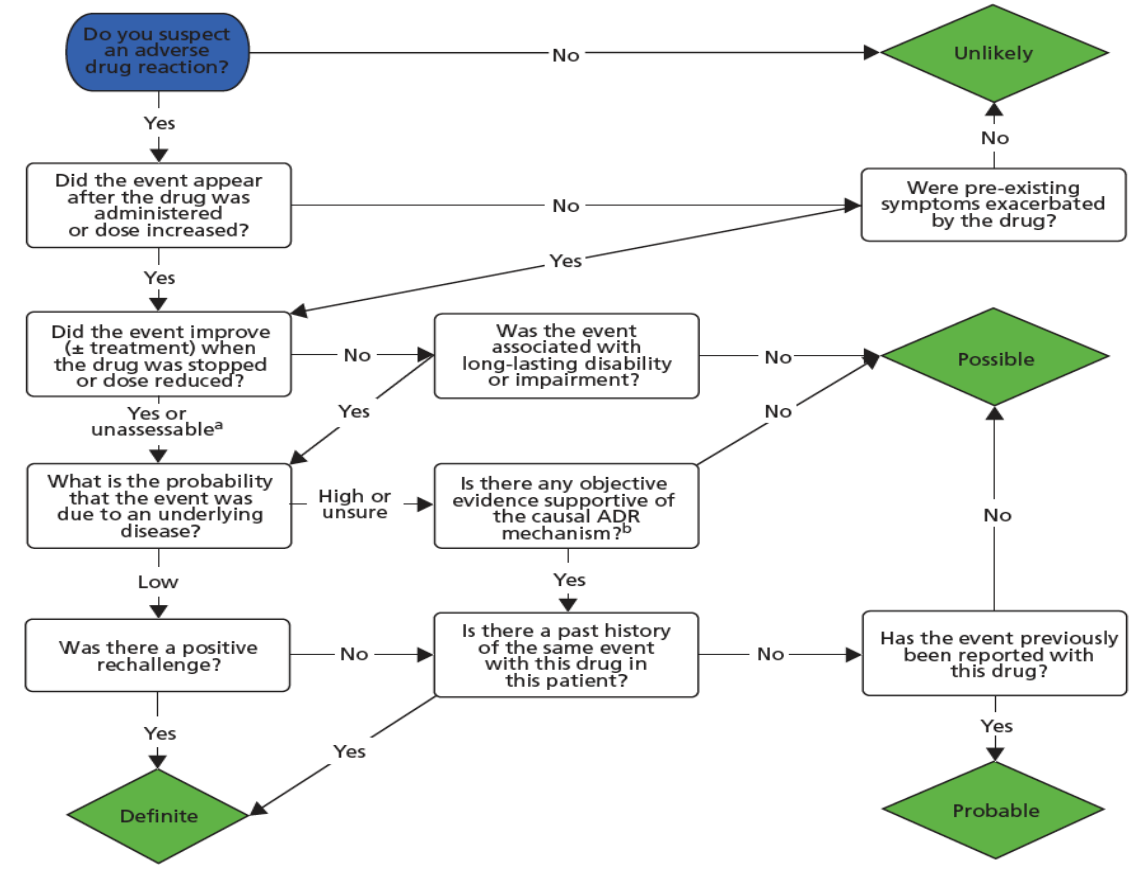
☐ Prescribing/ordering	☐ Dispensing	☐ Administration	☐ Monitoring

End of Appendix 11 (data collection form B)

Appendix 12: Adverse drug events case review (for expert panel use). *(multiple pages)*

Please complete one form for each ADE identified		
Patient study number	**Case number**	**ADE Detected**

Causality assessment



Unassessable refer to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressant).

**Examples of objective evidence: positive laboratory investigation of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient.

Assessment result	□ **Unlikely**	□ **Possible**	□ **Probable**	□ **Definite**

Comment:

.....
.....
.....
.....
.....
.....
.....

Please turn the page for the remaining assessment sections

Adverse drug events case review (continued)

Preventability assessment (Definite or probable ADE categories only)

Please answer the following questions

#	Question	Yes	No
1	Was there a history of allergy or previous reactions to the drug?		
2	Was the drug involved inappropriate for the patient's clinical condition?		
3	Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?		
4	Was a toxic serum drug concentration (or laboratory monitoring test) documented?		
5	Was required therapeutic drug monitoring or other necessary laboratory tests not performed?		
6	Was a drug interaction involved in the reaction?		
7	Was poor compliance involved in the adverse drug reaction?		

Any "yes" answer to one or more of the questions consider that the assessed ADE is preventable.

Assessment result	☐ **Preventable**	☐ **Non-preventable**

Comment:

.....
.....
.....
.....
.....
.....
.....

Severity Assessment

Please check only one of the NCC MERP index provided below

☐ **E.** An error occurred that resulted in the need for treatment or intervention and caused temporary patient harm.	☐ **F.** An error occurred that resulted in initial or prolonged hospitalization and caused temporary harm.	
☐ **G.** An error occurred that resulted in permanent patient harm.	☐ **H.** An error occurred that resulted in near-death event (e.g. anaphylaxis, cardiac arrest)	☐ **I.** An error occurred that resulted in patient death.

Comment:

.....
.....
.....
.....
.....
.....
.....
.....
.....

Appendix 12: Continued. Adverse drug events group case review form (to resolve any discrepancies).

Patient study number	**Case number**	**Reviewers** (decision)	**Causality assessment** ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite	**Preventability assessment** (Preventable: ☐Yes ☐No)	**Severity assessment** *NCC MERP index* scores: (☐E ☐F ☐G ☐H ☐I)
		R1			
		R2			
		R3			
		Final decision			
		R1			
		R2			
		R3			
		Final decision			
		R1			
		R2			
		R3			
		Final decision			
		R1			
		R2			
		R3			
		Final decision			
		R1			
		R2			
		R3			
		Final decision			
		R1			
		R2			
		R3			
		Final decision			
		R1			
		R2			
		R3			
		Final decision			
		R1			
		R2			
		R3			
		Final decision			

End of Appendix 12 (adverse drug events case review forms for expert panel use).

Appendix 13: Ethical approval for the study presented in Chapter 5.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Darren M Ashcroft
Professor of Pharmacoepidemiology,
Head of Drug Usage and Practice Division
University of Manchester
Oxford road
Room 1.182, Stopford Building
University of Manchester
M13 9PT

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

21 February 2019

Dear Professor Ashcroft

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Incidence and nature of adverse drug events in paediatric intensive care units: a prospective multicentre study**
IRAS project ID:	**248236**
Protocol number:	**NHS001521**
Sponsor	**University of Manchester**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

Appendix 14: Preventable ADEs, involved drug classes, level of severity and description of preventability reason.

Preventable ADEs (36/62, 58.1%)	Severity (NCC MERP index) No. (%)			
	E (21, 58.3%) (temporary patient harm)	F (10, 27.8%) (prolonged hospitalisation and temporary harm)	G (4, 11.1%) (permanent harm)	H (1, 2.7%) (near-death)
Drug class (Harm – preventability explanation)	Beta-adrenoceptor blocking drugs – 1 ADE (Hypotension – drug started with high dose)	Antiepileptics – 1 ADE * (Over sedation – drug used outside of guidelines)	Sympathomimetics – 1 ADE (Extravasation injury – use of peripheral canula site)	Beta-adrenoceptor blocking drugs – 1 ADE (Bradycardia – history of similar harm with same dose and also potential drug interaction with drug that has negative chronotropic effects)
	Anti-angiotensin – 1 ADE (Hypotension – drug was given at the same time with chloral hydrate)	Sympathomimetics – 1 ADE (Extravasation injury – use of peripheral canula site)	Parenteral anticoagulants – 1 ADE (Bleeding – error in programming infusion pump)	
	Parenteral anticoagulants – 2 ADEs (Gastrointestinal bleeding – drug level was not managed appropriately)	Corticosteroids – 1 ADE (Hypertension – close frequent review of drugs was not undertaken)	Penicillins – 1 ADE (Extravasation injury – wrong route and frequency)	
	Hypnotics – 2 ADEs (hypotension – excessive dosing)	Minerals – 1 ADE (Abnormal calcium level led to arrhythmia – doses omission)	Aminoglycosides – 1 ADE (Nephrotoxicity – drug level monitoring was not carried out)	
	Opioid Analgesics – 3 ADE * (Over sedation, agitation and confusion, and constipation – excessive dosing)	Benzodiazepines – 1 ADE * (Delirium – wrong dosing)		
	Antiviral Drugs – 1 ADE (Extravasation injury – wrong drug dilution and use of peripheral canula site)	Central antihypertensives – 2 ADEs * (Sedative as unlicensed indication that caused agitation and confusion - sedation weaning plan not followed)		
	Cephalosporins – 1 ADE (Diarrhoea – prolonged use of drugs)	Opioid Analgesics – 3 ADEs * (Agitation and confusion - prolonged use of drugs that started at early days of admission)		
	Aminoglycosides – 1 ADE (Nephrotoxicity – drug level monitoring was not carried out)			
	Corticosteroids – 3 ADEs (Hypertension and gastrointestinal bleeding – close frequent review of drugs was not undertaken)			
	Immunosuppressant – 1 ADE (Rash – history of allergy)			
	Fluids and electrolytes – 1 ADE (Hypoglycaemia - wrong drug dilution)			
	Minerals – 1 ADE (Diarrhoea – wrong dosing)			
	Intravenous Anaesthetics – 2 ADEs (Abnormal electrocardiograph, high pain score – drug used outside of guidelines)			
	Benzodiazepines – 1 ADE * (Sedation withdrawal – prolonged use of drugs)			

Abbreviations: ADE(s): adverse drug event(s); NCC MERP: National Co-ordinating Council for Medication Error Reporting and Prevention index.
* The most frequently detected preventable ADEs were associated with using sedative medications (11/36, 30.6%).

Appendix 15: Information fields in a National Reporting and Learning System medication-related incident report.

No.	Category	Description
1	Incident location	Intensive care unit/high dependency unit
2	Speciality in which incident occurred	Free text entry*
3	Date	Date of incident and date of reporting to National Reporting and Learning System
4	Patient age range	Under 28 days, One month to one year, Two years to four years, Five years to 11 years, and 12 years to 17 years
5	Degree of harm (severity)	No harm, Low harm, Moderate harm, Severe harm, or Death
6	Description of what happened	Free text entry*
7	Actions preventing incident reoccurrence	Free text entry*
8	Apparent causative factors	Free text entry*
9	Incident Category	Medications only
10	Stage of medication use process involved	Supply, Prescribing, Advice, Preparation/dispensing, Administration, and Monitoring
11	Medication error category	18 error types, for example: omitted medicine, wrong dose or wrong frequency
12	Approved drugs names of drugs involved	Free text entry*

* Non-compulsory entries.

Appendix 16: Categories coding framework applied to incident reports. *(presented in multiple pages)*

Medications classification and coding framework using the British National Formulary for Children
1 Gastro-intestinal system
1.1 Dyspepsia and gastro-oesophageal reflux disease
• 1.1.1 Antacids and simeticone
• 1.1.2 Compound alginate preparations
1.2 Antispasmodics and other drugs altering gut motility
1.3 Antisecretory drugs and mucosal protectants
• 1.3.1 H2-receptor antagonists
• 1.3.2 Selective antimuscarinics
• 1.3.3 Chelates and complexes
• 1.3.4 Prostaglandin analogues
• 1.3.5 Proton pump inhibitors
1.4 Acute diarrhoea
• 1.4.1 Adsorbents and bulk-forming drugs
• 1.4.2 Antimotility drugs
• 1.4.3 Enkephalinase inhibitors
1.5 Chronic bowel disorders
• 1.5.1 Aminosalicylates
• 1.5.2 Corticosteroids
• 1.5.3 Drugs affecting the immune response
• 1.5.4 Food allergy
1.6 Laxatives
• 1.6.1 Bulk-forming laxatives
• 1.6.2 Stimulant laxatives
• 1.6.3 Faecal softeners
• 1.6.4 Osmotic laxatives
• 1.6.5 Bowel cleansing preparations
• 1.6.6 Peripheral opioid-receptor antagonists
• 1.6.7 Other drugs used in constipation
1.7 Local preparations for anal and rectal disorders
• 1.7.1 Soothing anal and rectal preparations
• 1.7.2 Compound anal and rectal preparations with corticosteroids
• 1.7.3 Rectal sclerosants
• 1.7.4 Management of anal fissures
1.8 Stoma and enteral feeding tubes
1.9 Drugs affecting intestinal secretions
• 1.9.1 Drugs affecting biliary composition and flow
• 1.9.2 Bile acid sequestrants
• 1.9.3 Aprotinin
• 1.9.4 Pancreatin
2 Cardiovascular system
2.1 Positive inotropic drugs
• 2.1.1 Cardiac glycosides
• 2.1.2 Phosphodiesterase type-3 inhibitors
2.2 Diuretics
• 2.2.1 Thiazides and related diuretics
• 2.2.2 Loop diuretics
• 2.2.3 Potassium-sparing diuretics and aldosterone antagonists
• 2.2.4 Potassium-sparing diuretics with other diuretics

- 2.2.5 Osmotic diuretics
- 2.2.6 Mercurial diuretics
- 2.2.7 Carbonic anhydrase inhibitors
- 2.2.8 Diuretics with potassium

2.3 Anti-arrhythmic drugs

- 2.3.1 Management of arrhythmias
- 2.3.2 Drugs for arrhythmias

2.4 Beta-adrenoceptor blocking drugs

2.5 Hypertension

- 2.5.1 Vasodilator antihypertensive drugs and pulmonary hypertension
- 2.5.2 Centrally acting antihypertensive drugs
- 2.5.3 Adrenergic neurone blocking drugs
- 2.5.4 Alpha-adrenoceptor blocking drugs
- 2.5.5 Drugs affecting the renin-angiotensin system

2.6 Nitrates, calcium-channel blockers, and other antianginal drugs

- 2.6.1 Nitrates
- 2.6.2 Calcium-channel blockers
- 2.6.3 Other antianginal drugs
- 2.6.4 Peripheral vasodilators and related drugs

2.7 Sympathomimetics

- 2.7.1 Inotropic sympathomimetics
- 2.7.2 Vasoconstrictor sympathomimetics
- 2.7.3 Cardiopulmonary resuscitation

2.8 Anticoagulants and protamine

- 2.8.1 Parenteral anticoagulants
- 2.8.2 Oral anticoagulants
- 2.8.3 Protamine sulfate

2.9 Antiplatelet drugs

2.10 Myocardial infarction and fibrinolysis

- 2.10.1 Management of myocardial infarction
- 2.10.2 Fibrinolytic drugs

2.11 Antifibrinolytic drugs and haemostatics

2.12 Lipid-regulating drugs

2.13 Local sclerosants

2.14 Drugs affecting the ductus arteriosus

3 Respiratory system

3.1 Bronchodilators

- 3.1.1 Adrenoceptor agonists
- 3.1.2 Antimuscarinic bronchodilators
- 3.1.3 Theophylline
- 3.1.4 Compound bronchodilator preparations
- 3.1.5 Peak flow meters, inhaler devices, and nebulisers

3.2 Corticosteroids

3.3 Cromoglicate and related therapy and leukotriene receptor antagonists

- 3.3.1 Cromoglicate and related therapy
- 3.3.2 Leukotriene receptor antagonists

3.4 Antihistamines, immunotherapy, and allergic emergencies

- 3.4.1 Antihistamines
    - 3.4.1.1 Sedating antihistamines
- 3.4.2 Allergen immunotherapy
- 3.4.3 Allergic emergencies

3.5 Respiratory stimulants and pulmonary surfactants

- 3.5.1 Respiratory stimulants

• 3.5.2 Pulmonary surfactants
3.6 Oxygen
3.7 Mucolytics
3.8 Aromatic inhalations
3.9 Cough preparations
• 3.9.1 Cough suppressants
• 3.9.2 Expectorant and demulcent cough preparations
3.10 Systemic nasal decongestants
3.11 Antifibrotics
4 Central nervous system
4.1 Hypnotics and anxiolytics
• 4.1.1 Hypnotics
• 4.1.2 Anxiolytics
• 4.1.3 Barbiturates
4.2 Drugs used in psychoses and related disorders
• 4.2.1 Antipsychotic drugs
• 4.2.2 Antipsychotic depot injections
• 4.2.3 Drugs used for mania and hypomania
4.3 Antidepressant drugs
• 4.3.1 Tricyclic antidepressant drugs
• 4.3.2 Monoamine-oxidase inhibitors
• 4.3.3 Selective serotonin re-uptake inhibitors
• 4.3.4 Other antidepressant drugs
4.4 CNS stimulants and other drugs for attention deficit hyperactivity disorder
4.5 Obesity
4.6 Drugs used in nausea and vertigo
4.7 Analgesics
• 4.7.1 Non-opioid analgesics and compound analgesic preparations
• 4.7.2 Opioid analgesics
• 4.7.3 Neuropathic pain
• 4.7.4 Antimigraine drugs
4.8 Antiepileptics
• 4.8.1 Control of the epilepsies
• 4.8.2 Drugs used in status epilepticus
• 4.8.3 Febrile convulsions
4.9 Drugs used in dystonias and related disorders
• 4.9.1 Dopaminergic drugs used in dystonias
• 4.9.2 Antimuscarinic drugs used in dystonias
• 4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders
4.10 Drugs used in substance dependence
• 4.10.1 Alcohol dependence
• 4.10.2 Nicotine dependence
• 4.10.3 Opioid dependence
4.11 Drugs for dementia
5 Infections
5.1 Antibacterial drugs
• 5.1.1 Penicillins
• 5.1.2 Cephalosporins, carbapenems, and other beta-lactams
• 5.1.3 Tetracyclines
• 5.1.4 Aminoglycosides
• 5.1.5 Macrolides
• 5.1.6 Clindamycin
• 5.1.7 Some other antibacterials

• 5.1.8 Sulfonamides and trimethoprim
• 5.1.9 Antituberculosis drugs
• 5.1.10 Antileprotic drugs
• 5.1.11 Metronidazole
• 5.1.12 Quinolones
• 5.1.13 Urinary-tract infections
5.2 Antifungal drugs
• 5.2.1 Triazole antifungals
• 5.2.2 Imidazole antifungals
• 5.2.3 Polyene antifungals
• 5.2.4 Echinocandin antifungals
• 5.2.5 Other antifungals
5.3 Antiviral drugs
• 5.3.1 HIV infection
• 5.3.2 Herpesvirus infections
• 5.3.3 Viral hepatitis
• 5.3.4 Influenza
• 5.3.5 Respiratory syncytial virus
5.4 Antiprotozoal drugs
• 5.4.1 Antimalarials
• 5.4.2 Amoebicides
• 5.4.3 Trichomonacides
• 5.4.4 Antigiardial drugs
• 5.4.5 Leishmaniacides
• 5.4.6 Trypanocides
• 5.4.7 Drugs for toxoplasmosis
• 5.4.8 Drugs for pneumocystis pneumonia
5.5 Anthelmintics
• 5.5.1 Drugs for threadworms
• 5.5.2 Ascaricides
• 5.5.3 Drugs for tapeworm infections
• 5.5.4 Drugs for hookworms
• 5.5.5 Schistosomicides
• 5.5.6 Filaricides
• 5.5.7 Drugs for cutaneous larva migrans
• 5.5.8 Drugs for strongyloidiasis
• 5.111 Multiple anti-infectives
6 Endocrine system
6.1 Drugs used in diabetes
• 6.1.1 Insulins
• 6.1.2 Antidiabetic drugs
• 6.1.3 Diabetic ketoacidosis
• 6.1.4 Treatment of hypoglycaemia
• 6.1.5 Treatment of diabetic nephropathy and neuropathy
• 6.1.6 Diagnostic and monitoring devices for diabetes mellitus
6.2 Thyroid and antithyroid drugs
• 6.2.1 Thyroid hormones
• 6.2.2 Antithyroid drugs
6.3 Corticosteroids

• 6.3.1 Replacement therapy
• 6.3.2 Glucocorticoid therapy
6.4 Sex hormones
• 6.4.1 Female sex hormones
• 6.4.2 Male sex hormones and antagonists
• 6.4.3 Anabolic steroids
6.5 Hypothalamic and pituitary hormones
• 6.5.1 Hypothalamic and anterior pituitary hormones including growth hormone
• 6.5.2 Posterior pituitary hormones and antagonists
6.6 Drugs affecting bone metabolism
• 6.6.1 Calcitonin
• 6.6.2 Bisphosphonates
6.7 Other endocrine drugs
• 6.7.1 Bromocriptine and other dopaminergic drugs
• 6.7.2 Drugs affecting gonadotrophins
• 6.7.3 Cushing's Syndrome
• 6.7.4 Somatomedins
7 Obstetrics, gynaecology, and urinary-tract disorders
7.1 Drugs used in obstetrics
7.2 Treatment of vaginal and vulval conditions
7.3 Contraceptives
7.4 Drugs for genito-urinary disorders
8 Malignant disease and immunosuppression
8.1 Cytotoxic drugs
8.2 Drugs affecting the immune response
8.3 Sex hormones and hormone antagonists in malignant disease
9 Nutrition and blood
9.1 Anaemias and some other blood disorders
9.2 Fluids and electrolytes
• 9.2.1 Oral preparations for fluid and electrolyte imbalance
• 9.2.2 Parenteral preparations for fluid and electrolyte imbalance
9.3 Intravenous nutrition
9.4 Oral nutrition
9.5 Minerals
9.6 Vitamins
• 9.6.1 Vitamin A
• 9.6.4 Vitamin D
• 9.6.6 Vitamin K
• 9.6.7 Multivitamin preparations
9.7 Bitters and tonics
9.8 Metabolic disorders
10 Musculoskeletal and joint diseases
10.1 Drugs used in rheumatic diseases
10.2 Drugs used in neuromuscular disorders
10.3 Drugs for the treatment of soft-tissue disorders and topical pain relief
11 Eye
11.1 Administration of drugs to the eye
11.2 Control of microbial contamination
11.3 Anti-infective eye preparations
11.4 Corticosteroids and other anti-inflammatory preparations
11.5 Mydriatics and cycloplegics
11.6 Treatment of glaucoma
11.7 Local anaesthetics

11.8 Miscellaneous ophthalmic preparations
11.9 Contact lenses
12 Ear, nose, and oropharynx
12.1 Drugs acting on the ear
12.2 Drugs acting on the nose
12.3 Drugs acting on the oropharynx
13 Skin
13.1 Management of skin conditions
13.2 Emollient and barrier preparations
13.3 Topical antipruritics
13.4 Topical corticosteroids
13.5 Preparations for eczema and psoriasis
13.6 Acne and rosacea
13.7 Preparations for warts and calluses
13.8 Sunscreens and camouflagers
13.9 Shampoos and other preparations for scalp conditions
13.10 Anti-infective skin preparations
13.11 Skin cleansers, antiseptics, and desloughing agents
13.12 Hyperhidrosis
13.13 Topical circulatory preparations
14 Immunological products and vaccines
14.1 Active immunity
14.2 Passive immunity
14.3 Storage and use
14.4 Vaccines and antisera
14.5 Immunoglobulins
14.6 International travel
15 Anaesthesia
15.1 General anaesthesia
• 15.1.1 Intravenous anaesthetics
• 15.1.2 Inhalational anaesthetics
• 15.1.3 Antimuscarinic drugs
• 15.1.4 Sedative and analgesic peri-operative drugs
○ 15.1.4.3 Opioid analgesics (e.g. FENTANYL)
• 15.1.5 Neuromuscular blocking drugs
• 15.1.6 Drugs for reversal of neuromuscular blockade
• 15.1.7 Antagonists for central and respiratory depression
• 15.1.8 Drugs for malignant hyperthermia
15.2 Local anaesthesia
15.111 Multiple anaesthetics
102 Multiple drug categories

Appendix 16: Continued.

Coding framework for the structured categorical information	
1. Age	
Groups	Code
Under 28 days	1.1
1 month to 1 year	1.2
2 to 4 years	1.3
5 to 11 years	1.4
12 to 17 years	1.5
2. Harm	
Category	Code
No harm	2.1
Low	2.2
Moderate	2.3
Severe	2.4
Death	2.5
3. Stages of medication use process	
Category	Code
Advice	3.1
Supply or use of OTC	3.2
Administration / supply of a medicine from a clinical area	3.3
Prescribing	3.4
Monitoring / follow-up of medicine use	3.5
Preparation of medicines in all locations / dispensing in a pharmacy	3.6
Other	3.7
4. Error category	
Category	Code
Adverse drug reaction (when used as intended)	4.1
Contra-indication to the use of the medicine in relation to drugs or conditions	4.2
Mismatching between patient and medicine	4.3
Omitted medicine / ingredient	4.4
Patient allergic to treatment	4.5
Wrong / omitted / passed expiry date	4.6
Wrong / omitted patient information leaflet	4.7
Wrong / omitted verbal patient directions	4.8
Wrong / transposed / omitted medicine label	4.9
Wrong / unclear dose or strength	4.10
Wrong drug / medicine	4.11
Wrong formulation	4.12
Wrong frequency	4.13
Wrong method of preparation / supply	4.14
Wrong quantity	4.15
Wrong route	4.16
Wrong storage	4.17
Other/ Unknown	4.18

End of Appendix 16 (categories coding framework applied to incident reports).

Appendix 17: Descriptive analysis of incidents reports dataset.

Category	Number of reports (%)
	Incident reports per age group
Under 28 days	12235 (47.9%)
1 month to 1 year	9337 (36.5%)
2 to 4 years	1154 (4.5%)
5 to 11 years	1457 (5.7%)
12 to 17 years	1384 (5.4%)
Incident reports per medication use process stage	
Advice	119 (0.5%)
Supply or use of over-the-counter (OTC) medicine	46 (0.2%)
Administration / supply of a medicine from a clinical area	13668 (53.5%)
Prescribing	7412 (29%)
Monitoring / follow-up of medicine use	1058 (4.1%)
Preparation of medicines in all locations / dispensing in a pharmacy	1648 (6.4%)
Other	1616 (6.3%)
Incident reports per error category	
Adverse drug reaction (when used as intended)	182 (0.7%)
Contra-indication to the use of the medicine in relation to drugs or conditions	261 (1.02%)
Mismatching between patient and medicine	466 (1.8%)
Omitted medicine / ingredient	4812 (18.8%)
Patient allergic to treatment	56 (0.2%)
Wrong / omitted / passed expiry date	665 (2.6%)
Wrong / omitted patient information leaflet	24 (0.09%)
Wrong / omitted verbal patient directions	35 (0.13%)
Wrong / transposed / omitted medicine label	600 (2.3%)
Wrong / unclear dose or strength	4475 (17.5%)
Wrong drug / medicine	930 (3.6%)
Wrong formulation	623 (2.4%)
Wrong frequency	3193 (12.5%)
Wrong method of preparation / supply	594 (2.3%)
Wrong quantity	1825 (7.1%)
Wrong route	670 (2.6%)
Wrong storage	232 (0.9%)
Other/unknown	5924 (23.2%)
Incident reports per degree of harm (severity)	
No harm	22438 (87.8%)
Low	2833 (11.1%)
Moderate	286 (1.1%)
Severe/death	10 (0.04%)

Appendix 18: Medication classes involved with reported incidents and degree of harm caused by each drug category. *(presented in multiple pages)*

Category (*British National Formulary for Children*)	**Degree of harm (severity)/drug class**				**Number of incidents (%)**
Gastro-intestinal system	**Degree of harm (severity)**				**886 (3.5%)**
	No harm	Low	Moderate	Severe/death	
	790 (89.2%)	90 (10.2%)	6 (0.7%)	0	
	Drug class				
	Dyspepsia and gastro-oesophageal reflux disease				70 (7.9%)
	Antispasmodics and other drugs altering gut motility				165 (18.6%)
	Antisecretory drugs and mucosal protectants				520 (58.7%)
	Acute diarrhoea				16 (1.8%)
	Chronic bowel disorders				16 (1.8%)
	Laxatives				49 (5.5%)
	Drugs affecting intestinal secretions				50 (5.6%)
Cardiovascular system	**Degree of harm (severity)**				**2469 (9.7%)**
	No harm	Low	Moderate	Severe/death	
	2144 (86.8%)	297 (12%)	28 (1.1%)	0	
	Drug class				
	Positive inotropic drugs				236 (9.6%)
	Antifibrinolytic drugs and haemostatics				27 (1.1%)
	Diuretics				645 (26.1%)
	Anti-arrhythmic drugs				56 (2.3%)
	Beta-adrenoceptor blocking drugs				76 (3.1%)
	Hypertension				350 (14.2%)
	Nitrates, calcium-channel blockers, and other antianginal drugs				46 (1.9%)
	Sympathomimetics				491 (19.9%)
	Anticoagulants and protamine				487 (19.7%)
	Antiplatelet drugs				46 (1.9%)
	Myocardial infarction and fibrinolysis drugs				8 (0.3%)
	Lipid regulating drugs				1 (0.04%)
Respiratory system	**Degree of harm (severity)**				**861 (3.4%)**
	No harm	Low	Moderate	Severe/death	
	770 (89.4%)	84 (9.8%)	7 (0.8%)	0	
	Drug class				
	Bronchodilators				116 (13.5%)
	Inhaled corticosteroids				23 (2.7%)
	Antihistamines, immunotherapy, and allergic emergencies				47 (5.5%)
	Respiratory stimulants and pulmonary surfactants				609 (70.7%)
	Oxygen				33 (3.8%)
	Mucolytics				33 (3.8%)
Central Nervous System	**Degree of harm (severity)**				**2,613 (10.2%)**
	No harm	Low	Moderate	Severe/death	
	2283 (87.4%)	301 (11.5%)	29 (1.1%)	0	
	Drug class				
	Hypnotics and anxiolytics				93 (3.6%)
	Drugs used in psychoses and related disorders				29 (1.1%)
	Antidepressant drugs				5 (0.2%)
	CNS stimulants and other drugs for attention deficit hyperactivity disorder				3 (0.1%)
	Drugs used in nausea and vertigo				38 (1.5%)
	Analgesics				2028 (77.6%)
	Antiepileptics				401 (15.4%)
	Drugs used in dystonias and related disorders				16 (0.6%)

Infections	**Degree of harm (severity)**				**6,483 (25.4%)**
	No harm	Low	Moderate	Severe/death	
	5709 (88.1%)	728 (11.2%)	44 (0.7%)	2 (0.03%)	
	Drug class				
	Antibacterial drugs				5955 (91.7%)
	Antifungal Drugs				238 (3.7%)
	Antiviral Drugs				238 (3.7%)
	Antiprotozoal drugs				5 (0.1%)
	Multiple anti-infectives				47 (0.7%)
Endocrine System	**Degree of harm (severity)**				**845 (3.3%)**
	No harm	Low	Moderate	Severe/death	
	716 (84.7%)	118 (13.9%)	11 (1.3%)	0	
	Drug class				
	Drugs used in diabetes				359 (42.5%)
	Thyroid and Antithyroid Drugs				60 (7.1%)
	Corticosteroids				360 (42.6%)
	Sex Hormones				2 (0.2%)
	Hypothalamic and Pituitary Hormones				61 (7.2%)
	Drugs affecting bone metabolism				3 (0.4%)
Obstetrics, gynaecology, and urinary-tract disorders	**Degree of harm (severity)**				**3 (0.01%)**
	No harm	Low	Moderate	Severe/death	
	2 (66.7%)	1 (33.3%)	0	0	
	Drug class				
	Drugs for genito-urinary disorders				**3 (100%)**
Malignant disease and immunosuppression	**Degree of harm (severity)**				**131 (0.5%)**
	No harm	Low	Moderate	Severe/death	
	117 (89.3%)	12 (9.2%)	2 (1.5%)	0	
	Drug class				
	Drugs affecting the immune response				110 (83.9%)
	Cytotoxic Drugs				21 (16.03%)
Nutrition and blood	**Degree of harm (severity)**				**4,505 (17.6%)**
	No harm	Low	Moderate	Severe/death	
	3948 (87,6%)	502 (11.1%)	51 (1.1%)	4 (0.09%)	
	Drug class				
	Anaemias and some other blood disorders				294 (6.5%)
	Parenteral fluids and electrolytes				1747 (38.8%)
	Minerals				549 (12.2%)
	Vitamins				386 (8.8%)
	Intravenous nutrition				1496 (33.2%)
	Metabolic Disorders				33 (0.7%)
Musculoskeletal and joint diseases	**Degree of harm (severity)**				**149 (0.6%)**
	No harm	Low	Moderate	Severe/death	
	132 (88.6%)	15 (10.1%)	2 (1.3%)	0	
	Drug class				
	Drugs for Rheumatic Disease				113 (75.8%)
	Drugs for Neuromuscular disorders				36 (24.2%)
Eye	**Degree of harm (severity)**				**110 (0.4%)**
	No harm	Low	Moderate	Severe/death	
	102 (92.7%)	7 (6.4%)	1 (0.9%)	0	
	Drug class				
	Mydriatics and cycloplegics				40 (36.7%)
	Treatment of glaucoma				12 (11.01%)

	Anti-infective preparations				46 (42.2%)
	Miscellaneous ophthalmic preparations				12 (10.9%)
Ear, nose, and oropharynx	**Degree of harm (severity)**				**17 (0.1%)**
	No harm	Low	Moderate	Severe/death	
	16 (94.1%)	1 (5.9%)	0	0	
	Drug class				
	Drugs acting on the nose (nasal infection)				14 (82.4%)
	Drugs for oropharynx				3 (17.6%)
Skin	**Degree of harm (severity)**				**143 (0.6%)**
	No harm	Low	Moderate	Severe/death	
	130 (90.9%)	13 (9.1%)	0	0	
	Drug class				
	Preparations for eczema and psoriasis				1 (0.7%)
	Topical Corticosteroids				9 (6.3%)
	Emollient and barrier preparations				18 (12.6%)
	Skin cleansers, antiseptics, and desloughing agents				17 (11.9%)
	Anti-infective/antifungal skin preparations				98 (68.5%)
Immunological products and vaccines	**Degree of harm (severity)**				**169 (0.7%)**
	No harm	Low	Moderate	Severe/death	
	150 (88.8%)	15 (8.9%)	4 (2.4%)	0	
	Drug class				
	Vaccines and antisera				130 (76.9%)
	Immunoglobulins				39 (23.1%)
Anaesthesia	**Degree of harm (severity)**				**780 (3.1%)**
	No harm	Low	Moderate	Severe/death	
	696 (89.2%)	72 (%)	12 (%)	0	
	Drug class				
	General anaesthesia				732 (93.8%)
	Local anaesthesia				32 (4.1%)
	Multiple anaesthetics				16 (2.1%)
Multiple drug categories involved	**Degree of harm (severity)**				**22 (0.1%)**
	No harm	Low	Moderate	Severe/death	
	18 (81.8%)	3 (13.6%)	1 (4.5%)	0	
	Drug class				
	Low harm	Anaemias, antiepileptics, metabolic disorders and muscle Relaxants			3 (13.6%)
	Moderate harm	Sympathomimetics and mydriatics and cycloplegics			1 (4.5%)
Unknown drugs	**Degree of harm (severity)**				**5,381 (21.1%)**
	No harm	Low	Moderate	Severe/death	
	4715 (87.6%)	574 (10.7%)	88 (1.6%)	4 (0.1%)	
Total					**25,567**

End of Appendix 18 (medication classes involved with reported incidents and degree of harm caused by each drug category).

Appendix 19: Frequency of medication use process stage, error types and level harm involved in incidents reported in neonates under 28 days old. *(presented in multiple pages)*

Category	**Number of reports**							**(%)**
Incident reports per degree of harm (severity)	**12235 incident reports**							**47.9%**
No harm	10665							87.2%
Low	1402							11.5%
Moderate	163							1.3%
Severe/death	5							0.04%
Incident reports per medication use process stage	**Number of reports (%)**	**Degree of harm (severity) (%)**				**Error type involved**	**Number of incidents**	**(%)**
		No harm	Low	Moderate	Severe/death			
Administration / supply of a medicine from a clinical area	6465 (52.8%)	5491 (84.9%)	865 (13.4%)	104 (1.6%)	5 (0.08%)	Adverse drug reaction (when used as intended)	81	1.3%
						Contra-indication	56	0.9%
						Mismatching between patient and medicine	132	2.0%
						Omitted medicine / ingredient	1750	27.1%
						Patient allergic to treatment	4	0.1%
						Wrong / omitted / passed expiry date	197	3.0%
						Wrong / omitted patient information leaflet	2	0.0%
						Wrong / omitted verbal patient directions	5	0.1%
						Wrong / transposed / omitted medicine label	82	1.3%
						Wrong / unclear dose or strength	721	11.2%
						Wrong drug / medicine	213	3.3%
						Wrong formulation	123	1.9%
						Wrong frequency	1067	16.5%
						Wrong method of preparation / supply	142	2.2%
						Wrong quantity	452	7.0%
						Wrong route	162	2.5%
						Wrong storage	26	0.4%
						Unknown	1250	19.3%
Prescribing	3476 (28.4%)	3159 (90.9%)	285 (8.2%)	32 (0.9%)	0 (0.00%)	Contra-indication	24	0.69%
						Mismatching between patient and medicine	77	2.22%
						Omitted medicine / ingredient	292	8.40%
						Wrong / omitted / passed expiry date	7	0.20%
						Wrong / omitted patient information leaflet	3	0.09%
						Wrong / omitted verbal patient directions	7	0.20%
						Wrong / transposed / omitted medicine label	83	2.39%
						Wrong / unclear dose or strength	1011	29.09%
						Wrong drug / medicine	114	3.28%
						Wrong formulation	106	3.05%
						Wrong frequency	667	19.19%
						Wrong method of preparation / supply	28	0.81%
						Wrong quantity	302	8.69%
						Wrong route	46	1.32%
						Wrong storage	1	0.03%

						Unknown	708	20.37%
Advice	41 (0.3%)	31 (75.6%)	8 (19.5%)	2 (4.9%)	0 (0.00%)	Contra-indication	2	4.88%
						Mismatching between patient and medicine	1	2.44%
						Omitted medicine / ingredient	5	12.20%
						Wrong / omitted verbal patient directions	1	2.44%
						Wrong / unclear dose or strength	6	14.63%
						Wrong drug / medicine	1	2.44%
						Wrong frequency	5	12.20%
						Wrong method of preparation / supply	1	2.44%
						Wrong quantity	2	4.88%
						Unknown	17	41.46%
Supply or use of over-the-counter (OTC) medicine	18 (0.1%)	15 (83.3%)	3 (16.7%)	0 (0.00%)	0 (0.00%)	Mismatching between patient and medicine	1	5.56%
						Omitted medicine / ingredient	5	27.78%
						Wrong / omitted / passed expiry date	4	22.22%
						Wrong method of preparation / supply	1	5.56%
						Wrong quantity	2	11.11%
						Unknown	5	27.78%
Monitoring / follow-up of medicine use	561 (4.6%)	475 (84.7%)	79 (14.1%)	7 (1.2%)	0 (0.00%)	Adverse drug reaction (when used as intended)	13	2.32%
						Contra-indication	21	3.74%
						Mismatching between patient and medicine	9	1.60%
						Omitted medicine / ingredient	54	9.63%
						Patient allergic to treatment	1	0.18%
						Wrong / omitted / passed expiry date	27	4.81%
						Wrong / omitted verbal patient directions	1	0.18%
						Wrong / transposed / omitted medicine label	8	1.43%
						Wrong / unclear dose or strength	41	7.31%
						Wrong drug / medicine	4	0.71%
						Wrong formulation	6	1.07%
						Wrong frequency	57	10.16%
						Wrong method of preparation / supply	8	1.43%
						Wrong quantity	25	4.46%
						Wrong storage	5	0.89%
						Unknown	281	50.09%
Preparation of medicines in all locations / dispensing in a pharmacy	722 (5.9%)	643 (89.1%)	72 (10%)	7 (1%)	0 (0.00%)	Adverse drug reaction (when used as intended)	1	0.14%
						Contra-indication	3	0.42%
						Mismatching between patient and medicine	35	4.85%
						Omitted medicine / ingredient	83	11.50%
						Wrong / omitted / passed expiry date	46	6.37%
						Wrong / omitted patient information leaflet	5	0.69%
						Wrong / transposed / omitted medicine label	93	12.88%
						Wrong / unclear dose or strength	76	10.53%
						Wrong drug / medicine	24	3.32%
						Wrong formulation	30	4.16%
						Wrong frequency	35	4.85%
						Wrong method of preparation / supply	63	8.73%
						Wrong quantity	36	4.99%

						Wrong route	2	0.28%
						Wrong storage	9	1.25%
						Unknown	181	25.07%
Other/unknown	952 (7.8%)	851 (89.4%)	90 (9.5%)	11 (1.2%)	0 (0.00%)	Adverse drug reaction (when used as intended)	7	0.74%
						Mismatching between patient and medicine	15	1.58%
						Omitted medicine / ingredient	162	17.02%
						Patient allergic to treatment	2	0.21%
						Wrong / omitted / passed expiry date	20	2.10%
						Wrong / transposed / omitted medicine label	16	1.68%
						Wrong / unclear dose or strength	23	2.42%
						Wrong drug / medicine	9	0.95%
						Wrong formulation	8	0.84%
						Wrong frequency	51	5.36%
						Wrong method of preparation / supply	10	1.05%
						Wrong quantity	46	4.83%
						Wrong route	3	0.32%
						Wrong storage	16	1.68%
						Unknown	564	59.24%

Appendix 19: Continued. Medication classes involved with reported incidents in neonates under 28 days old.

Drug classes and their top three drug sub-classes involved in incidents reported in neonates under 28 days old at administration and prescribing stages.				
Medication classes involved with incidents at administration stage	**Number incidents (%)**	**Top medications subclasses**	**Number of reports**	**(%)**
Gastro-intestinal system	130 (2.01%)	Prostaglandin analogues	51	39.2%
		H2 receptor antagonists	46	35.4%
		Antispasmodics	11	8.5%
Cardiovascular system	381 (5.9%)	Sympathomimetics	137	36.0%
		Parenteral anticoagulants	86	22.6%
		Loop diuretics	47	12.3%
Respiratory system	268 (4.2%)	Respiratory stimulants	253	94.4%
		Bronchodilators	5	1.9%
		Mucolytics	4	1.5%
Central Nervous System	380 (5.9%)	Opioid Analgesics	274	72.1%
		None Opioid Analgesics	58	15.3%
		Antiepileptics	43	11.3%
Infections	2146 (33.2%)	Aminoglycosides	1029	47.9%
		Penicillins	577	26.9%
		Glycopeptides	154	7.2%
Endocrine System	158 (2.4%)	Insulins	82	51.9%
		Corticosteroids	43	27.2%
		Drugs for hypoglycaemia	15	9.5%
Obstetrics, gynaecology, and urinary-tract disorders	1 (0.02%)	Genito urinary disorders	1	100%
Malignant disease and immunosuppression	3 (0.05%)	Immunosuppressant	2	66.7%
Nutrition and blood	1206 (18.7%)	Intravenous nutrition	484	40.1%
		Parenteral fluids and electrolytes	439	36.4%
		Minerals	126	10.4%
Musculoskeletal and joint diseases	24 (0.4%)	NSAIDs	24	100%
Eye	18 (0.3%)	Anti-infectives	11	57.9%
Ear, nose, and oropharynx	1 (0.02%)	Drugs for nasal infection	5	100%
Skin	32 (0.5%)	Antifungal skin (topical)	18	56.3%
		Skin cleansers	5	15.6%
		Emollient	4	12.5%
Immunological products and vaccines	9 (0.1%)	Vaccines	6	66.7%
Anaesthesia	92 (1.4%)	Neuromuscular blocking drugs	51	55.4%
		Benzodiazepines	24	26.1%
		Intravenous anaesthetics	7	7.6%
Unknown	1612 (24.9%)	-	-	-
Multiple drug categories involved	4 (0.1%)	Multiple	-	-
Total	**6465/12235 incident reports**			**52.8%**

End of Appendix 19 (frequency of medication use process stages, error types and level harm involved in incidents reported in neonates under 28 days old).

Appendix 20: Frequency of medication use process stage, error types and level harm involved in incidents reported in children aged one-month to two-years old. *(presented in multiple pages)*

Category	**Number of reports**							**(%)**
Incident reports per degree of harm (severity)	**9,337 incident reports**							**36.5%**
No harm	8,282							88.7%
Low	967							10.4%
Moderate	84							0.9%
Severe/death	4							0.04%
Incident reports per medication use process stage	**Number of reports (%)**	**Degree of harm (severity) (%)**				**Error type involved**	**Number of incidents**	**(%)**
		No harm	Low	Moderate	Severe/death			
Administration / supply of a medicine from a clinical area	5,082 (54.4%)	4419 (86.9%)	600 (11.8%)	61 (1.2%)	2 (0.04%)	Adverse drug reaction (when used as intended)	43	0.85%
						Contra-indication	51	1.00%
						Mismatching between patient and medicine	82	1.61%
						Omitted medicine / ingredient	1443	28.39%
						Wrong storage	51	1.00%
						Patient allergic to treatment	8	0.16%
						Wrong route	202	3.97%
						Wrong / omitted / passed expiry date	197	3.88%
						Wrong / omitted patient information leaflet	5	0.10%
						Wrong / omitted verbal patient directions	9	0.18%
						Wrong / transposed / omitted medicine label	64	1.26%
						Wrong / unclear dose or strength	622	12.24%
						Wrong drug / medicine	231	4.55%
						Wrong formulation	107	2.11%
						Wrong frequency	579	11.39%
						Wrong method of preparation / supply	123	2.42%
						Wrong quantity	334	6.57%
						Unknown	931	18.32%
Prescribing	2,737 (29.3%)	2493 (91.1%)	231 (8.4%)	12 (0.4%)	1 (0.04%)			
						Adverse drug reaction (when used as intended)	1	0.04%
						Contra-indication	37	1.35%
						Mismatching between patient and medicine	37	1.35%
						Omitted medicine / ingredient	208	7.60%
						Wrong storage	4	0.15%
						Patient allergic to treatment	6	0.22%
						Wrong route	63	2.30%
						Wrong / omitted / passed expiry date	3	0.11%
						Wrong / omitted verbal patient directions	4	0.15%
						Wrong / transposed / omitted medicine label	77	2.81%
						Wrong / unclear dose or strength	965	35.26%
						Wrong drug / medicine	98	3.58%
						Wrong formulation	82	3.00%
						Wrong frequency	379	13.85%
						Wrong method of preparation / supply	35	1.28%
						Wrong quantity	223	8.15%

						Unknown	515	18.82%
Advice	58 (0.6%)	53 (91.4%)	5 (8.6%)	0 (0.00%)	0 (0.00%)			
						Mismatching between patient and medicine	2	3.45%
						Omitted medicine / ingredient	12	20.69%
						Wrong storage	1	1.72%
						Wrong / omitted / passed expiry date	1	1.72%
						Wrong / omitted patient information leaflet	1	1.72%
						Wrong / unclear dose or strength	13	22.41%
						Wrong drug / medicine	1	1.72%
						Wrong formulation	2	3.45%
						Wrong frequency	4	6.90%
						Wrong method of preparation / supply	1	1.72%
						Wrong quantity	2	3.45%
						Unknown	18	31.03%
Supply or use of over-the-counter (OTC) medicine	20 (0.2%)	20 (100%)	0 (0.00%)	0 (0.00%)	0 (0.00%)			
						Mismatching between patient and medicine	1	5.00%
						Omitted medicine / ingredient	3	15.00%
						Wrong storage	2	10.00%
						Wrong / omitted / passed expiry date	2	10.00%
						Wrong / unclear dose or strength	1	5.00%
						Wrong drug / medicine	1	5.00%
						Wrong method of preparation / supply	2	10.00%
						Unknown	8	40.00%
Monitoring / follow-up of medicine use	338 (3.6%)	288 (85.2%)	47 (13.9%)	3 (0.9%)	0 (0.00%)			
						Adverse drug reaction (when used as intended)	5	1.48%
						Contra-indication	5	1.48%
						Mismatching between patient and medicine	7	2.07%
						Omitted medicine / ingredient	35	10.36%
						Wrong storage	10	2.96%
						Patient allergic to treatment	2	0.59%
						Wrong / omitted / passed expiry date	16	4.73%
						Wrong / omitted patient information leaflet	1	0.30%
						Wrong / transposed / omitted medicine label	22	6.51%
						Wrong / unclear dose or strength	18	5.33%
						Wrong drug / medicine	3	0.89%
						Wrong formulation	8	2.37%
						Wrong frequency	25	7.40%
						Wrong method of preparation / supply	4	1.18%
						Wrong quantity	24	7.10%
						Wrong route	4	1.18%
						Unknown	149	44.08%
Preparation of medicines in all locations / dispensing in a pharmacy	614 (6.6%)	559 (91.0%)	53 (8.6%)	2 (0.3%)	0 (0.00%)			
						Contra-indication	4	0.65%
						Mismatching between patient and medicine	14	2.28%
						Omitted medicine / ingredient	95	15.47%
						Wrong storage	20	3.26%

						Wrong / omitted / passed expiry date	37	6.03%
						Wrong / omitted verbal patient directions	1	0.16%
						Wrong / transposed / omitted medicine label	67	10.91%
						Wrong / unclear dose or strength	75	12.21%
						Wrong drug / medicine	27	4.40%
						Wrong formulation	20	3.26%
						Wrong frequency	14	2.28%
						Wrong method of preparation / supply	55	8.96%
						Wrong quantity	35	5.70%
						Wrong route	9	1.47%
						Unknown	141	22.96%
Other/unknown	488 (5.2%)	450 (92.2%)	31 (6.4%)	6 (1.2%)	1 (0.2%)			
						Adverse drug reaction (when used as intended)	3	0.61%
						Mismatching between patient and medicine	11	2.25%
						Omitted medicine / ingredient	90	18.44%
						Wrong storage	33	6.76%
						Patient allergic to treatment	2	0.41%
						Wrong / omitted / passed expiry date	15	3.07%
						Wrong / omitted patient information leaflet	2	0.41%
						Wrong / transposed / omitted medicine label	8	1.64%
						Wrong / unclear dose or strength	17	3.48%
						Wrong drug / medicine	12	2.46%
						Wrong formulation	4	0.82%
						Wrong frequency	18	3.69%
						Wrong method of preparation / supply	4	0.82%
						Wrong quantity	23	4.71%
						Wrong route	1	0.20%
						Unknown	245	50.20%

Appendix 20: Continued. Medication classes involved with reported incidents in children aged one-month to two-years old.

Drug classes and their top three drug sub-classes involved in incidents reported in children aged one-month to two-years old at administration and prescribing stages.				
Medication classes involved with incidents at administration stage	**Number incidents (%)**	**Top medications subclasses**	**Number of reports**	**(%)**
Gastro-intestinal system	298 (5.9%)	H2 receptor antagonists	97	32.55%
		Antispasmodics	68	22.82%
		Proton pump inhibitors	40	13.42%
Cardiovascular system	696 (13.7%)	Loop diuretics	124	17.82%
		Parenteral anticoagulants	89	12.79%
		Potassium sparing diuretics	87	12.50%
Respiratory system	160 (3.1%)	Respiratory stimulants	91	56.88%
		Bronchodilators	21	13.13%
		Oxygen	20	12.50%
Central Nervous System	531 (10.4%)	Opioid Analgesics	308	58.00%
		None Opioid Analgesics	121	22.79%
		Antiepileptics	68	12.81%
Infections	869 (17.1%)	Aminoglycosides	209	24.05%
		Penicillins	196	22.55%
		Glycopeptides	147	16.92%
Endocrine System	174 (3.4%)	Corticosteroids	113	64.94%
		Drugs for hypoglycaemia	18	10.34%
		Insulins	16	9.20%
Obstetrics, gynaecology, and urinary-tract disorders	0 (0.0%)	Genito urinary disorders	0	0
Malignant disease and immunosuppression	23 (0.5%)	Immunosuppressant	20	86.95%
Nutrition and blood	900 (17.7%)	Parenteral Fluids and electrolytes	381	42.33%
		Intravenous nutrition	236	26.22%
		Drugs for anaemias	65	7.22%
Musculoskeletal and joint diseases	12 (0.2%)	Muscle relaxants	6	50.0%
		NSAIDs	5	41.66%
Eye	49 (0.9%)	Mydriatics and cycloplegics	21	42.85%
		Anti-infectives	20	40.81%
Ear, nose, and oropharynx	7 (0.1%)	Drugs for nasal infection	4	57.14%
Skin	27 (0.5%)	Antifungal skin (topical)	14	51.85%
Immunological products and vaccines	49 (0.9%)	Vaccines	46	93.87%
Anaesthesia	171 (3.4%)	Benzodiazepines	74	43.27%
		Neuromuscular Blocking Drugs	57	33.33%
		Intravenous Anaesthetics	31	18.13%
Unknown	1111 (21.9%)	-	-	-
Multiple drug categories involved	5 (0.1%)	Multiple	-	-
Total	**5,082/9,337 incident reports**			**54.4%**

End of Appendix 20 (frequency of medication use process stage, error types and level harm involved in incidents reported in children aged one-month to two-years old).

Appendix 21: Frequency of medication use process stage, error types and level harm involved in incidents reported in children older than two years of age. *(presented in multiple pages)*

Category	Number of reports						(%)
Incident reports per degree of harm (severity)	3995 incident reports						15.6%
No harm	3491						87.4%
Low	464						11.6%
Moderate	39						1.0%
Severe/death	1						0.03%
Incident reports per medication use process stage	**Number of reports (%)**	**Degree of harm (severity) (%)**				**Error type involved**	**Number of incidents**	**(%)**
		No harm	Low	Moderate	Severe/death			
Administration / supply of a medicine from a clinical area	2121 (53.1%)	1803 (85.0%)	294 (13.9%)	23 (1.1%)	1 (0.05%)	Adverse drug reaction (when used as intended)	21	1.0%
						Contra-indication	31	1.5%
						Mismatching between patient and medicine	19	0.9%
						Omitted medicine / ingredient	397	18.7%
						Wrong storage	24	1.1%
						Patient allergic to treatment	9	0.4%
						Wrong / omitted / passed expiry date	63	3.0%
						Wrong / omitted patient information leaflet	2	0.1%
						Wrong / omitted verbal patient directions	2	0.1%
						Wrong / transposed / omitted medicine label	34	1.6%
						Wrong / unclear dose or strength	331	15.6%
						Wrong drug / medicine	137	6.5%
						Wrong formulation	70	3.3%
						Wrong frequency	164	7.7%
						Wrong method of preparation / supply	72	3.4%
						Wrong quantity	195	9.2%
						Wrong route	136	6.4%
						Unknown	414	19.5%
Prescribing	1199 (30.0%)	1084 (90.4%)	104 (8.7%)	11 (0.9%)	0 (0.0%)			
						Contra-indication	22	1.8%
						Mismatching between patient and medicine	14	1.2%
						Omitted medicine / ingredient	100	8.3%
						Wrong route	31	2.6%
						Patient allergic to treatment	18	1.5%
						Wrong / omitted / passed expiry date	4	0.3%
						Wrong / omitted patient information leaflet	2	0.2%
						Wrong / omitted verbal patient directions	4	0.3%
						Wrong / transposed / omitted medicine label	6	0.5%
						Wrong / unclear dose or strength	474	39.5%
						Wrong drug / medicine	37	3.1%

						Wrong formulation	38	3.2%
						Wrong frequency	110	9.2%
						Wrong method of preparation / supply	14	1.2%
						Wrong quantity	89	7.4%
						Unknown	236	19.7%
Advice	20 (0.5%)	19 (95.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)			
						Contra-indication	1	5.0%
						Omitted medicine / ingredient	2	10.0%
						Wrong / unclear dose or strength	3	15.0%
						Wrong frequency	1	5.0%
						Wrong quantity	1	5.0%
						Wrong route	1	5.0%
						Wrong storage	1	5.0%
						Unknown	10	50.0%
Supply or use of over-the-counter (OTC) medicine	8 (0.2%)	8 (100%)	0 (%)	0 (0.0%)	0 (0.0%)			
						Wrong / omitted / passed expiry date	2	25.0%
						Wrong storage	2	25.0%
						Unknown	4	50.0%
Monitoring / follow-up of medicine use	159 (4.0%)	132 (83.0%)	26 (16.4%)	1 (0.6%)	0 (0.0%)			
						Adverse drug reaction (when used as intended)	3	1.9%
						Contra-indication	1	0.6%
						Omitted medicine / ingredient	15	9.4%
						Patient allergic to treatment	2	1.3%
						Wrong / omitted / passed expiry date	3	1.9%
						Wrong / transposed / omitted medicine label	13	8.2%
						Wrong / unclear dose or strength	22	13.8%
						Wrong drug / medicine	3	1.9%
						Wrong formulation	1	0.6%
						Wrong frequency	8	5.0%
						Wrong quantity	10	6.3%
						Wrong route	3	1.9%
						Wrong storage	6	3.8%
						Unknown	69	43.4%
Preparation of medicines in all locations / dispensing in a pharmacy	312 (7.8%)	286 (91.7%)	24 (7.7%)	2 (0.6%)	0 (0.0%)			
						Adverse drug reaction (when used as intended)	1	0.3%
						Contra-indication	3	1.0%
						Mismatching between patient and medicine	7	2.2%
						Omitted medicine / ingredient	45	14.4%
						Wrong storage	5	1.6%
						Patient allergic to treatment	1	0.3%
						Wrong / omitted / passed expiry date	19	6.1%
						Wrong / omitted verbal patient directions	1	0.3%

						Wrong / transposed / omitted medicine label	25	8.0%
						Wrong / unclear dose or strength	37	11.9%
						Wrong drug / medicine	13	4.2%
						Wrong formulation	16	5.1%
						Wrong frequency	5	1.6%
						Wrong method of preparation / supply	28	9.0%
						Wrong quantity	16	5.1%
						Wrong route	4	1.3%
						Unknown	86	27.6%
Other/unknown	176 (4.4%)	159 (90.3%)	15 (8.5%)	2 (1.1%)	0 (0.0%)			
						Adverse drug reaction (when used as intended)	3	1.7%
						Mismatching between patient and medicine	2	1.1%
						Omitted medicine / ingredient	16	9.1%
						Wrong storage	16	9.1%
						Patient allergic to treatment	1	0.6%
						Wrong / omitted / passed expiry date	2	1.1%
						Wrong / omitted patient information leaflet	1	0.6%
						Wrong / transposed / omitted medicine label	2	1.1%
						Wrong / unclear dose or strength	19	10.8%
						Wrong drug / medicine	2	1.1%
						Wrong formulation	2	1.1%
						Wrong frequency	4	2.3%
						Wrong method of preparation / supply	3	1.7%
						Wrong quantity	8	4.5%
						Wrong route	3	1.7%
						Unknown	92	52.3%

Appendix 21: Continued. Medication classes involved with reported incidents in children older than two years of age.

Drug classes and their top three drug sub-classes involved in incidents reported in children older than years of age at administration and prescribing stages.				
Medication classes involved with incidents at administration stage	**Number incidents (%)**	**Top medications subclasses**	**Number of reports**	**(%)**
Gastro-intestinal system	79 (3.7%)	Proton pump inhibitors	20	25.3%
		H2 receptor antagonists	19	24.1%
		Antispasmodics	16	20.3%
Cardiovascular system	290 (13.7%)	Sympathomimetics	72	24.8%
		Parenteral anticoagulants	66	22.8%
		Positive inotropic drugs	30	10.3%
Respiratory system	50 (2.4%)	Bronchodilators	33	66.0%
		Mucolytics	6	12.0%
		Sedating antihistamines	4	8.0%
Central Nervous System	411 (19.4%)	Opioid Analgesics	187	45.5%
		Antiepileptics	96	23.4%
		None Opioid Analgesics	73	17.8%
Infections	302 (14.2%)	Penicillins	62	20.5%
		Glycopeptides	42	13.9%
		Cephalosporins	28	9.3%
Endocrine System	84 (3.9%)	Insulins	36	42.9%
		Corticosteroids	28	33.3%
		Hypothalamic and Pituitary Hormones	9	10.7%
Obstetrics, gynaecology, and urinary-tract disorders	0	-	0	0
Malignant disease and immunosuppression	43 (2.03%)	Immunosuppressant	35	81.4%
Nutrition and blood	292 (13.8%)	Parenteral Fluids and electrolytes	172	58.9%
		Intravenous nutrition	62	21.2%
		Minerals	38	13.0%
Musculoskeletal and joint diseases	35 (1.7%)	NSAIDs	14	40.0%
		Drugs for rheumatic disease	8	22.9%
Eye	5 (0.2%)	Anti-infectives	3	60.0%
Ear, nose, and oropharynx	2 (0.09%)	Drugs for nasal infection	2	(100%)
Skin	7 (0.3%)	Antifungal skin	3	42.9%
Immunological products and vaccines	10 (0.5%)	Immunoglobulins	9	90.0%
Anaesthesia	128 (6.03%)	Benzodiazepines	69	53.9%
		Intravenous Anaesthetics	36	28.1%
		Neuromuscular Blocking Drugs	14	10.9%
Multiple drug categories involved	1 (0.05%)	Multiple	-	-
Unknown	382 (18.01%)	-	-	-
Total	**2121/3995 incident reports**			**53.1%**

End of Appendix 21 (frequency of medication use process stage, error types and level harm involved in incidents reported in children older than two years of age).