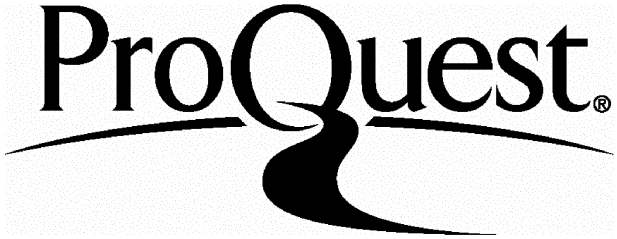
International Paediatric Drug Safety Studies

Asia Nasser Rashed

School of Pharmacy, University of London

PhD Thesis

January 2012



Plagiarism Statement

This thesis describes research conducted in the School of Pharmacy, University of London between April 2008 and September 2010 under the supervision of Professor Ian Wong and Dr Imogen Savage. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

Signature

10/01/2012

Date

To: Latifah and Nasser

Abstract

There are limited data on incidences of drug related problems (DRPs) including adverse drug reactions (ADRs) in children. The aim of this thesis is to increase knowledge of the incidence of ADRs and other DRPs and to enhance the understanding of risk factors for ADRs across several countries. This should facilitate the development of appropriate prevention strategies.

Two large prospective cohort studies were conducted; ADVISE" recruited patients from five countries to investigate the incidence and characteristics of ADRs. Multivariable regression analysis was conducted to identify risk factors associated with ADRs in hospitalised children.

The second study investigated DRPs in children attending the A&E department and/or admitted to a hospital in the Kingdom of Saudi Arabia (KSA) and the UK. ADRs and other DRPs were identified using intensive chart review.

In the ADVISE study, 1278 children were included (Australia n=149, Germany n=376, UK n=313, HK n=143, Malaysia n=300). The overall ADR incidence was 18.5% (95% CI, 16.3-20.9). There was significant variation in incidence between countries ($p<0.001$), the highest was in the UK (34.9%). The use of ≥five low risk drugs per patient or ≥three high risk drugs (e.g. opioids) were strong predictors for ADRs (OR 4.7, 95% CI, 2.4-9.3; OR 6.5, 95% CI, 2.7-16.0; respectively, $p<0.001$).

In the second study, 990 children were included (KSA n=507, UK n=483). The overall incidence of DRPs was 39.2% (95% CI, 36.1-42.3). Incidence was highest in the paediatric intensive care units (59.7%; 95% CI, 47.0-71.5). Dosing problems were the most frequent DRP (n=303, 55.5%). 80.0% (n=437) of DRPs were preventable.

Using standardised methods in both studies enabled comparison of incidences of ADRs and DRPs between countries. The variation between countries was considered to be mainly due to differences in treatment strategies.

These studies indicated that improvements to current procedures could reduce DRPs and hence improve patients' health. Also, a focus on paediatric pharmacology and pharmacotherapy within paediatric medical education is important to improve prescribing practices and paediatric patient safety.

Acknowledgments

First of all I acknowledge that in my weakness, God (Allah) was my strength.

"Those who do not thank people, they do not thank Allah"

The funding of my PhD study came from the Yamani Cultural and Charitable Foundation (YCCF) based in London, United Kingdom. I am extremely grateful to the founder Dr Yamani, whom sadly I never met in person, and Dr Thorunn Lonsdale for her help, support, and understanding.

It would not have been possible to write this doctoral thesis without the help and support of the kind people around me. Therefore, I would like to thank all those who helped, support and guided me during this work, specifically, Professor Ian Wong and Dr Antje Neubert for their supervision, guidance, support, and patience throughout the last few years and my second supervisor, Dr Imogen Savage, for her encouragement and kindness.

I would like to thank all ADVISE's participants as well as the staff in the paediatric medical wards in the hospitals in the five countries which participated in this study. Also, I would like to extend my thank you to DRPs teams (physicians, nurses, and pharmacists) in Saudi Arabia and in the UK, in particular Mr Hani Alhamdan, and Aisha Alazmi in King Abdul-Aziz Medical City in Jeddah, Saudi Arabia and to all the staff (pharmacists, nurses and physicians) at Evelina Children's Hospital for their help in relation to the DRPs study. Also, I would like to thank Ben Cross who designed the ADVISE online database which was vital for the success of the study.

Special thanks must go to Mr Stephen Tomlin at Evelina Children's Hospital for his help and support in relation to the two studies conducted in this thesis.

I am also grateful for the statistical advice received from Professor Stephen Evans and Dr Angie Wade. A special thanks must go to Dr Lynda Wilton for proof-reading this thesis and for reviewing the three manuscripts that have been submitted from this work and for her advice and support throughout this research.

A big thank you to Dr Khuloud and Dr Wafa Al-Jamal without whose support, help and friendship my PhD might not have had such a smooth start.

Thank you to all in the Centre for Paediatric Pharmacy Research (CPPR), staff and PhD students, especially Yingfen Hsia, Liz Jamieson, and Julie Bennett for their help with programming and proof-reading. Thank you to BeeLian Sim for her kindness and friendship and a special thank you to Ruth Acker and her parents for their kindness and friendship during my stay in the UK.

I thank my parents, sisters and brothers, who have given me their unequivocal support throughout, as always, for which my mere expression of thanks likewise does not suffice. Heartfelt thanks to my sister 'Fatma' who supported me financially to enable me to pursue my PhD.

Last, but by no means least, I thank my friends in Yemen, Saudi Arabia, and Great Britain, and elsewhere for their support and encouragement throughout, some of whom have already been named.

Publications and presentations

To date, the results of this thesis have been presented on the following occasions:

Peer review journals

Rashed AN, Wong ICK, Cranswick N, Hefele B, Tomlin S, Jackman J, Lee K, Hon KLE, Ong J, Ghaleb M, Chua SS, Hui TM, Rascher W, Neubert A. Adverse drug reactions in children – international surveillance and evaluation (ADVISE): a multicentre cohort study. Drug Saf (*In press*).

Rashed AN, Wong ICK, Cranswick N, Tomlin S, Rascher W, Neubert A. Risk factors associated with adverse drug reactions in hospitalised children: international multicentre study. Eur J Clin Pharmacol 2012; 68(5):801-810, doi:10.1007/s00228-011-1183-4 [Published online first: 14 December 2011].

Rashed AN, Neubert A, Tomlin S, Jackman J, Alhamdan H, AlShaikh A, Attar A, Aseeri M, Wilton L, Wong IC. Epidemiology and potential associated risk factors of drug-related problems in hospitalised children in United Kingdom and Saudi Arabia. Eur J Clin Pharmacol 2012 (*In press*).

Schramm A, Rashed AN, Hefele B, Rascher W, Neubert A. Adverse drug reactions in hospitalised children in Germany are decreasing: Results of a nice year cohort-based comparison. PLoS ONE (*Accepted*).

Rashed AN, Neubert A, Alhamdan H, Attar A, Tomlin S, Wilton L, Wong ICK. Drug-related problems found in children when they attended an emergency department in Saudi Arabia and in the United Kingdom. Pharmacoepidemiol Drug Saf (*Submitted*).

Published oral/poster presentations

The 11th International Society of Pharmcovigilance (ISOP) Annual Meeting 'Next Stop': Istanbul – Bridging the continents!' Istanbul, Turkey 26 – 28 October 2011.

Rashed AN, Neubert A, Tomlin S, Jackman J, Alhamdan H, Shaikh A, Attar A, Aseeri M, Wong IC. Drug-related problems in hospitalised children in the United Kingdom and Saudi Arabia. Drug Saf 2011; 34 (10):983. (Poster)

PRIMM: Prescribing and Research In Medicines Management (UK & Ireland), ADRs: 'Is the patient voice loud enough?' International conference, 26th June 2011, Friend House, London

Rashed AN, Wong I, Cranswick N, Tomlin S, Lee K, Chua SS, Rascher W, Neubert A. ADVISE: adverse drug reactions in children – international surveillance and evaluation: a multicentre cohort study. Pharmacoepidemiol Drug Saf 2011; Doi: 10.1002/pds.2222 [Epub ahead of print]. (Poster)

The 39th European Symposium on Clinical Pharmacy (ESCP) 2010, Lyon, France – 21-23 October 2010

Rashed A, Hefele B, Cranswick N, Tomlin S, Jackman J, Rascher W, Wong I, Neubert A. ADVISE – Adverse Drug Reactions in Children International Surveillance and Evaluation – Results from three countries Int J Clin Pharm 2011; 33 (2):344. (Poster & Short Oral presentation)

The 26th International Conference on Pharmacoepidemiology (ICPE) & Therapeutic Risk Management, Brighton, UK – August 2010

Rashed A, Lee K, Cranswick N, Tomlin S, Rascher W, Wong I, Neubert A. Drug utilization in paediatric hospital: International perspective. Pharmacoepidemiology and Drug Saf 2010; 16 (S1): S41-S42. (Poster)

Unpublished oral/poster presentations

The 6th Asian Conference on Pharmacoepidemiology (ACPE) and 2011 Anuual Meeting of the Committee of Pharmacoepidemiology of Chinese Pharmaceutical Association (AMCP-CPA), Beijing, China 28-30th October 2011.

Rashed A, Wong I, , Cranswick N, Tomlin S, Rascher W, Neubert A. Risk factors associated with adverse drug reactions in hospitalised children. Conference proceedings, http://cn93173.chinaw3.com/Final%20Program.pdf (Poster)

13th Biannual Congress of the European Society for Developmental Perinatal and Paediatric Pharmacology (ESDP): Drug Therapy in Neonates and Children - Recent Advances, Oslo, Norway 15-17 June 2011.

Rashed A, Wong I, , Cranswick N, Tomlin S, Rascher W, Neubert A. Risk factors associated with adverse drug reactions in hospitalised children: an international multicentre study (ADVISE). (Oral)

Rashed A, Wong I, Tomlin S, Jackman J, Alhamdan H, AlShaikh A, Attar A, Alazmi A, Aseeri M, Neubert A. Drug-related problems in children: a pharmacoepidemiological study in two countries. (Poster)
http://img3.custompublish.com/getfile.php/1365009.1263.xbtcreyruf/Program_13th+ESDP+Congress_OSLO_2011.pdf?return=www.esdppp.org

The 16th Annual Meeting of Japanese Society for Pharmcoepidemiology (JSPE) and the 5th Asian Conference on Pharmacoepidemiology (ACPE), Joint Meeting, Tokyo, Japan 29-31 October 2010.

Rashed A, Neubert A, Cranswick N, Lee K, Tomlin S, Hefele B, Rascher W, Chua SS, Wong I. Adverse Drug Reactions in Children: International Surveillance and Evaluation (ADVISE) - a comparison Study. Conference proceedings,
http://acpe-japan.org/forms/finalprogram.pdf (Oral)

Table of Contents

Index of Tables

Index of Figures

List of Abbreviations

ADR	Adverse Drug Reaction
ART	Adverse Reaction Terminology
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
BNF-C	British National Formulary for Children
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Science
DRP	Drug-Related Problem
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GP	General Practitioner
HK	Hong Kong
ICD	International Classification of Diseases
ICD-10	International statistical Classification of Diseases and related health problems 10^{th} revision version
ICH	International Conference on Harmonisation
IQR	Interquartile range
KAMC	King Abdulaziz Medical City
KSA	Kingdom of Saudi Arabia
NCC-MERP	National Coordinating Council for Medication Error Reporting and Prevention
NPPG	Neonatal Paediatric Pharmacist Group

NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning System
OR	Odds ratio
PCNE	Pharmaceutical Care Network Europe
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
SD	Standard Deviation
SPCs	Summary of Product Characteristics
UK	United Kingdom
US	United State
WHO	World Health Organisation
κ	Kappa

Preface

The safe use of medicines is of particular concern in both paediatric and adult patients. However, many drugs have not been tested in children, resulting in limited knowledge of their adverse effects and problems related to the use of drugs in the paediatric population when such medicines are prescribed in clinical practice. Particularly because the safety data of a drug cannot be extrapolated from adults' data to children due to the fact that the adverse drug reaction (ADR) profile and severity of ADRs are not always the same in adults and children. Furthermore, problems involving the use of drugs are different; for example in children many dosages are calculated based on the patient's weight, hence smaller doses are needed which may require changes to the formulation. Few structured investigations on large paediatric populations have been conducted to investigate the extent of ADRs and other drug related problems (DRPs) in hospitalised paediatric patients. However, thorough investigation is important to identify risk factors and areas of concern to improve treatment strategies in this vulnerable population.

Therefore, the aim of this thesis was to evaluate drug safety in children in secondary care at international level using standardised methods with a focus on ADRs. The thesis is comprised of four chapters. The first chapter, the introduction begins with a general overview of paediatric drug safety, then the epidemiology of drug-related problems based on the literature is described and an overview of the current evidence on ADRs in children is given.

The introduction is followed by the research questions based on the introduction and the overall aim of the thesis. In Chapter 2 the first study that was conducted (ADVISE) is described. This study focuses on the epidemiology and risk factors for adverse drug reactions in hospitalised children in five countries. In Chapter 3 the second study which investigated drug related problems is reported. This study was conducted in the UK and the KSA and describes the epidemiology of DRPs observed in one hospital in each country.

The final chapter of this thesis is an overall discussion of the topic and a summary of the studies' findings (Chapter 4). The final chapter also presents the overall conclusions and discusses the implications of these for healthcare professionals. Future work based on this project's findings is also discussed here.

Chapter ONE: General Introduction

This chapter will discuss the need to conduct research in paediatric medication safety. An overview of different aspects of drug safety in children is given, together with a description of the drug-related problems (DRPs) and in particular, adverse drug reactions (ADRs).

The search strategy used to identify the relevant articles for this chapter included searching the databases (MEDLINE, EMBASE, CINAHL, BIOSIS, International Pharmaceutical Abstract (IPA), and PubMed), and also conference proceedings citation Index-Science on ISI Web of knowledge. Search criteria were limited to studies on medicines or drug related problems from 1969 to April 2011 and reported in the English language. Search terms used in various combinations included:

- Children/child/neonate/infant/adolescents/paediatric/pediatric/young/baby/babies/teenage/toddler.
- Medicine related problems/medication related problems
- Drug therapy problems
- Drug related problems
- Adverse drug reactions/adverse drug events/adverse drug effects

Bibliographies of the relevant studies and systematic reviews identified were hand searched to identify any articles that might have not been captured by the search strategies.

1.1 Drug Safety in Paediatric populations

Medication use in children is a complex process with specific challenges due to the differences in physical size, physiological maturity, and cognitive skills which complicate the process of prescribing, administering, and monitoring drug therapy (Warner 1986; Ghaleb et al. 2006a). Drug safety in children is becoming an area of increasing interest. Nineteen percent of medication incidents reported to National Patient Safety Agency (NPSA) through National Reporting and Learning System (NRLS) from hospitals in the United Kingdom (UK) involved children aged 0-17 years (NPSA 2007). In the last two decades medication safety in paediatric populations has received considerable attention at a global level and has become a multi-professional concern (NPSA 2007; Vernacchio et al. 2009; Wong et al. 2004).

In general, most medicines are used safely and effectively, but problems can occur at all stages of the medication process (**Figure 1.1**). However, despite the fact that pharmacotherapy for children follows the same principles as that for adults, the developmental differences between children and adults and the complexity of the process of administering medicines to children can result in children being at greater risk when treated with medicines (Casavant & Griffith 2010). The developmental differences in children from birth to adolescence are recognised in the following classification which is widely used in studies of paediatric populations (**Table 1.1**).

Figure 1.1: Medication process (taken from NPSA 2007)

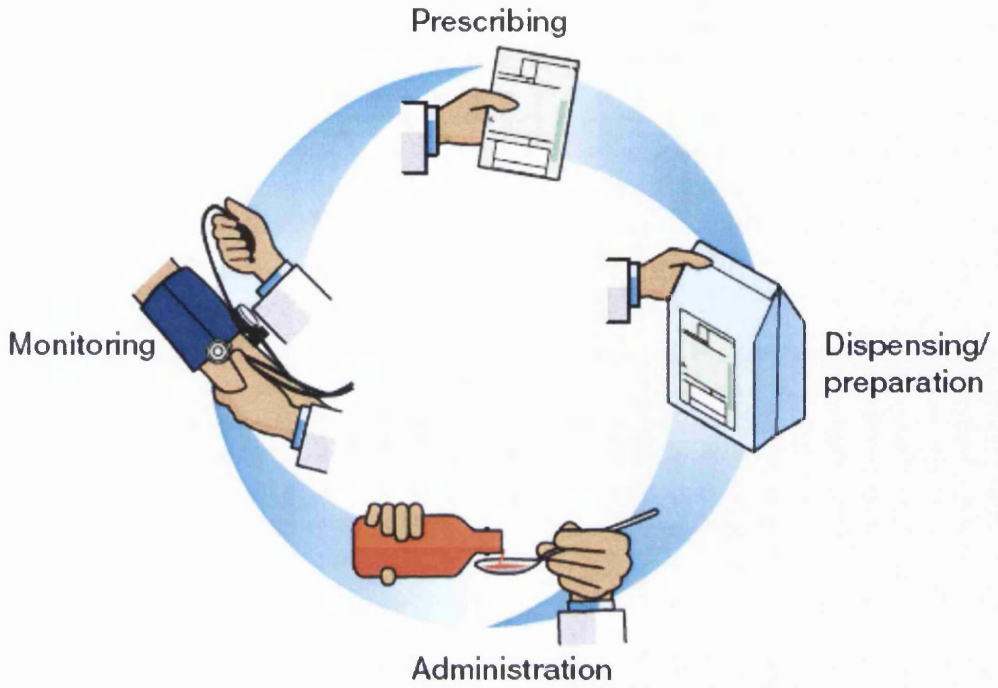


Table 1.1: Subgroups of paediatric populations, classified according to age range[a]

Group	Age
Preterm newborn infants	Born at less than 37 weeks gestation
Term newborn infants	0-27 days
Infants and toddlers	28 days to 23 months
Children	2 to 11 years
Adolescents	12 to 18 years (varies according to country/region)

[a](ICH guidelines 2001)

Children are in a constant state of growth, so monitoring their medication and reviewing all phases of therapy should be performed at regular intervals. Any change needed in a child's medication initiates another possibility for errors to happen at any stage of the medication processes (Choonara et al. 1996). Several studies have tried to classify the different types of problem related to medications that might cause harm to patients. Three main categories have been used in the literature; medication errors (MEs), adverse drug events (ADEs), and ADRs (Dean et al. 2005; van den Bemt et al. 2000a). Generally, ADRs are considered unavoidable, while MEs are considered to be potential and/or preventable ADEs.

Currently, research into DRPs is limited, especially for children who might be more susceptible to any problems which might be associated with their medications.
The following sections will give more details about problems related to drug use in the population and in particular in children, as well as an overview of ADRs.

1.2 Drug related problems

The main purpose of this section is to look at DRPs concerning the paediatric population. However, the following objectives will be addressed;

- Identify the different definitions used.
- Identify the importance of addressing and resolving DRPs in healthcare.
- Identify the causes of DRPs in paediatrics and explain why the paediatric population is vulnerable to them.

1.2.1 Drug-related problems: definition

There are a number of definitions for DRPs reported including; a rather unspecific definition;

> *"Problems relating to the use of approved drugs"* (Meyboom et al. 2000).

Strand et al (1990) defined a DRP as an "undesirable patient experience involving drug therapy that actually or potentially interferes with a desired patient outcome". In recent years this definition has been modified to by the Pharmaceutical Care Network in Europe (PCNE);

> *"an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"* (PCNE 2006).

Today this is the definition largely accepted and used in the literature. But this has not always been the case. Therefore, there is a lack of uniformity between studies in the definitions of the term 'drug-related problem' and the classification of DRP subtypes used in literature. This poses a large problem when comparing studies containing DRP data (van den Bemt et al. 2000a; van Mil et al. 2004). Studies refer to or imply the term DRP by using other terms such as 'medicine/medication related problems', 'drug-related therapy problems (DTP's)', 'drug-related hospitalisations', 'drug-related illness' (Major et al. 1998; Hewitt, 1995; Westerlund et al. 2001; Westerlund et al. 2008; Hammerlein et al. 2007; Yosselson-Superstine & Weiss 1982).

Other definitions which have been used in previous studies to contextualise problems related to drug use in patients are given in **Table 1.2**. Some of these studies have failed to state the exact meaning of such terms (Baena et al. 2006).

Table 1.2: Definitions of DRPs reported in previous studies

Study	Definition
Hepler & Strand 1990	A drug-related problem is an event or circumstance involving drug treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care.
Denneboom et al. 2005	User-related pharmaceutical care problem is non-adherence to prescribed treatment; problems with correct self-administration of medications; inappropriate medicine-taking practice.
Gordon et al. 2005	A medicine-related problem is any problem experienced by a patient that may impact on their ability to manage or use their medicines effectively.
AbuRuz et al. 2006	A treatment-related problem is an event or circumstance involving patient treatment that actually or potentially interferes with an optimum outcome for a specific patient.

1.2.2 Types of drug-related problems

A DRP encompasses many subtypes of problems such as adverse drug reactions (ADRs), medication errors (MEs) including prescribing errors, and administration errors. However, many studies do not present data on all subtypes of DRPs which are included in

the overall DRP definition, but instead choose which DRP subtypes they wish to include. There are also numerous studies that focus on just one single aspect or subtype of DRP, particularly ADRs, therefore making it impossible to compare general DRP data (Clavenna & Bonati 2009).

The main ADR definition used by many studies is the World Health Organisation (WHO) definition of an ADR;

> *"any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function"* (WHO 1972).

ADRs are synonymous with intrinsic toxicity aspects (problems that involve no errors) of DRPs (van den Bemt & Egberts 2007).

Other subtypes of DRP include medication errors, which are defined as;

> *"any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer"* (National Coordinating Council for Medication Error Reporting and Prevention 'NCC-MERP' 2011).

And prescribing errors which are defined as errors that;

> *"occur when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (i) reduction in the probability of treatment being timely and effective or (ii) increase in the risk of harm when compared with generally accepted practice"* (Ghaleb et al. 2005).

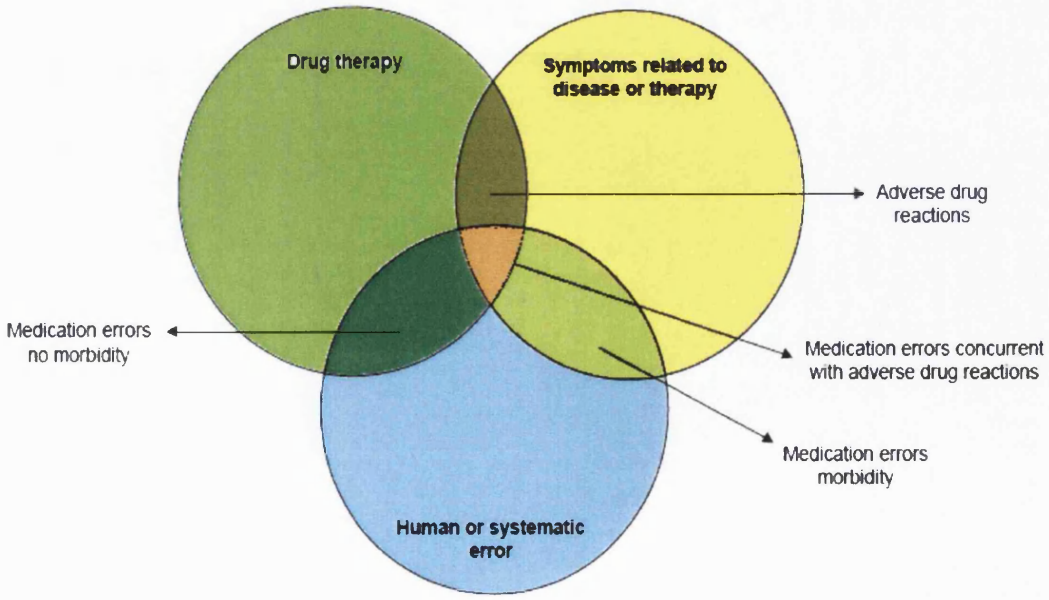
Medication and prescribing errors are linked to the extrinsic toxicity aspect of DRPs, which refers to the "problems caused by the handling of the drug either by the healthcare professional or by the patient" (van den Bemt & Egberts 2007). **Figure 1.2** shows the relationship between the problems associated with medication (DRPs).

Non-compliance (non-adherence) is another major type of DRP. Where the opposite is compliance which defined as;

> *"the extent to which a person's behaviour coincides with medical or health advice"* (Winnick et al. 2005).

Non-compliance would be; the extent to which a person's behaviour does not coincides with medical or health advice.

Figure 1.2: Relationships between the problems associated with pharmacotherapy (adapted from van den Bemt et al. 2000a)



Strand et al (1990) understood the need for uniformity and hence devised a uniform definition and classification for DRPs into eight categories. The purpose of this classification was to help in the development of a systematic method through which the pharmacist contributes significantly to the overall positive patient's outcome and to give to pharmacy practice a vocabulary consistent with that of other healthcare professions (Strand et al. 1990). Furthermore, results from studies that utilised a unified classification/definition such as Strand's system could now be communicated more clearly and compared.

Strand et al (1990) set out two criteria that must be met for a DRP event to occur:

- Patient must be experiencing, or must be likely to experience, a disease or symptomatology and
- These conditions must have an identifiable or suspected relationship with drug therapy.

If the event meets such criteria then the DRP is classified according to one of eight DRP categories (**Table 1.3**) defined by Strand et al (1990).

It is important to note that although Strand et al (1990) makes reference to non-compliance in category 7 only, categories 3 and 4 could also be interpreted as patient's non-adherence, for example if patients themselves either decrease or increase the prescribed dose or do not take the medicine at the frequency prescribed.

Table 1.3: Categories of drug-related problems according to Strand et al (1990)

	Category	Description
1	Untreated indication	For example, inadequate prescribing including untreated primary and secondary indications, disruption in continuity of treatment. Non-prophylactic or premedication prescribed, non prescribing of synergistic medicines (additional medicine therapy such as that used in active tuberculosis).
2	Inappropriate medicine prescribed	For example, medicine currently used may be ineffective, a more effective medicine may be available, patient has a known medicine allergy status, and contraindications exist for the medicine use in this patient.
3	Under-dosage	For example, suboptimal medicine where desired patient outcome not realised, suboptimal dose, suboptimal interval, suboptimal regimen, suboptimal medicine form.
4	Over-dosage	For example, inappropriate rapid increase in medicine dose, regimen for particular patient, inappropriate change in medicine form leading to toxicity, excessive use of medicine for particular patient.
5	Adverse drug reaction	Including Type A (e.g. dose dependent, common, consistent with pharmacology of the medicine and fairly predictable) and Type B reactions (idiosyncratic reaction independent of medicine pharmacology).
6	Interaction	For example, milk and iron tablets, warfarin and aspirin, effect due to enzymatic inhibition/induction, displacement of medicine from binding site.
7	Medicine not taken	For example, intentional and non intentional non-adherence, failure in medicine supply system, failure in medicine administration system, medicine formulation problems for particular patient.
8	Medicine use without indication	For example, inappropriate self-treatment, substance abuse, unnecessary drug therapy.

However, there are different classification systems that have been reported in the literature. A review conducted by van Mil et al (2004) identified the different classification systems reported in previous studies and discusses the suitability of each system for documenting DRPs. These classifications and their evaluations are summarised in **Table 1.4**.

Table 1.4: Overview of DRP classifications reported by different studies (adapted from van Mil et al. 2004)

System	Main categories (N†)	Based on clinical definition	Hierarchical problem classification	Causes classification	Validation published	Intervention classification	Used in published study
Meyboom (ABC)	3	No	No	I*	No	No	No
[1]ASHP	13	Yes	No	I	No	No	Yes
Cipolle et al.	7	Yes	No	No	No	Yes	Yes
Granada consensus	6	Yes	No	I	No	No	Yes
Hanlon	10	No	No	I	No	No	Yes
Hepler/Strand	8	Yes	No	No	No	No	Yes
Krska et al.	13	Yes	No	No	No	I	Yes
Mackie	13	Yes	No	No	No	No	Yes
[2]NCC-MERP	14	Yes	No	I	No	Yes	Yes
[3]PAS	5	No	Yes	Yes	Yes	Yes	No
[4]PCNE	6	Yes	Yes	Yes	Yes	Yes	Yes
[5]PI-Doc	6	No	Yes	I	No	Yes	Yes
[6]SHB-SEP	10	No	Yes	Yes	No	Yes	No
Westerlund	13	Yes	No	I	Yes	Yes	Yes

[1]ASHP=American Society of Health-System Pharmacist; I=cause/intervention integrated in the problem description; [2]NCC-MERP=National Coordinating Council for Medication Error Reporting and Prevention; [3]PAS=Problem, Assessment, and Solutions; [4]PCNE=Pharmaceutical Care Network Europe; [5]PI-Doc=Problem-Intervention Documentation; [6]SHB-SEP=Health Base Foundation Subjective Evaluation Plan. †N=number of main categories.

1.2.3 Drug-related problems: epidemiology

Many studies have established that the percentage of hospital admissions related to drugs was between 2% and 24% (Prince et al. 1992; Einarson 1993; Zargarzadeh et al. 2007). Winterstein et al (2002) reviewed fifteen studies (1980 – 1999) investigating drug-related hospital admissions (DRAs) and the number of preventable drug-related admissions (PDRAs). The review concluded that drug-related morbidity is a significant healthcare problem and a great proportion is preventable. However, all the studies reviewed by Winterstein et al (2002) were conducted in adult populations. For paediatric populations, although the available data are limited, drug-related admissions have been reported to be as high as 18% (Yosselson-Superstine & Weiss 1982). Furthermore, many studies have addressed drug-related emergency visits; a review of four prospective and eight retrospective studies found that 28% of the emergency visits were drug related (Patel & Zed 2002).

For pharmacists, pharmaceutical care is at the heart of pharmacy practice; with pharmaceutical care being defined as;

> *"a practice in which the practitioner takes responsibility for a patient's drug-related needs and holds him/herself accountable for meeting these needs"* (Strand 1997).

By working closely in cooperation with patients and physicians, pharmacists should constantly strive to achieve the core objectives of pharmaceutical care, which are to identify, resolve, and prevent potential DRPs (Nahata 2000; Westerlund et al. 1999). Addressing DRPs should become an increasing priority particularly, due to the

complexity of today's drug therapy, which consequently makes appropriate drug prescribing increasingly challenging (Blix et al. 2006).

However, if DRPs are left unrecognised and/or unresolved, then DRPs potentially can lead to significant drug-related morbidity and/or mortality (Lassetter & Warnick 2003). This would contradict and defeat the key objectives of pharmaceutical care and the roles of pharmacists and other health practitioners alike.

1.2.3.1 Causes of drug-related problems

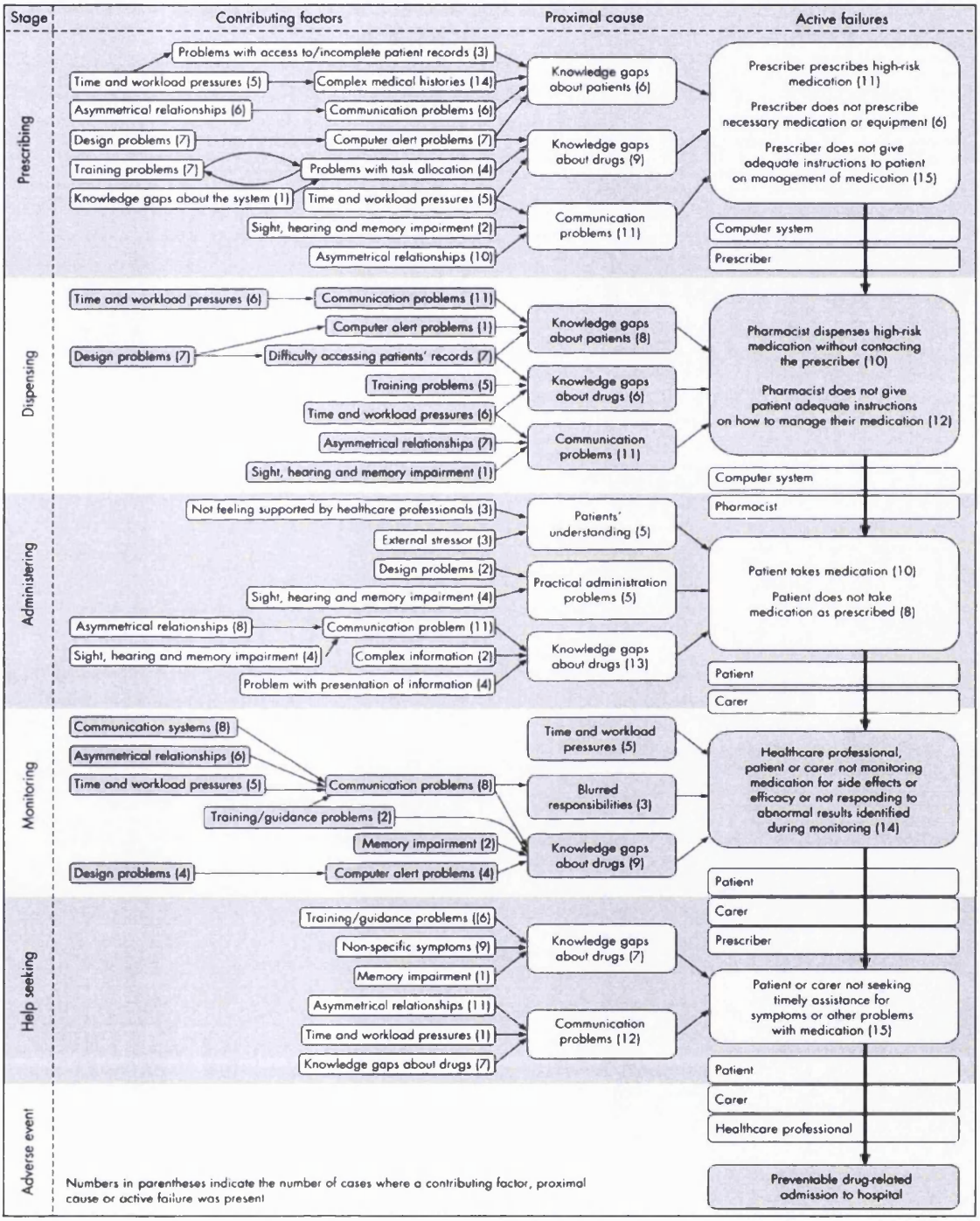
The possible causes of DRPs occurring have been reported in several studies (Howard et al. 2008; Leendertse et al. 2008; van den Bemt et al. 2000a; Hepler & Strand 1990). These include;

a) Inappropriate prescribing
b) Non-adherence
c) Communication failures
d) Knowledge gaps
e) Inadequate monitoring
f) Inadequate review of medicines use
g) Inappropriate delivery of drug, such as unavailability of the drug or dispensing errors.

A more comprehensive study on the causes of DRP is given by Howard et al (2008). This study, conducted in an adult population, sought to identify causes of preventable DRPs. The following diagram (**Figure 1.3**) taken from the study by Howard et al (2008) clearly illustrates the variety of contributing factors, proximal causes and active failures leading

to preventable drug-related admissions; most of which have root causes resulting from lack of knowledge of healthcare professionals, who are therefore partly at fault for many of the paediatric DRPs reported.

Figure 1.3: A Cascade diagram, illustrating the contributing factors, proximal causes and active failures resulting in preventable DRP admissions (taken from Howard et al. 2008)



Many DRPs are the consequences of fundamental incidents during the prescribing, dispensing, administering and monitoring processes; all of which involve healthcare professionals, including pharmacists. The cascade diagram (**Figure 1.3**) clearly depicts the central involvement that healthcare professionals have with DRPs. Contributing factors include time and workload pressures; lack of training; communication problems between healthcare professionals, GP's and pharmacists and/or hospital doctors, and communication problems between patient and healthcare professionals. These contributing factors lead to proximal causes consisting of further communication breakdown, knowledge gaps about patients and/or drugs, lack of patient understanding, and administration problems. Examples of communication failures reported in the study included the doctor prescribing high-risk medication, pharmacist dispensing incorrect drug and/or dosage, patient not taking medication as prescribed or reluctant to question healthcare professional about their medications, and insufficient counselling provided to patients by the pharmacists. Ultimately, the end result was a large number of preventable DRPs being reported.

The main findings in Howard's study were that communication problems, knowledge gaps about medications and knowledge gaps regarding a patient's medical and medication history were often lacking in healthcare professionals and therefore predisposed patients to DRPs (Howard et al. 2008).

1.2.3.2 Economic impact of DRPs

The economic implications of DRPs are mammoth, with the main costs incurred in cases where treatment of the DRP is required. This may be via additional visits to the physician,

or emergency department, hospital admissions or via long term care admissions (Lassetter & Warnick 2003; Tafreshi et al. 1999). Other costs that are incurred include changing drug therapy, additional prescriptions and monitoring tests (Tafreshi et al. 1999). A number of studies present the economic impact of DRPs. Johnson and Bootman (1995) created a 'Cost-of-Illness Model' to describe the societal cost of drug-related morbidity and mortality. They outlined costs in the ambulatory setting at $76.6 billion per year in the US; 62% of such costs had been incurred as a result of drug-related hospitalisations. The extent of such costs were highlighted again by Ernst and Grizzle (2001) using the Johnson and Bootman model, with DRPs in the ambulatory setting costing the US a staggering $177 billion annually, more than double that of the previous study, with $121 billion or 69% of the total cost accounting for hospital admissions. A study in the UK focusing on hospital bed occupancy due to DRPs (Ghose 1980) concluded that 8.8% of hospital admissions were due to DRPs, with an average DRP patient occupying a medical bed for 8 days, while Prince et al's (1992) study from the US specifies costs relating to drug-related hospital admissions at an average of $8888 per admission.

However, the astounding aspect is that many of the DRPs are preventable and the drug-related morbidity and mortality that results from preventable DRPs are critical problems that require urgent expert attention (Lassetter & Warnick 2003; Johnson & Bottman 1995). It has been reported that the preventability of DRPs ranges from 43% to 83% (Tafreshi et al. 1999; Easton et al. 1998; Easton et al. 2003; Easton et al. 2004; Roughead 1999; Winterstein et al. 2002; Al-Olah & Al-Thiab 2008). Johnson and Bootman (1995) pointed out that a significant proportion of drug-related morbidity and mortality resulting from inappropriate behaviours (such as inappropriate prescribing or non-compliance)

were preventable and preventing such cases would result in significant cost saving to healthcare organisations. Tafreshi et al (1999) interviewed 253 patients in the United State (US) presenting to the emergency department and found that the averaged cost to the institution was $1444 per preventable medication-related visit.

Therefore, there are potentially vast cost savings that can be made in healthcare systems by more fully using the skills of the pharmacist and provision of pharmacy service (Johnson & Bootman 1997). Importantly by placing particular emphasis on preventing DRPs occurring in the first place, as well as effectively identifying and resolving those DRPs that are unpreventable. Although many studies do not present solutions needed to minimize the occurrence of preventable DRPs, the studies of Guerreiro et al (2005) and of Westerlund and Marklund (2009) concluded that the economic impact of preventable drug-related morbidity are so substantial that even expensive interventions to deal with a problem may be cost-effective.

Some studies actually outline the costs associated with DRPs that could be saved; potential savings in Sweden at the national level were calculated at a colossal €358 million in 2006 (Westerlund & Marklund 2009), while two studies conducted at Australian hospitals and also a Saudi Arabian study in the tertiary hospital setting, reported that large potential savings could have been made due to preventable DRPs (Easton et al. 2004; Easton et al. 2003; Al-Olah & Al-Thiab 2008).

Therefore, it can be seen that the economic consequences of DRPs are substantial as well as their impact on healthcare organisations, which make great efforts to maintain patient health and welfare at a minimal cost.

1.2.4 Drug-related problems in paediatric population

The majority of the published studies on DRPs focus on the elderly population, and do not consider the paediatric population. However, the majority of the available paediatric studies focus only on a single subtype of DRP, mainly ADRs (Impicciatore et al. 2001; Martinez-Mir et al. 1996), without addressing all subtypes that encompass the broader definition of DRPs. Numerous studies acknowledge the limited research on DRPs in paediatric populations (Westerlund et al. 2008; Yosselson-Superstine & Weiss 1982; Easton et al. 1998; Easton et al. 2004; Easton et al. 2003; Barata et al. 2007). Although the elderly population is a sector of society vulnerable to DRPs, paediatric population also prone to DRPs.

1.2.4.1 Importance of addressing and resolving DRPs in paediatric population

Lack of suitable formulations

There are a number of factors associated with problems related to drug treatment in paediatric populations, firstly a lack of suitable formulations (Conroy 2003; Leff & Roberts 1987). Many commercially available drug formulations cater only for the adult population, so they are inappropriate for use in paediatric populations (Leff & Roberts 1987). With such a small anticipated market for paediatric formulations for certain drugs, drug companies are reluctant to invest time and financial resources, where the resulting

financial gains are minimal, plus the recruitment of paediatric patients for clinical trials also poses a difficult problem to overcome (Morkane et al. 2007; Leff & Roberts 1987). Thus today we have many dosage forms available that have not been formulated for paediatrics (e.g. sildenafil has been used to treat pulmonary hypertension in babies), and therefore many dosages must be prepared extemporaneously with an increased risk of the patient suffering from a DRP (Conroy 2003).

Despite the attempts that have been made by regulatory agencies to encourage and motivate pharmaceutical companies to conduct clinical trials involving paediatric population, the majority of drugs currently available are still lacking a license for use in children (Neubert 2011; Conroy 2011).

However, in the European Union (EU) a new paediatric regulation on the development and authorisation of drug use in children came into force in January 2007 (EMA 2007). This regulation was introduced to require pharmaceutical companies to conduct appropriate clinical trials in children. The paediatric regulation aims to improve paediatric health in Europe by facilitating the development and availability of drugs for children aged 0-17 years, and by increasing high quality, ethical research and information on drugs for children. This regulation is applicable to all new marketing authorisations for new chemical entities and to line extensions. All companies should submit their paediatric investigation plan (PIP) to the paediatric committee (PDCO) at the European Medicines Agency (EMA) before the start of phase II clinical trials. However, in certain situations, a waiver can be requested from the PDCO for a medicinal product, if for example, the product treats a condition that does not occur in children (Paediatric Regulation 2006).

An important example, of the lack of suitable formulation affecting many children worldwide today is the treatment for AIDS. Although recently there have been some improvements in antiretroviral treatment for children, under the current WHO guidelines, not all antiretrovirals can be used in children because of formulation problems (WHO 2005).

Off-label and unlicensed drug use

The consequence of limited formulations for use in paediatrics has resulted in substantial off-label and unlicensed drug prescribing for children (Conroy 2003; Impicciatore et al. 2002), which in turn has impacted on the number of DRPs reported. In children 'off-label' use refers to the "use of a drug outside the terms of the product license", whilst an unlicensed drug means "drug not licensed for use in children" ('t Jong et al. 2002). A study conducted by Kimland et al (2007) which analysed the questions received by the drug information centre in Karolinska University hospital in Sweden, reported that 31% and 24% of DRPs were due to off-label and unlicensed drug treatment, respectively. However, this study defined off-label as "any drug that was explicitly not recommended or was given for an unproven indication, dose and/or age-group in children", while unlicensed was defined as "all drugs that were not listed in the Swedish catalogue of medical products (FASS).

Potentially, the health of paediatric patients can be compromised if off-label and/or unlicensed drugs are prescribed and administered, as there is limited data on such use. ADRs are more likely to be reported for paediatric patients if unlicensed and/or off-label drugs are used, as there are no age-related ADRs profiles for these drugs (Cuzzolin et al.

2003). Many off-label and unlicensed drugs also contain undesirable excipients in their formulations, causing adverse reactions when they are administered to paediatric patients, such as benzyl alcohol induced gasping syndrome (Leff & Roberts 1987).

Drug dose calculations

Drug dose calculations for paediatric patients are more complicated than those for adults, as they are based on the individual patient and must take into consideration a number of factors such as age, body surface area, weight and condition (Ghaleb & Wong 2006b; Morkane et al. 2007). Hence miscalculations for small paediatric doses can easily lead to fatal consequences, for example a premature baby girl died 28 hours after birth as a junior doctor prescribed 15mg of intravenous morphine instead of 0.15mg, which resulted in the baby being given a 100 times overdose (Jacqz-Aigrain & Choonara 2006). Hence, the paediatric population is at an increased risk of prescribing and medication errors, compared to adults, some of which have the potential to be fatal (Wong et al. 2004).

Furthermore, dosing intervals in paediatric patients vary significantly from those in adults, due to large differences in pharmacokinetics and pharmacodynamics (Bennett & Brown 2003). Large differences in pharmacokinetics occur within the paediatric group, depending on the stage of development of the child, which varies from neonates to adolescents (Choonara et al. 1996; Conroy 2003). Also consideration must be given to the fact that children are constantly growing, hence dosing must be reviewed regularly (Barata et al. 2007).

Bearing all this in mind, dosing for paediatrics is extremely challenging and dosing errors can easily be made, thereby affecting drug and therapeutic effectiveness. This may be via prolonged dosing intervals leading to therapy failure (due to decreased drug efficacy or sub-therapeutic effects) or via too-frequent dosing (leading to drug accumulation and toxicity) with potentially fatal consequences (Choonara et al. 1996). This applies particularly to the treatment of acquired immunodeficiency syndrome (AIDs) in children, where for some currently used antiretrovirals, the dosage adjustments for weight and age are lacking or unclear and therefore result in underdosing of antiretrovirals in children (Menson et al. 2006).

Errors also can be made during prescribing of drugs, including written instructions and interpretation. Greenall et al (2009) reported a case of a physician, in the emergency department, who accidentally wrote an order for hydromorphone 4mg to be given orally on an infant's chart, which was meant to be prescribed for an adult patient. The nurse confirmed the order with the physician verbally and administered the drug to the infant. Later, after the nurse had administered the drug to the infant, she discovered the mistake because she was informed by the mother that her baby had not yet been examined by the doctor. Activated charcoal by nasogastric tube and intravenous naloxone were given and the infant was discharged next day.

Adverse drug reactions (ADRs)

Paediatric patients are more predisposed to ADRs because medicines are dealt with differently by children at different ages (premature, newborns, school children, and adolescents) as their physiology and biochemistry change with age.

Two studies (Major et al. 1998; Easton et al. 2003) identified ADRs as the most frequently reported type of DRP in paediatric populations, again highlighting that ADRs are one of the most common sub-type of DRPs affecting the paediatric population and thus need to be urgently addressed. ADRs will be discussed in detail in section 1.3.

Non-adherence

Non-adherence is another common subtype of DRP significantly affecting a large proportion of the paediatric population today and in many cases can often be the fundamental reason for therapy failure (Winnick et al. 2005). Two studies conducted by Easton et al (1998 & 2004) showed that non-adherence accounted for 56.0% and 34.6%, respectively, of DRPs in children. Another study by Yosselson-Superstine and Weiss (1982) showed that the most common classes of drugs associated with non-compliance were antimicrobial agents (64.5%), followed by anticonvulsants (22.6%). Therefore, it is evident that non-compliance is of particular concern in paediatrics, but additionally it is important to note that there are only a handful of studies that report paediatric non-compliance data, thus presenting a large gap in paediatric research of this type of DRP.

There are various reasons to explain why non-compliance is often observed within the paediatric population. Factors such as palatability (appearance, taste) and type of formulation can deter children from adhering to a medication regimen, while experiencing adverse effects can also contribute to non-compliance (Winnick et al. 2005). Therefore, in such scenarios one type of DRP (ADR) can lead to another DRP (non-compliance). Although it might have been expected that non-compliance in paediatric patients would decrease over time due to familiarity with regimen, Winnick et al. (2005)

found that the longer the duration and the more complex a medication regimen the patient has to endure, the greater the risk of non-compliance. An obvious explanation for non-compliance would be that children and some teenagers do not understand the reasons behind taking medication, due to children being too young to do so and/or due to lack of patient education (Winnick et al. 2005; Morkane et al. 2007). Kyngäs et al (2000) pointed out that psychological factors, such as the positive personal understanding of disease and treatment, attitude and therapeutic motivation heavily impacts on adolescents' compliance. Also, in the adolescent age group non-compliance can be a result of peer pressure and a desire to "fit in" (Kyngäs et al. 2000).

In many instances it is the parents themselves that are the crucial determinants of paediatric compliance, particularly for the younger paediatric age groups (Winnick et al. 2005). Parents and/or guardians are responsible for their child's welfare, as children are unable to do so by themselves, thus parents are the 'caregivers' of the communication triad (consisting of the health professional-caregiver-patient) (Sanz 2003). Parents' morals, beliefs, culture, extent of health literacy, lifestyle, and financial status will therefore impact on a child's compliance with their medication regimen and the resulting health outcomes (Winnick et al. 2005). Two cases of paediatric non-compliance taken from a study by Yosselson-Superstine and Weiss (1982) are; a mother experiencing difficulty with the directions for use of the medication for her child and another mother who thought that her child had recovered from the illness, thus she made the decision not to continue the treatment. These two examples illustrate the negative impact that parents (the caregivers) can sometimes have on paediatric compliance, with negative implications for reaching the desired health outcomes for their children.

Howard et al's (2008) study did not specifically look into the causes of DRPs in paediatric populations, but investigated the causes of preventable DRPs. The study's findings demonstrated that the potential errors of healthcare professionals, combined with the increased risk for paediatric patients, elevate the risk of DRPs occurring in children even further.

Although effective pharmaceutical care is much more challenging and demanding, due to the complex nature of the paediatric population, in many cases the risk of DRPs in paediatric patients could have been minimised by effective management by healthcare professionals, particularly pharmacists.

1.2.5 Interventions to reduce Drug-related problems

Vulnerable patients such as children and older patients, who are at higher risk of suffering from DRPs, are the groups that would most benefit from an intervention to prevent or resolve a DRP.

Identification, prevention and resolution of DRPs require a multidisciplinary team. A review of eight retrospective and four prospective studies on drug-related Emergency department (ED) visits carried out by Patel and Zed (2002) concluded that 70% of the problems were preventable. Therefore, all healthcare professionals including physicians and pharmacists should work together to provide care plans and monitor patients to avoid preventable drug-related ED visits which would result in a reduction in morbidity and mortality.

There has been special focus on pharmacist-led interventions to reduce and resolve DRPs, and also to improve patient adherence to treatment (Clifford et al. 2006; Blix et al. 2006; Westerlund et al. 2009; Hammerlein et al. 2007). Part of the professional responsibility of pharmacists is to provide efficient pharmaceutical care and improve patient safety in cooperation with other healthcare professionals and also to involve patients (Hepler & Strand 1990).

Several studies have shown the importance of direct supervision by the pharmacist on the medication process. A systematic review by Krähenbühl -Melcher et al (2007) on DRPs in hospitals involved 35 studies and concluded that inadequate pharmacy support was an important factor for medication error incidents, therefore involvement of clinical pharmacists on the wards (to supervise drug preparation and administration processes) would have an impact on reducing DRP incidence. Another systematic review was conducted to evaluate the impact of pharmacists' interventions on drug therapy in hospitalised children. This review included 18 studies and concluded that pharmacists reviewing patients' medication charts is very important and is likely to be the most effective method to improve paediatric drug therapy (Sanghera et al. 2006). However, the benefit from the pharmacist's intervention is not only in improving the patient's quality of life, but would also have an impact on the economic outcomes of the healthcare system. Hatoum et al (1988) reported that accepting and implementing the interventions made by clinical pharmacists would lead to a potential saving of $897,550 per year in a hospital's resources in the United States, while Virani and Crown (2003) reported a cost saving of $5485 annually, in the child and adolescent mental health unit of the Izaak Walton Killam

(IWK) Health Centre in Halifax Nova Scotia, due to the impact of pharmacist-initiated interventions.

Though most of the available studies had an emphasis on the role of the pharmacist in preventing or reducing DRPs, other healthcare professionals (such as nurses, physicians) also contribute to the identification and implementation of strategies to reduce DRP incidence in patients. Cunningham et al (1997) conducted a study where an educational intervention was used to reduce DRPs and drug-related admissions caused by NSAIDs in Tayside, Scotland. The intervention included written educational information to general practitioners (GPs), a patient information leaflet distributed to the patients by community pharmacists and an oral presentation to trainee GPs in the area. In the first four months post intervention, a reduction in NSAID related DRPs was observed but did not persist and the authors concluded that inappropriate NSAID prescribing decreased in the region compared to other areas during the study time.

1.3 Adverse drug reactions (ADRs)

During the last decade, several studies have highlighted the importance of ADRs in hospitalised patients, both adult and children in terms of frequency, implications for patients' safety, and costs for the hospitals (Pirmohamed et al. 2004; Impicciatore et al. 2001; Classen et al. 1997).

Several systematic reviews concerning ADRs in children and adults have been published (Lazarous et al. 1998; Impicciatore et al. 2001; Pirmohamed et al. 1998; Kongkaew et al. 2008). For the paediatric population the latest two reviews were conducted in 2010 and in

2009 (Aagaard et al. 2010; Clavenna & Botani 2009). Therefore, an in depth systematic literature review on ADRs has not been carried out for this thesis. The following sections will give a general overview on ADRs including definitions, importance of detecting ADRs, and special focus on ADRs in children.

1.3.1 General overview on ADRs

The drug therapeutic effect is the desirable effect in order to treat or prevent illness or to improve the patient's quality of life. However, most drugs produce several other effects which may be regarded as unwanted, whether they are intrinsically harmful or not. For example, certain antihistamines cause drowsiness as well as controlling the symptoms of allergies. When an over-the-counter sleep aid containing an antihistamine is taken, drowsiness is considered a therapeutic effect. But when an antihistamine is taken to control allergy symptoms during the daytime, drowsiness is considered an unwanted effect. A major global problem of drug therapy that challenges all physicians on a daily basis is the risk of ADRs (Dormann et al. 2004a).

The fact that no drug is 100% safe for all people in all situations is a truth little acknowledged or understood (WHO 1972). Given that even the most seemingly and familiar drugs, such as penicillin and aspirin, can cause serious illness, even death for some people (e.g. penicillin anaphylaxis reaction may result in death), it is not surprising that among the many thousands of other drugs on the market, there are many which can have minor or major adverse effects.

ADRs are an important clinical problem and represent a major contributor to mortality and morbidity in adults (Pirmohamed et al. 2004; Classen et al. 1997). Although most research to date has largely been confined to adults (Davies et al. 2009), the significance of ADRs in children has been increasingly recognised (Star et al. 2011). ADRs in children differ from those manifested in adults in term of frequency, nature and severity (Kunac et al. 2009; Holdsworth et al. 2003).

The thalidomide tragedy of the 1960s – when large numbers of children were born with physical deformities (including phocomelia) because their mothers took the drug during the first trimester of pregnancy – was the principal motivation behind establishing modern pharmacovigilance systems, in particular spontaneous reporting systems for monitoring suspected ADRs in many countries and also the well-known international system "Uppsala Monitoring Centre" [WHO] which collects suspected ADR reports data from member countries of the WHO Programme for International Drug Monitoring (WHO 2002). These are submitted by healthcare professionals, and in some countries by patients, to their own national authorities, who then submit them to the WHO. Such systems are the corners stone of current pharmacovigilance systems. Pharmacovigilance is defined as;

> *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems"* (WHO 2002).

A meta-analysis by Lazarous et al (1998) concluded that the average proportion of adults and children suffering from an ADR during a hospital stay was 10.9% (95% CI, 7.9%-

13.9%), of which 2.1% (95% CI, 1.9%-2.3%) were found to be serious and 0.19% (95% CI, 0.13%-0.26%) had a fatal outcome. Another study, from US, demonstrated that ADRs were associated with an average of 243 reported deaths each year, among young children, from newborn to younger than two years of age (Moore et al. 2002).

ADRs have become an important economic burden with estimated annual cost of over £400 million per year for the NHS in the UK (Pirmohamed et al. 2004). Furthermore, Green et al (2000) who conducted a study in adults, admitted to an acute medical assessment unit at the Royal Liverpool and Broadgreen University hospital in the UK, found that the absolute number of hospital admissions due to ADRs has increased, although the proportion of ADR-related admissions has remained relatively constant, and consequently the cost of these has increased.

1.3.2 Definitions and Terminology

Adverse drug reaction

The ADR definition established by WHO, which has been in use for more than 30 years, is;

> *"A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function"* (WHO 1972).

This is very similar to that given in 'Volume 9A' for the regulatory authorities in Europe (Volume 9A 2008);

> *"A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function"*

These definitions exclude adverse events caused by errors in drug administration or noncompliance (taking more or less of a drug than the prescribed amount).

The terms "adverse reaction" and "adverse effect" are used interchangeably; an adverse reaction is seen from the point of view of the patients while adverse effect is seen from the point of view of the drug. These terms should be distinguished from the term "adverse event", as this term includes medication error and other medical events that might occur during the therapy process (Edwards & Aronson 2000). **Table 1.5** shows other related terms and definitions that have been used in other studies.

Table 1.5: Related terms and definitions (taken from Edwards & Aronson 2000)

Term	Definition
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug.
Adverse Event / Adverse Experience	Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.
Side Effect	Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.

1.3.3 ADR Classifications

There are different classifications of ADRs available in various studies. ADRs form the intrinsic toxicity aspect of DRPs; intrinsic toxicity is caused by the "interaction of the pharmaceutical, chemical and/or pharmacological characteristics of the drug itself and the human biosystem" (van den Bemt & Egberts 2007). The more common classification is the classification proposed by Rawlins and Thompson (1991). In this classification, ADRs were divided into two types:

- Dose-related reactions (type A); pharmacological reactions which are common and related to the drug's desired effect. Examples are toxic effects or side effects.
- Non-dose-related reactions (type B); idiosyncratic reactions that are uncommon, not predictable and unrelated to dose or serum drug concentration. Examples are immunological reactions.

Another four categories have been added to this classification by Edwards & Aronson (2000);

- Dose and time related reactions (type C); this type is associated with long-term use and involves dose accumulation. Example, hypothalamic pituitary adrenal axis suppression by corticosteroids, interstitial nephritis from the long-term use of phenacetin, and ocular toxicity due to antimalarials.
- Delayed reactions (type D); which occurred sometime after the use of the drug such as teratogenesis (e.g., fetal hydantion syndrome) or carcinogenesis (e.g., vaginal adenocarcinoma in daughters of mothers who took stilboestrol during their pregnancy in 1960s).
- Withdrawal reactions (type E); these occur at the end-of-treatment, i.e., where discontinuation is too abrupt, for example, rebound adrenocortical insufficiency, lung oedema after stopping diuretics or opiate withdrawal syndrome.
- Unexpected failure of therapy (type F); failure of treatment, often caused by drug interaction or inadequate drug dosage. Example, inadequate dose of an oral contraceptive when used with specific enzyme-inducing drugs.

To be memorised more easily these categories have been named as follows (Edwards & Aronson 2000);

- Type A ↔ Augmented
- Type B ↔ Bizarre
- Type C ↔ Chronic
- Type D ↔ Delayed
- Type E ↔ End of use
- Type F ↔ Failure

1.3.4 Factors that predispose to ADRs

Numerous studies have reported various factors that predispose to ADRs (Zopf et al. 2009; Zopf et al. 2008a & 2008b; Kanneh 2004; Thurmann 2001; van den Bemt et al. 2000b; Martinez-Mir et al. 1999). **Table 1.6** shows the risk factors most reported frequently in the literature.

Table 1.6: Most frequently reported risk factors in the literature

Reported Risk factors
Gender (Zopf et al. 2008a & 2008b)
Age (Thurmann 2001)
Number of drugs used per patient (polypharmacy) (Davies et al. 2009)
Organ dysfunction (e.g. liver or renal disease) (Sánchez Muñoz-Torrero et al. 2010)
Multiple morbidity/number of clinical diagnosis (Dormann et al. 2004b)
Serious illness (chronic diseases) (Choonara & Harris 1984)
Genetic predisposition (pharmacogenetics) (Choonara & Rieder 2002)
Newly prescribed drug during hospitalisation (van den Bemt et al. 2000b)
Duration of hospital stay (Weiss et al. 2002)
Cessation of drug on hospital admission (van den Bemt et al. 2000b)
Most often prescribed drugs (five classes); gastrointestinal drugs, central nervous system drugs, cardiovascular drugs, drugs acting on the blood, antibiotics (Impicciatore et al. 2001, Lazarous et al. 1998)
Inappropriate medication prescribing, use, or monitoring (Kunac & Reith 2005)
Altered physiology (Pirmohamed 1998)
History of previous adverse drug reactions (dos Santos et al. 2006)
Dose and duration of exposure (Holdsworth et al. 2003)
Differences in drug metabolism/distribution (Casavant & Griffith 2010)
Drug interaction (Pirmohamed et al. 2004)
Race/ethnicity (Kanneh 2004)
Body temperature , erythrocyte count, thrombocyte count (Zopf et al. 2008)

Most of the studies consider age and number of concurrent medications taken as the most important factors enhancing the risk of an ADR. For that reason more studies have been conducted on elderly patients who often have co-morbidities, than in paediatric patients (Thurmann 2001). In addition, female gender has been found to be more often related

with ADRs both in adult and paediatric patients (Zopf et al. 2009; Zopf et al. 2008b; Thurmann 2001; Martinez-Mir et al. 1999).

1.3.5 Importance of detecting and preventing ADRs

1.3.5.1 Importance of ADR detection in the general population

The importance of acknowledging ADRs comes from the fact that ADRs rank as one of the top ten leading causes of death and illness all over the world. The cost is huge both in terms of financial burden and also of human suffering. In 1994 ADRs were between the fourth and sixth major cause of death in US; where it is estimated that over 100,000 hospitalised patients die each year as a result of ADRs (Lazarous et al. 1998). Furthermore, ADRs are associated with an increase in hospital stay of two days which resulted in an increase of the average cost by approximately $2,000 per ADR in US (Classen et al. 1997). Pirmohamed et al (2004) assessed 18,820 hospitalised patients in the UK and showed that ADRs were responsible for 6.5% of all hospital admissions. Dormann et al (2004b) conducted a study in Germany on the economic impact of ADR-related hospital admissions and readmissions. Their study showed that ADRs resulted in hospitalisation of 6.2% of first time admissions and 4.2% of readmitted patients within the 18-month study period. ADR-related cost was found to be more than 350,000 Euros for the 12 month of study period. In addition, patients with ADRs had a two-fold increased risk of death (Classen et al. 1991).

1.3.5.2 Importance of ADR detection in paediatric population

The safety of medicines in the paediatric population is a key issue that requires more in-depth study (Gupta & Waldhauser 1997). Some disease processes and their treatment are more common in childhood than in adulthood, consequently, the impact of disease in the paediatric population is different from that in adults. Neonates in particular are a sub-group of paediatrics who are at an elevated risk of experiencing drug toxicity and ADRs (Choonara & Rieder 2002; Choonara et al. 1996; Warner 1986). Details were given in section 1.2.4.1.

In addition, the identification and reporting of ADRs in children is more difficult. Many children, especially young children are unable to express their feelings, or to evaluate symptoms that maybe related to their medication or to describe adverse events that they might experience. This is an important issue that makes it more difficult to detect ADRs in children, in many instances preliminary indicators of an impending ADR in a child are missed and hence an ADR occurs (Carleton et al. 2007; Morkane et al. 2007). Other reasons have been discussed in detail in the previous section (1.2.4.1) and are summarised with examples in **Table 1.7**.

Table 1.7: Examples of the reasons that distinguish children from adults

Reason	Example
Children have pharmacokinetic and pharmacodynamic differences compared to adults	Chloramphenicol causes 'grey baby' syndrome if given to neonates due to their impaired metabolism (Bennett & Brown 2003).
Children are growing and may be susceptible to developmental disorders, as well as, delayed ADRs not seen in adults	Tetracycline may permanently discolour tooth enamel if given to children during the period when their teeth are being formed (up to age 8 years), (BNFC 2011).
Efficacy of drugs in children cannot always be assumed from adult efficacy data	The dose of chloramphenicol used in infants that led to 'grey baby' syndrome was extrapolated from adult dosage (Choonara & Rieder 2002).
Lack of appropriate dosing information may lead to higher doses which may result in an increase risk of type A reaction (pharmacological reaction)	Morphine dosage in children should be calculated carefully and needs to be adjusted individually particularly in neonates as high doses of morphine may lead to serious effects such as hypoventilation (BNFC 2011).
Lack of appropriate liquid preparations	Licensed phenobarbital liquid contains 38% alcohol which is not suitable for young children especially neonates (BNFC 2011).
Excipients in adult liquid preparations may have an independent risk of ADRs	Lorazepam injection contains benzyl alcohol as preservative which is contraindicated in infants or children up to 3 years old (BNFC 2011; Lorazepam SPC 2010).
Off-label or unlicensed prescribing in children	Salbutamol tablets (2mg) licensed for use in children >3 years old, given to a 3 month child to treat bronchiolitis (Impicciatore et al. 2002). Clonidine not licensed for use in children, but it has been used in hospitals for several indications such as sedation, opioid withdrawal, ADHD[a], and for GH[b] deficiency diagnosis (BNFC 2011; Impicciatore et al. 2002).

[a]ADHD: Attention deficit hyperactivity disorder; [b]GH: Growth hormone

1.3.6 Overview on ADR studies in children

Compared to adults, there are far less data available regarding the incidence of and risk factors for ADRs in children.

The systematic collection of information regarding the frequency, severity, and types of drugs most frequently involved in ADRs in the paediatric population is of particular interest, especially since information on the risks and benefits of drugs usually comes from pre-marketing clinical trials on adults that usually do not involve children.

A recent pilot study conducted by Gallagher et al (2011) in the UK investigated hospital admissions of children as a result of ADRs and found that 4% of admissions were related to an ADR and in 71% of the cases ADRs were the direct cause of admission and 33% of the ADRs were possibly avoidable. A previous study conducted by Allen et al (1988) found that the proportion of hospital admissions prompted by ADRs increased between infancy and 5 years of age.

A systematic review and meta-analysis on the incidence of ADRs in children has shown that 2.1% of children's hospital admissions were due to ADRs (Impicciatore et al. 2001). This review showed that the overall incidence of ADRs is about 9.5% in hospitalised children and 12% of these ADRs may be serious. However, there is substantial variability in the reported incidence of ADRs which varies between 4.4% and 16.7% among studies (Impicciatore et al. 2001).

Clarkson and Choonara (2002) indicated that drug toxicity in children is different than that in adults. In their study, using yellow cards, which is the UK's spontaneous ADR

reporting scheme for monitoring safety of medicines that was introduced in 1964 after the thalidomide tragedy, found that 390 drugs were suspected to be related to 331 deaths in children aged 16 years or less. Another study done by Clarkson et al (2001), also using yellow card suspected ADR reports, showed that the types of ADRs in children in UK may be as broad as that in adults, and 26 (15%) of detected ADRs in this study were medically significant.

As stated in the previous section (1.2.4.1), another risk factor particularly attributed to paediatric drug safety is the fact that many drugs are used unlicensed or off-label. Many of the drugs prescribed for children admitted to paediatric wards in many hospitals have been found to be used off-label. Previous studies suggested that the highest risk of a severe ADR in children is associated with the off-label or unlicensed use of drugs (Turner et al. 1999). Clarkson et al (2004) conducted a study in children using yellow card reports and found that 27% of identified ADRs concerned unlicensed or off-label drugs. Some of the reported fatal ADRs were also found to be associated with medicines used off-label or unlicensed.

Several surveillance studies have attempted to determine the incidence of ADRs in children. The overall incidence reported in paediatric inpatients is between 5.6% - 16.8% (Choonara & Harris 1984; McKenzie et al. 1976; Mitchell et al. 1979). The most frequent medicines associated with ADRs in children include antineoplastics, anticonvulsants, antibiotics, steroids, and theophylline.

As expected, the incidence of ADRs in neonatal intensive care units (NICUs) is much higher. Bonati et al (1990) found a greater number of ADRs in premature infants when

any of the following factors were present: gestational age < 28 weeks, diseases such as respiratory distress syndrome, apnoea, use of mechanical ventilation, use of total parenteral nutrition, and impaired renal or hepatic function.

Le et al (2006) studied the incidence and common types of ADRs with respect to severity among hospitalised children. They found that ADRs rated higher in severity were significantly more common among reactions that led to hospital admission or occurred during surgery and were associated with certain drug classes, including anticonvulsants and antineoplastic agents. Forty percent of the identified ADRs were life threatening. Another study reported that the highest number of ADRs was associated with the administration of respiratory drugs (35%), followed by anti-infective drugs (25%) and drugs acting on the central nervous system (15%), (Martinez-Mir et al. 1996). The most common types of ADRs reported were those to do with the central nervous system (40.5%), gastro-intestinal system (16.7%) and the skin/appendages (14.3%). Of the ADRs reported in this study, a high proportion, 38%, were classified as severe (Martinez-Mir et al. 1996).

A recent study conducted on hospitalised children in New Zealand, identified 38/67 (56.7%) adverse drug events (ADEs) (which included ADRs or medication errors) which were considered preventable, and 77 potential ADEs. This study concluded that ADEs signify a substantial danger for inpatient children and a large cost burden to the healthcare sector (Kunac et al. 2009). Another study conducted in Brazil, found that the majority of the 47 detected ADRs (78.6%) were evaluated as moderate to severe, and resulted in the introduction of special treatment, or changing the drug treatment plan, and/or extending

the hospital stay of paediatric patients who experienced the ADRs (dos Santos & Coelho 2006).

Moreover, ADRs may affect children's behaviour. A report of ADRs during the use of inhaled steroids in children with asthma, in the Netherlands, showed that there is an association between the use of inhaled corticosteroids and behavioural changes in young children (de Vries et al. 2006). Alteration of behaviour (agitation, hyperactivity) was the most frequently reported ADR due to inhaled corticosteroids in these children. In this study adrenal insufficiency was the only reported potentially life-threatening ADR.

1.4 Summary of general introduction

One cannot overemphasise the importance of DRPs, due to the substantial morbidity, physical, psychological and huge economic implications they have for patients in particular and society in general, but also that for pharmacists as healthcare professionals, effective recognition, prevention and resolution of DRPs are at the heart of effective pharmaceutical care and pharmacy practice.

The major challenge of research into DRPs is that there is an overwhelming lack of uniformity in the definition and classification of DRPs, as observed across many studies. However, Strand et al's (1990) definition and categorisation of different subtypes of DRPs has allowed published studies to report DRP data more clearly, hence studies can be utilised for the purposes of DRP research; though it must be noted that to date, only a handful of studies actually have used this classification system.

The overriding opinion from many studies is that there is a need for more research into DRPs in the paediatric population, who are equally, if not at more risk of DRPs, compared to the elderly population. Paediatric patients are predisposed to DRPs for a variety of reasons; firstly due to substantial off-label and unlicensed drug prescribing for children as a result of lack of suitable formulations, leading to substantial extemporaneous preparation of medicines. Off-label and unlicensed use of drugs is particularly associated with a high proportion of paediatric ADRs.

Healthcare professionals play a vital role in DRPs in paediatrics (as well as across all ages in society); the cascade diagram (section 1.2.3.1, figure 1.3) by Howard et al (2008) clearly illustrates fundamental flaws that occur amongst healthcare professionals themselves, from the prescribing process to the administration and monitoring processes. Thus the paediatric population are at risk of all kinds of preventable and unpreventable DRPs.

As discussed in the previous sections, there is a large gap in research that focuses on DRPs in paediatrics. It would be of great benefit to understand the overall extent of DRPs, as well as to ascertain the extent of certain DRP subtypes; mainly problems at the prescribing stage and also ADRs, which are arguably two of the most important sub-types of DRP affecting large numbers of the paediatric population today. Further research needs to be undertaken on paediatric non-compliance in particular, as there are only a few studies which report non-compliance data, and additionally it would be useful to gain an appreciation of the risk factors for paediatric ADRs. Furthermore, only a few studies present us with figures on how many DRP cases could have been prevented, and such

studies often do not provide solutions for preventing DRPs. Thus, further research needs to be undertaken to explore possible ways for preventing DRPs, so we can reduce the very large impact and burden that DRPs have on our society today.

1.5 Focus of the thesis

This overview of the literature has demonstrated that DRPs are reported to occur frequently in children but there is a lack of evidence about the DRP extent, and therefore, there is a need to gain a comprehensive understanding of DRPs extent and characteristics in a broader sense in the paediatric population.

Additionally, ADRs can be regarded as the top of a pyramid containing all DRPs. There are several studies that have been conducted to determine the incidence and nature of ADRs in paediatric population. However, variation in methods, setting, design, size of studies, definitions and statistics used, make it difficult to extrapolate the data on an international level. A standardised methodology and the involvement of a wide range of countries in one cohort would significantly enhance the knowledge of DRPs in a wider context and in particular of ADRs in paediatric hospitalised patients at international level.

1.6 Research questions

The hypothesis behind the studies described in this thesis is that the incidences of DRPs/ADRs are different in different countries. Based on the above considerations the following research questions were derived for this thesis;

- What is the epidemiology of and the characteristics of DRPs in children?
- What are the predisposing factors for ADRs in children?

- What is the incidence of ADRs in hospitalised children at international level?

The overall aim of this thesis is to assess the safety of medication use in children at an international level based on data from developed and developing countries. The research questions (above) arising from this aim were investigated in two studies; ADR study (ADVISE) and DRPs study.

The specific aim and objectives for each study in this thesis are discussed in the following two chapters; ADRs in hospitalised children (ADVISE) in chapter two and DRPs in hospitalised children in chapter three.

Candidate's involvement and input to the two studies

In the ADVISE study, I joined the team at the protocol development stage. I finalized the protocol and applied for the NHS ethics approval. I designed the data collection form and conducted the study at the UK site. I designed the ADVISE website to give our collaborators and potential participants information about the study. I arranged the teleconferences and meetings with the collaborators from the participating countries when needed. Also, I followed up data collection and communicated with the involved researchers in each country. After data was retrieved from participating countries I conducted data cleaning, management, analysis, and wrote the papers.

In the DRP study, I conducted the initial literature research and wrote the protocol, which was then submitted for NPPG grant application which was successful. I contacted the KSA team and invited them to join the study. I applied for ethics amendments at the UK site and helped the KSA team with their ethics application at their site. I designed the

Access database that was used for the data collection in both countries and I trained the staff involved in the data collection in the two countries. I followed up the data collection from both countries and arranged teleconferences and meetings when needed. Also, I conducted the data collection at the emergency department at the UK site. I retrieved the data collected from the two countries and performed data management including data cleaning, analysis and wrote the papers.

Chapter TWO: Adverse drug reaction in hospitalised children

This chapter discusses a study on investigating the incidence of ADRs and potential associated risk factors in hospitalised children in five countries using pharmacoepidemiological techniques. Pharmacoepidemiology combines both the fields of pharmacology i.e. the study of the effects of drugs; and epidemiology, which is the distribution of conditions or diseases in populations, and is defined as;

> *'the study of the use of and effects of drugs in large numbers of people'* (Strom 2006).

The methodology used in the ADVISE study is given including details of data collection, study period, the study cohort and ethical approval. Statistical methods are described.

2.1 Adverse Drug Reactions in Children – International Surveillance and Evaluation (ADVISE): a multicentre cohort study

A paper on this study is currently in press for publication by the journal Drug Safety.

2.1.1 Introduction

Adverse drug reactions (ADRs) are an important clinical problem globally and represent a major contributor to mortality and morbidity in adults (Classen et al. 1997; Lazarou et al. 1998; Pirmohamed et al. 2004). Although most research to date has been confined to adults; the significance of ADRs in children has been increasingly recognised (Impicciatore et al. 2001). Children are thought to be at a higher risk of adverse drug

events including medication errors and ADRs than the adults due to their physiology and immature mechanisms for metabolising drugs (Choonara et al. 1996; Ghaleb et al. 2010). Thus ADRs in children differ from those manifested in adults in terms of frequency, nature and severity due to the distinct pharmacokinetics and pharmacodynamics of drugs in children (Leary 1991; Choonara 2006; Kearn et al. 2003). In addition children are at a higher risk for ADRs because many drugs are used without being studied adequately in this population (Neubert et al. 2004; Turner et al. 1998).

A meta-analysis of 17 studies conducted in 2001 by Impicciatore et al identified that the ADR incidence in hospitalised children is about 9.5% (Impicciatore et al. 2001). However, the confidence interval (CI) was quite large (95% CI, 6.8-12.3) indicating variation between the studies. In 2009, a review and a meta-analysis of six prospective studies of ADRs in hospitalised children conducted by Clavenna and Bonati estimated that the incidence of ADRs was 10.9%, though the CI (95% CI, 4.8-17.0) was wider (Clavenna & Bonati 2009).

Major reasons for the differences in reported ADR incidences are the varying methods used for identifying ADRs and differing definitions of ADRs (Thurmann 2001; Haffner et al. 2005). In the previous meta-analyses lower ADR incidences were reported from studies using intensified spontaneous reporting (Choonara & Harris 1984; Gill et al. 1995), compared to studies using chart review as part of their data collection (Martinez-Mir et al. 1999; Neubert et al. 2006; González-Martin et al. 1998; McKenzie et al. 1973; dos Santos & Coelho 2006). The highest incidence was reported from a study which

investigated adverse events and thus also included medication errors and overdosing (Buajordet et al. 2002).

Appendix 1 provides a summary of the studies reported in those two meta-analyses.

Moreover, previous studies and reviews have reported different factors that predispose to ADRs (Kanneh 2004; Martinez-Mir et al. 1999; Thurmann 2001; Fattinger et al. 2000; van den Bemt et al. 2000b; Zopf et al. 2008a & 2008b). In some of these studies female gender was considered as an important risk factor for ADRs (Martinez-Mir et al. 1999; Thurmann 2001; Fattinger et al. 2000; Zopf et al. 2008b). However, compared to adults fewer data are available regarding risk factors for ADRs in children (McKenzie et al. 1973; González-Martin et al. 1998; Martinez-Mir et al. 1999). Impicciatore et al's meta-analysis reported that the number of drugs administered to the children was a potential predictor for ADRs (Impicciatore et al. 2001). Other predictors, such as patient age, diagnosis and drug prescription patterns were not considered as they were not adequately reported in the studies included in the meta-analysis. A more recent qualitative review conducted by Aagaard et al (2010) provides comprehensive information on ADRs (including occurrence and characteristics of ADRs, therapeutic drug groups, category of reporter, and distribution of ADRs by age and gender) in children from prospective and retrospective studies, however, the authors did not report on risk factors.

Furthermore, although ADRs are a global problem limited research in multicentre research has been carried out in the paediatric population in different countries. It has been recognised that the nature of the population under study affects patterns of drug utilization, which in turn affects the nature and frequency of ADRs as well as increasing

the burden on the healthcare system (Choonara & Harris 1984). Most of the studies have been conducted at a national level, mainly in North America and Europe (Impicciatore et al. 2001). In Europe a disproportionate number of studies came from the UK. No studies investigating ADRs in hospitalised children were found from Asia and Australia.

Literature showed that only a few multicentre studies in adults and in children used intensive prospective chart review for ADR detection, which is considered to be the "gold standard" for data collection in pharmacoepidemiological studies (Egger et al. 2003; Dormann et al. 2004a; Bowman et al. 1996). However, these studies were conducted only at a national level (Thomas & Brennan 2000; Caamaño et al. 2005; Takata et al. 2008).

Non-standardised reporting methods and a lack of data from various countries make it difficult to extrapolate and understand the results at an international level. A standardised methodology and the involvement of a wide range of countries in one study would significantly enhance the knowledge on ADRs in paediatric hospitalised patients. In addition, a study involving hospitalized children from different countries would be an interesting population for studying potential risk factors that could predispose paediatric patients to ADRs.

Given this background, the ADVISE study (Adverse Drug Reaction in Children – International Surveillance and Evaluation) was designed to investigate the incidence and characteristics of ADRs in paediatric hospitalised patients in five countries and also to identify potential risk factors associated with the ADRs.

The study was initiated by the Centre for Paediatric Pharmacy Research (CPPR) at the School of Pharmacy, University of London in collaboration with the Paediatric University Hospital Erlangen/Nuremberg, Germany and the Royal Children's Hospital, Melbourne, Australia. Later during development of the protocol, two other countries; China (Hong Kong) and Malaysia joined the ADVISE project.

In the following sections of this chapter, the methodology, and results of the ADVISE study will be given; including the incidences of ADRs from the five European and non-European countries. Statistical analysis of potential risk factors associated with the ADRs and the findings are discussed. But, first, an overview of ADR detection methods that have been used in previous studies is given.

2.1.2 Overview on ADR detection methods

The detection of ADRs is a vital step in monitoring patient safety. Different detection methods can be found in the literature. In this section, a brief overview will be given on the common methods of ADR detection that have been used in previous studies in adults and paediatric populations from different countries, as well as identifying the strengths and weaknesses of the most commonly used detection methods.

2.1.2.1 Most commonly used methods

Below is a brief description of the methods most commonly used in previous studies;

2.1.2.1.1 Traditional method/manual method

1. Spontaneous reporting

This is the most well known and established detection method. This method has made important contributions to clinical science and to drug safety. The UK Yellow Card System is a well known example of a spontaneous reporting system. Healthcare professionals and more recently patients are advised to report ADRs to the Regulatory Authority in the UK. However, the percentage of ADRs reported by this method is very low compared to other detection methods (Bates 2002; Thurmann 2001; Jha et al. 1998). Also common ADRs are likely to be missed by this method as health professionals tend to report new or serious ADRs or unexpected ADRs more frequently (van den Bemt et al. 1999; Kimland et al. 2005; Clarkson & Choonara 2002).

2. Stimulated spontaneous reporting

Questionnaires, face-to-face or telephone interviews with patients, carers or guardians, or with healthcare professionals, have been used to enhance ADR reporting. Also, an email service has been used to encourage healthcare professionals to report ADRs. Stimulated reporting helps in identifying problems that may be perceived as being related to the drug therapy, and contributes to increase reporting of ADRs. The proportion of ADRs reported by this method is higher than that reported by spontaneous reporting method (Clarkson et al. 2004; Turner et al. 1999).

3. Intensive monitoring/chart review

This method is considered the 'gold standard method' in pharmacoepidemiological studies, although it requires more resources and prospective access to patients' charts, it

provides denominator data allowing the incidence of ADRs to be determined and risk factors to be identified. It is widely used as a data collection method in many studies in hospital populations such as those examining incidence and prevalence of ADRs (Weiss et al. 2002; Zopf et al. 2009). The literature indicates that the proportion of ADRs identified by this method is higher than that reported by other methods and also can be done in a short time (Jha et al. 1998). Also, the common ADRs are less likely to be missed using an intensive monitoring approach than with voluntary reporting methods (Gandhi et al. 2000; Thurmann 2001).

2.1.2.1.2 Computerised ADR surveillance methods

Computerised methods have been developed to help in the earlier identification of ADR and hence reduce their impact on adult and paediatric populations (Seger et al. 2007; Dormann et al. 2004a; Tegeder et al. 1999; Tavassoli et al. 2007; Neubert et al. 2006; Shalviri et al. 2007). Such methods could also identify early signs and symptoms of an ADR, and therefore help by preventing or decreasing ADR incidence.

These methods can be performed using;

1. Computerised monitoring of data from inpatient hospital information systems.
2. Signals/Alerts, such as abnormal laboratory data (e.g. elevation of liver enzymes) or the use of an antidote (e.g nalaxone for morphine overdose), or methods supported by information technology.

Moreover, using a combination of intensive monitoring with computerised surveillance methods resulted in a higher number of ADRs being detected (Azaz-Livshits et al. 1998; Dormann et al. 2000) than either method alone. Also, a study conducted by Haffner et al

(2005) found that combining the two methods resulted in detection of a higher incidence of ADRs in children (14.1%).

Another example of computerised surveillance methods to investigate ADRs is use of computerised clinical databases such as the General Practice Research Database (GPRD) and The Health Improvement Network (THIN) in the UK. These databases contain anonymised primary care records for patients from general practices in the UK and have been used to conduct studies, e.g. case control or cohort study, to monitor and examine particular ADRs to specific drugs. For example, Ackers et al (2011) conducted a retrospective cohort study using GPRD to investigate mortality rates and causes of death in epileptic paediatric patients prescribed antiepileptic drugs. The study found that of the 151 children who died, antiepileptic drugs were probably (n=2) or possibly (n=3) causally associated with the death of five children.

2.1.2.2 Summary

Methods such as spontaneous reporting, chart review and computerised monitoring were the most commonly methods used to identify and report ADRs in an inpatient and outpatient populations. **Table 2.1** summarises the detection methods that were found in the literature to be the most frequently used and also gives their advantages and disadvantages.

Based on the above and although intensive chart review was found to be expensive and time consuming, we have chosen this method for our ADR study because the proportion of ADRs reported in the population under investigation is higher than using other

methods. Jha et al (1998) conducted a study to identify ADEs using three methods to detect ADEs; intensive chart review, computer monitoring and voluntary reporting. Their study found that chart review identified the highest percentage of ADEs (65%) and the lowest percentage (4%) of ADEs was identified by voluntary reporting.

Moreover, as mentioned before, intensive chart review is considered the 'gold standard method' in pharmacoepidemiology studies. Also, unlike traditional spontaneous reporting methodology, this method is less likely to miss common adverse reactions (Thurmann 2001; Neubert & Rascher 2007).

Table 2.1: The most commonly used methods for detecting ADRs and their advantages and disadvantages[a]

Detection Method	Advantages	Disadvantages
Spontaneous reporting	Find ADRs and potential ADRs Inexpensive	Under-reporting (low detection rate of ADRs) More people need to report
Stimulated spontaneous reporting	Targets major issues Inexpensive	Finds major adverse events but not daily issues or trends Cannot be done on a routine daily basis
Intensive monitoring/chart review	High yield of ADRs detected in short time Best for detecting prescribing errors Effective in detecting symptom-related ADRs Provides denominator data No reporting bias	Requires dedicated observers Expensive as it requires employing more staff to inspect each element in a patient`s record and to conduct training for chart reviewers Time consuming Needs medical staff to document events that occur Highly dependent upon reviewers and their ability to conduct adequate chart review and distinguish between ADRs and other effects of drugs in the medical records as well as consistency in extracting data from charts

Continued..

Table 2.1: Continued

Detection Method	Advantages	Disadvantages
Computerised monitoring	Inexpensive More sensitive Can be done automatically based on rules (using signals or trigger tools) More effective in detecting ADRs associated with laboratory data and certain medications Effective in detecting more severe ADRs Improves patient outcomes as a result of earlier detection of ADRs	Requires electronic medical records and programming Number of identified ADRs depends on integrated information system links Low specificity
Intensified monitoring supported by computerised system	High rates of identifying ADRs saves hospital resources More effective in detecting ADRs associated with laboratory tests Utilises automated triggers or signals More sensitive and can help in detecting an ADR early in the time of ADR occurrence Effective in detecting more severe ADRs Improves patient outcomes as a result of earlier detection of ADRs	Requires electronic medical records and programming Needs trained reviewer

[a]Dorman et al. 2004a; Dorman et al. 2004b; Azaz-Livshits et al. 1998; Neubert et al. 2006; Haffner et al. 2005; Thuermann et al. 2002; Ferranti et al. 2008; Dormann et al. 2001; Levy et al. 1999; Jha et al. 1998; Jha et al. 2008; Temple et al. 2004; Gandhi et al. 2000; Bates, 2002

2.1.3 Aim and objectives

To investigate the incidence and characteristics of ADRs in paediatric hospitalised patients in five European and non-European countries. The objectives were to identify the incidence of ADRs in each study site, to compare the incidences of ADRs in all participating countries, to determine the overall incidence of ADRs and to identify potential risk factors for ADRs using logistic regression.

2.1.4 Methods

2.1.4.1 Study design

A multi-centre cohort study was conducted in paediatric general medical wards in five hospitals in five countries [Australia, Germany, China (Hong Kong "HK"), Malaysia and the United Kingdom (UK)]. In each country data were collected over a three-month period, with the exception of Australia (see below), between 1st October 2008 to 31st December 2009.

2.1.4.2 Study setting

Data were collected prospectively from general paediatric wards which had at least 20 beds, over a period of three months except in Australia where, due to limited resources, data collection was over one month only. **Table 2.2** gives details of participating hospitals and individual study wards.

Table 2.2: Characteristics of participating study's wards

	Australia	Germany	China	Malaysia	UK
City	Melbourne	Erlangen	HK	Serdang	London
Name of hospital	Royal Children's Hospital	University Hospital for Children & Adolescents, University of Erlangen-Nuremberg	Prince of Wales Hospital	Serdang Hospital	Evelina Children's Hospital
Type of Hospital	Paediatric hospital	Paediatric hospital	General hospital	General hospital	Paediatric hospital
Number of beds total	~250	120	1200	620	180
Number of beds on study ward	36	24	30	28	40

2.1.4.3 Study population

All children (0-18years) admitted to the study ward for at least 24 hours over a three month study period with the exception of Australia, where data were collected over a one month period only due to resource limitations. Patients with a hospital stay of less than 24 hours were excluded because of insufficient time to obtain enough information to identify and classify an ADR.

2.1.4.4 Sample size calculation

A previous meta-analysis suggested an incidence of ADRs in hospitalised children of 9.5% with a 95% Confidence Interval (CI) of 6.8-12.6 (Impicciatore et al. 2001). Assuming the incidence of patients with ADRs is 9% (95% CI, 6% - 12%), the sample size calculation was performed using the following formula adapted from Wade (2001) after discussion with the author (personnel communication), who is a statistician from UCL Institute of Child Health.

$n = [4 \times 1.96 \times 1.96 \times p \times (1 - p)] / w^2$

$n = [4 \times 1.96 \times 1.96 \times 0.09 \times 0.91] / 0.06 \times 0.06$

Where:

n= number of patients

p= probability value

w= CI width

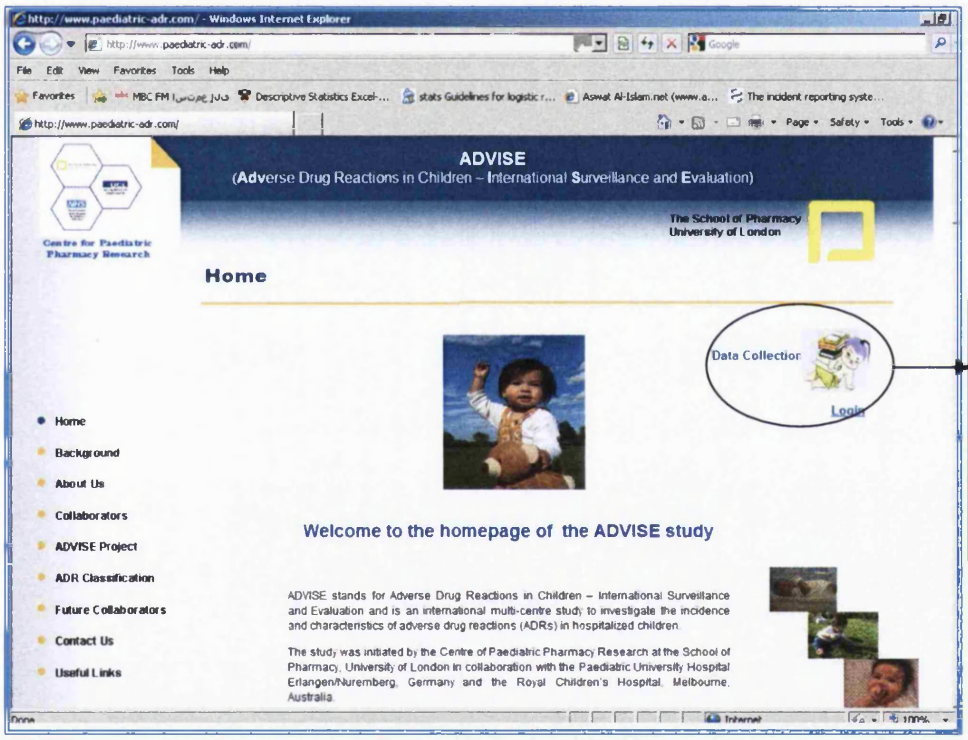
Consequently, considering practicalities such as the resources needed from the participating sites, the number needed for each site will be 350 patients (rounded up to the nearest whole number).

2.1.4.5 Database and data collection

Data were collected in a standardised format using an online database application designed specifically for this project (www.paediatric-adr.com), (**Figure 2.1**). The data collected comprised patient demographics (age, gender), medications (dosage, route of administration, frequency, start and end date of each prescription), and admission

diagnosis (data collection form is given in Appendix 3). For prescribed drugs, each chemical compound or combination of compounds [based on the Anatomical Therapeutic Chemical (ATC) classification] was considered only once per patient irrespective of whether the dose was changed or prescriptions were repeated during the hospital stay. Fluid and electrolyte infusions and parenteral nutrition were not documented.

Figure 2.1: ADVISE website homepage



[a]Centre for Paediatric Pharmacy Research (CPPR) controls the website and has access to all the data from all countries

For standardisation the following established international terminologies were used:

Medications

The WHO-ATC classification was used for medications. The ATC classification classifies drugs into distinct groups at five different levels according to the organ system

which they act on and their therapeutic, pharmacological and chemical properties (WHO Collaborating Centre for Drug Statistics Methodology 2011), (**Figure 2.2**).

Figure 2.2: Example of WHO-ATC hierarchy for classification of medications

Diazepam – N05BA01

N Nervous system (Anatomical group, 1st level)
N05 Psycholeptics (Therapeutic subgroup, 2nd level)
N05B Anxiolytics (Pharmacological subgroup, 3rd level)
N05BA Benzodiazepine derivatives (Chemical subgroup, 4th level)
N05BA01 Diazepam (Chemical substance, 5th level)

Diagnoses

International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) was used for classifying diagnoses (WHO 2007). The ICD is a hierarchical classification system, which includes twenty two chapter 'blocks' used to classify diseases. It has become an international standard for the recording of clinical data for epidemiological and quality purposes. In addition, it provides the basis for the compilation of the World Health Organisation's national mortality and morbidity statistics. The first edition, known as the International List of Causes of Death, was implemented for use by the International Statistical Institute in 1893. In 1948 the ICD was created, encompassing causes of morbidity in addition to mortality, and the World Health Organisation (WHO) assumed responsibility for the management of the classification system. ICD-10 is the latest revision in the series, having been approved by

the forty-third World Health Assembly in May 1990 and introduced for use from 1994 (WHO 2007).

ADR classification

ADRs were classified according to WHO Adverse Reaction Terminology (WHO-ART), which classifies ADRs into system-organ classes (e.g. gastro-intestinal system) and into preferred terms for the ADRs. WHO-ART has been developed over more than 30 years for coding ADRs (WHO 2003).

In order to establish consistent data collection across all participating sites, a flowchart and check list for chart review were provided (**Figures 2.3, 2.4**). The data were entered onto an electronic database at each site and retrieved, managed and analysed at CPPR.

Figure 2.3: ADVISE study flowchart

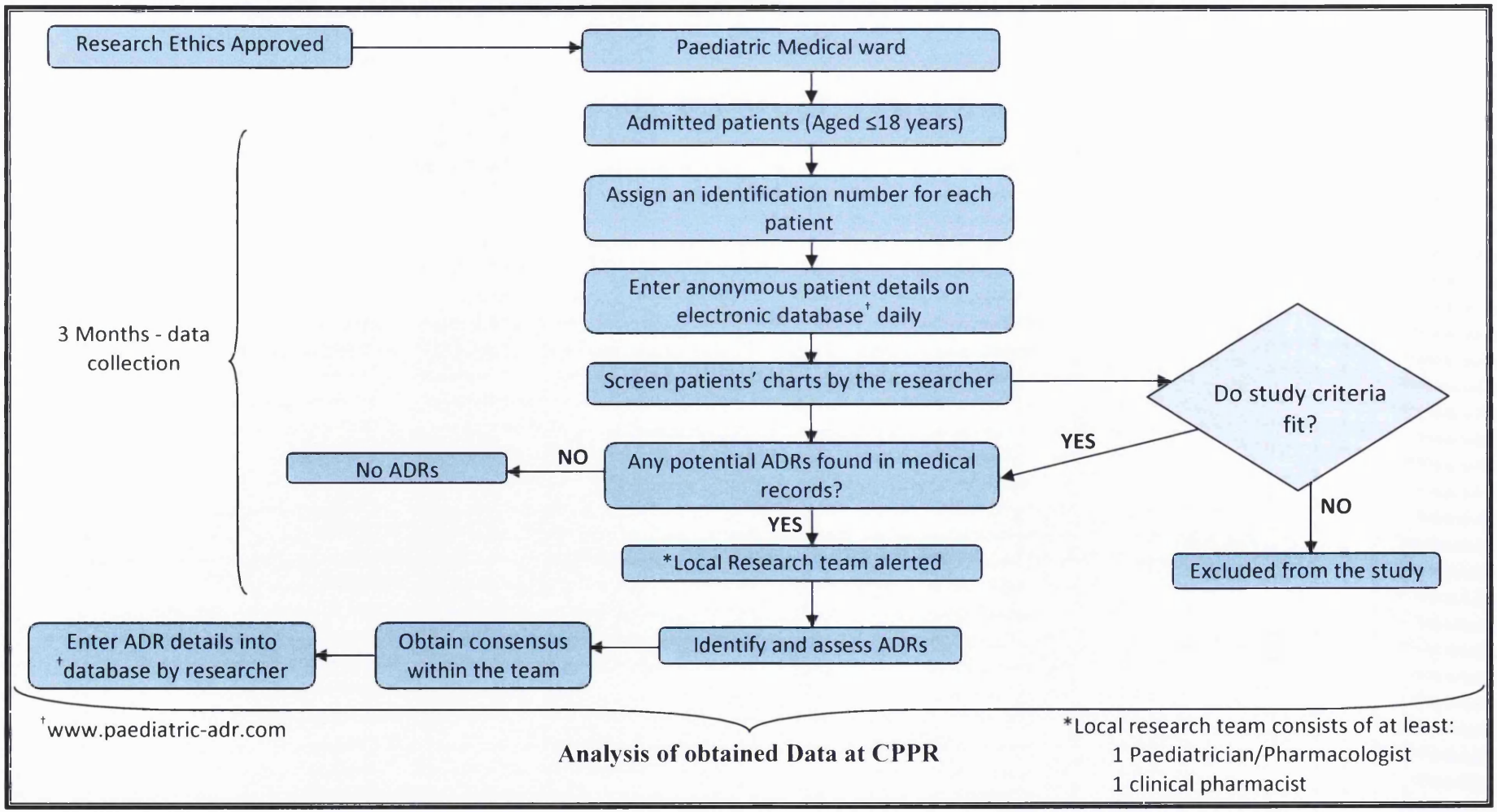
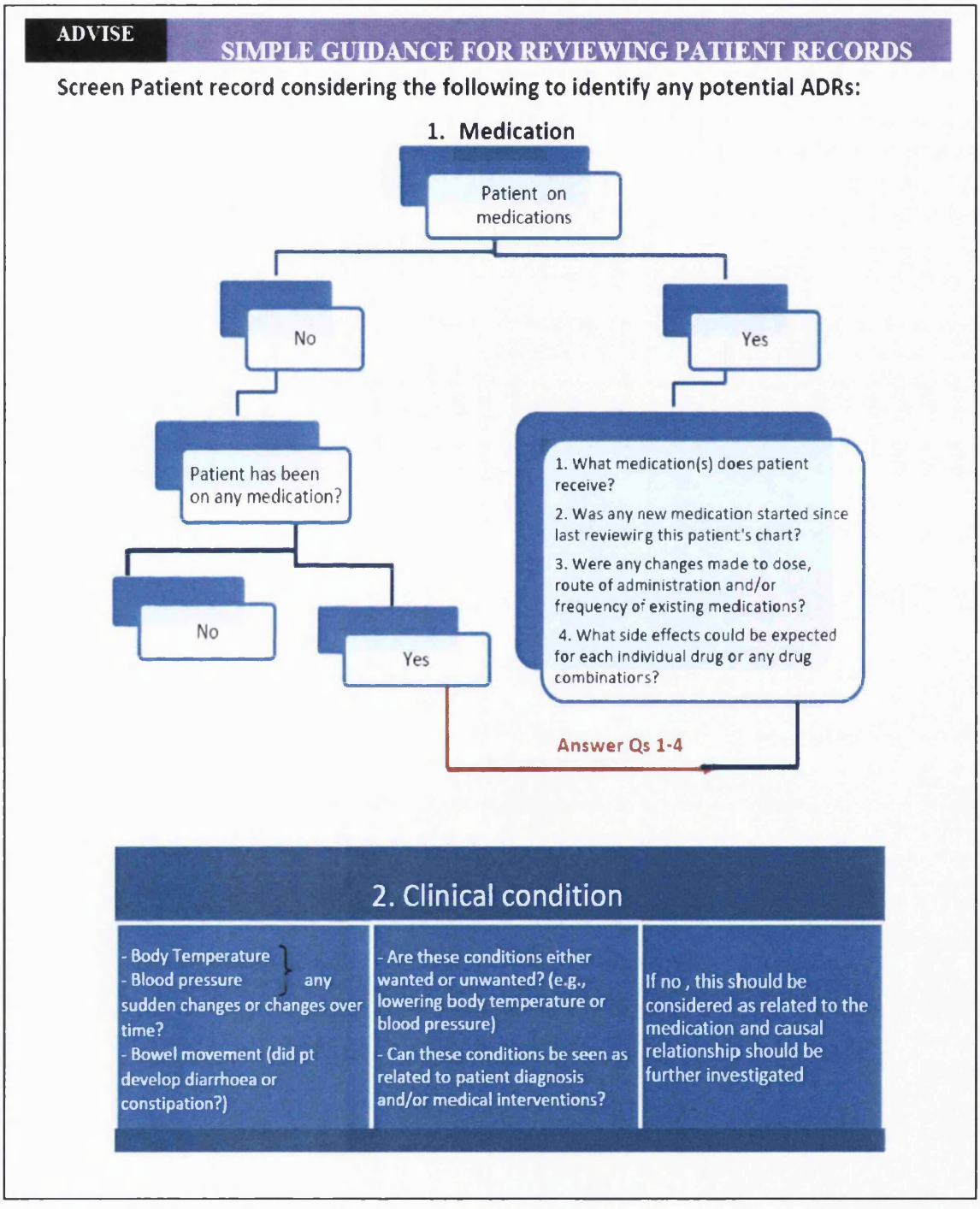
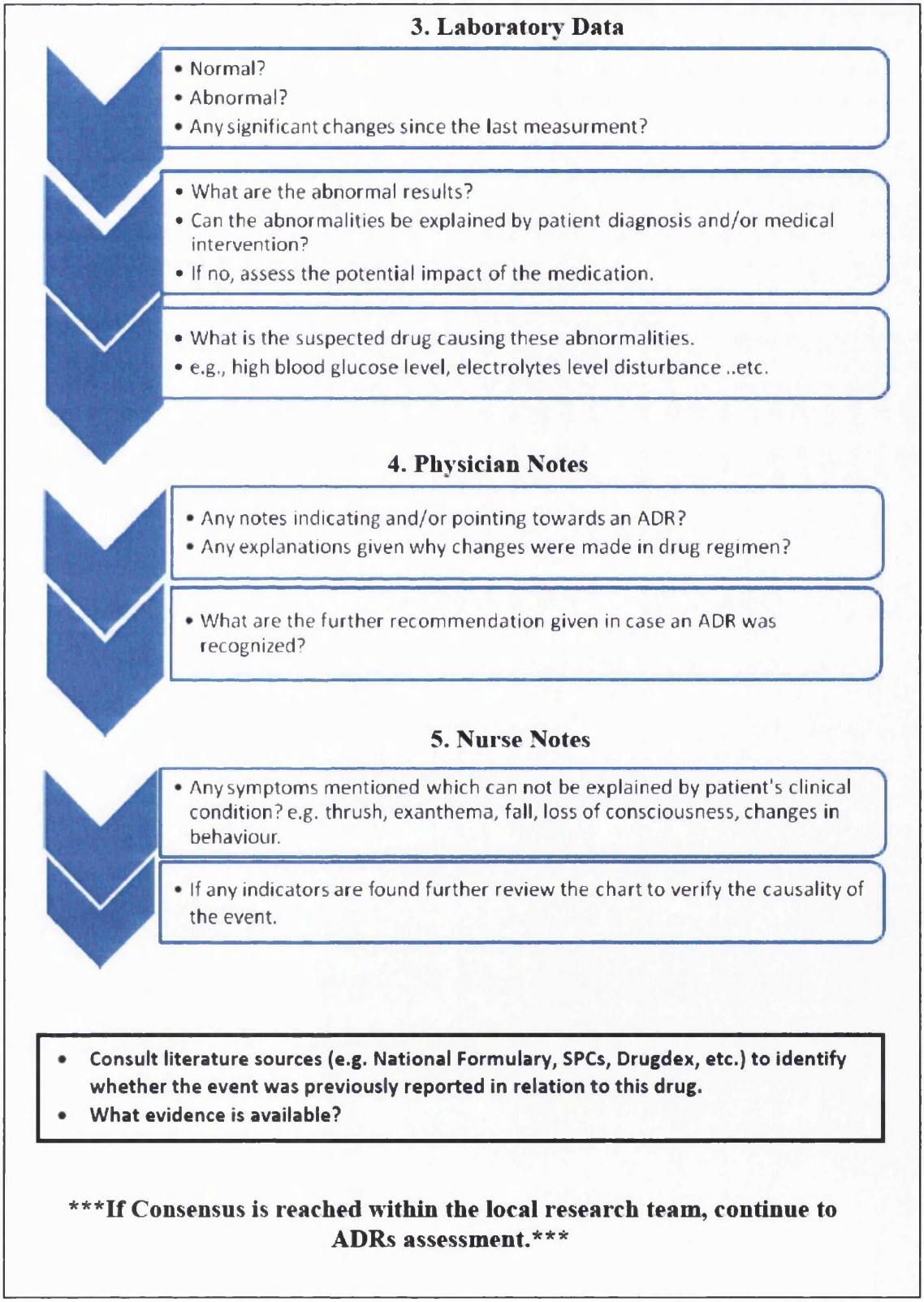


Figure 2.4: Check list for reviewing patient records



Continued..

Figure 2.4: Continued



2.1.4.6 High-risk drugs definition

Based on drug groups being described as most frequently involved in the occurrence of ADRs in the literature (Pirmohamed et al. 2004; Thuermann et al. 2002; Thurmann 2001; van der Hooft et al. 2008; Temple et al. 2004; van den Bemt et al. 2000b) and the opinions of two paediatric clinical pharmacologists involved in the project (Professor Wolfgang Rascher from Germany and Associate Professor Noel Cranswick from Australia) we defined five drug groups (ATC Therapeutic level) as high risk which comprised of analgesics (N02), antiepileptics (N03), antibacterials and antimycotics for systemic use (J01, J02), corticosteroids for systemic use (H02), and immunosuppressant agents (L04). For the risk factor analysis all other prescribed drugs were grouped as low risk drugs.

2.1.4.7 Associated diagnoses

To identify the potential impact of diagnosis on the occurrence of ADRs, the main diagnosis for each patient was recorded based on WHO-ICD10 (WHO 2007). The higher levels of ICD10 'blocks' were used in the analyses. The inclusion of diagnoses in the multivariable analysis was based on the significance of the association between each 'block' of disease and the occurrence of ADRs in the univariable analysis.

2.1.4.8 Identification of ADRs

ADRs were identified by intensive chart review, which has been recognised as the 'gold standard' method for obtaining data which will be used in the calculation of the incidence of ADRs (Weiss et al. 2002; Murff et al. 2003).

One researcher in each team, who was either a qualified pharmacist or a clinician, screened all patient records daily to identify all events potentially related to medications. All suspected ADRs were presented to the local research team consisting of at least one clinical pharmacist and one paediatrician/paediatric pharmacologist. The team reviewed the patient record including laboratory data and assessed whether the event was an ADR as defined by the WHO Technical Report No 498 as;

> '*any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function'* (WHO 1972).

A final decision was made by consensus after thorough discussion within the group. All events evaluated by the local research team as an ADR were documented in the study database and electronically linked to the patient's anonymised data. The process is summarised in **Figures 2.4** and **2.5**.

2.1.4.9 Assessment of ADRs

All identified ADRs were assessed using previously established algorithms. The causality of ADRs was estimated using the Naranjo score algorithm (Naranjo et al. 1981) while severity was assessed using a weighted score employed by Dormann et al (2000). **Tables 2.3 and 2.4** show the criteria for these algorithms.

Table 2.3: Naranjo's causality algorithm[a] for ADRs

Criteria	Yes	No	Unknown
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administrated?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or specific antagonist was administrated?	+1	0	0
Did the adverse event reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than drug) that could on their own have caused the reaction?	-1	+2	0
Did the adverse event reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

[a]The achievable scores are between –4 and 13: Unlikely ADR: scores ≤ 0; possible: 1 to 4; probable: 5 to 8; certain/definite: ≥ 9

Table 2.4: Severity assessment scales[a] (Dormann et al. 2000)

Criteria	Yes	No	Unknown
Did the adverse drug reaction impair the patient's quality of life?	+1	-1	0
Was the (immediate) discontinuance of the drug necessary or recommended?	+1	-0	0
Was the use of a different drug or other therapy necessary or recommended?	+1	0	0
Did the adverse drug reaction prolong or lead to hospitalisation?	+1	0	0
Did the adverse drug reaction cause temporary malfunction of an organ (system)?	+2	0	0
Did the adverse drug reaction cause temporary inability to work?	+1	0	0
Did the adverse drug reaction lead to permanent inability to work?	+2	0	0
Was the adverse drug reaction:			
Potentially dangerous (treated on ward)	+1	0	0
Potentially life threatening (treated on a critical care unit)	+2	0	0
Or fatal?	+3	0	0

[a]A total score of 1 to 4 indicates a mild; 5 to 8 a moderate, and >8 a severe ADR.

Whereas severity usually describes the intensity of an event (i.e. mild, moderate, severe), seriousness is based more on patient/event outcome or action criteria (ICH Guideline 1995). Widely established and accepted criteria to assess seriousness are given by the International Conference on Harmonisation (ICH) with input from the Council for International Organizations of Medical Science (CIOMS) (ICH Guideline 1995) on which we based the assessment of seriousness. **Table 2.5** shows the adapted seriousness criteria.

Table 2.5: Seriousness criteria[a]

A serious adverse event is:
1. Fatal
2. Life-threatening
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. Results in persistent or significant disability/incapacity

[a]Adapted from: ICH Guideline (1995).

Furthermore, we also established the preventability of each ADR using the criteria provided by Schumock and Thornton (1992). **Table 2.6** shows Schumock and Thornton preventability criteria.

Table 2.6: Preventability criteria (Schumock & Thornton 1992)

"Answering yes to one or more of the questions suggests that the ADR in question may indeed have been preventable";
1. Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?
2. Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?
3. Was the required therapeutic drug monitoring or other necessary laboratory test not performed?
4. Was there a history of allergy or previous reactions to the drug?
5. Was a drug interaction involved in the reaction?
6. Was a toxic serum drug level (or laboratory monitoring test) documented?
7. Was poor compliance involved in the reaction?

Additionally, the predictability of ADRs was assessed using the classification published by Rieder (1994). Rieder classifies ADRs as being predictable or not based on the mechanism of action of drug and patient's response. **Table 2.7** shows Rieder classification

Table 2.7: Rieder (1994) Predictability classification

Mnemonic	Features	Examples
Type of reaction: Predictable		
Toxicity	Refers to the untoward effects produced on specific organ systems or to the patient in general when drugs taken in supratherapeutic amounts (overdose)	Gentamicin in supratherapeutic doses produces ototoxicity and nephrotoxicity. Paracetamol in supratherapeutic doses produced hepatotoxicity
Side effect	Biological responses produced by medication, often related to the desired effect. Common	Tremor by ß2-agonists
Interaction	Drug-drug interaction	Cimetidine inhibits specific enzymes of cytochrome P450 , phenytoin taken concurrently will have exaggerated effects
	Drug-disease, genetic polymorphisms and enzyme activity	Amoxicillin and maculopapular rash when given during the course of infectious mononucleosis. Pharmacokinetic changes produced by renal, hepatic diseases or genetic changes
	Drug environment	Metabolic changes induced by the environment. Factors like body weight, sex, age, dosage forms, time of administration influences the response to a drug.
Secondary effect	Predictable but not inevitable consequences of the biological activity of a drug.	Clindamycin and pseuomembraneous colitis. Penicillin in syphilis associated with Jarish-Herxheimer reaction.

Continued..

Table 2.7: Continued

Mnemonic	Features	Examples
Type of reaction: Unpredictable		
Intolerance	Subsets of patients. Drug level within the therapeutic range. Involves an exaggerated response which in most patients is mediated on pharmacological basis	Erythromycin causes nausea and vomiting. Aspirin causes symptoms of salicylate toxicity (tinnitus)
Idiosyncratic	Uncommon ADRs which do not fit into any of the other classifications described. Unknown mechanism. These ADRs are often the consequence of pharmacogenetic variations in drug bioactivation and drug metabolite, and detoxification. This category is a "waiting box" until mechanism of action is better known	Hepatitis associated with anticonvulsants Halothane hepatitis Sulphonamides associated with Stevens-Johnson Syndrome (SJS).
Immuno-Allergic	Anaphylactic reaction	Hypersensitivity or allergic/immunological reactions depend on the four pathomechanisms described by Coombs and Gell (1968).
	Pseudoallergic Anaphylactoid reaction	Involves a direct release of inflammatory mediators. At the first manifestation of such a reaction, they are absolutely unpredictable, often serious.

For each reported ADR the time of occurrence, e.g. before, during admission or leading to admission was documented.

All drugs that were likely to be involved in an individual ADR were documented. If there was more than one drug involved, the most likely one was considered as the main ADR causative drug. This decision was based on pharmacological properties and side effect profiles of the drug from the literature and the Summary of Product Characteristics (SPCs).

2.1.4.10 Reliability of ADR detection and assessment across countries

The effectiveness of the methodology for ADR detection and its reliability across the study sites was assessed. We randomly selected 10 patients from each study site and a second reviewer (Dr Antje Neubert) assessed the selected patients with respect to the presence of an ADR. In order to assess the reliability of ADR assessment (causality/severity) we randomly selected 20 ADR cases from the study cohort and sent them to four raters for re-assessment using Narajo scale for causality and Dormann et al (2000) for severity.

2.1.4.11 Statistical analysis

2.1.4.11.1 Descriptive statistical analysis

Statistical analyses were performed using Stata 11 (StataCorp, College Station, Texas, USA). Since the data did not exhibit a normal distribution, Kruskal-Wallis analysis of ranks and Wilcoxon rank-sum tests were used to compare numerical variables, Chi-

Square test was used to compare the proportions of categorical variables. In all statistical tests significant differences were considered at *p*-value <0.05.

Kappa (κ) statistics were used to assess the inter-rater reliability between the two reviewers for ADR detection and between the four reviewers for ADR assessment (Landis & Koch 1977).

Kappa is widely used to measure interobserver variability, that is, how often two or more observers agree in their interpretations. The κ is the preferred statistics because it provides an indication of the level of agreement between two judges, taking into account agreement by chance.

κ is calculated by the equation; (O – E)/(1 – E), where O = observed agreement and E = expected agreement by chance.

The Generalised kappa statistic, which is Fleiss' extension of kappa, was used to measure the inter-rater reliability between the four reviewers (STATA-11 2009).

κ value of 0 indicates poor agreement (no agreement better than chance) and 1 indicates total agreement (Landis & Koch 1977).

2.1.4.11.2 Statistical modelling

Regression

Regression is a mathematical method used to estimate the relationship between data variables; the predictor (or independent) variable and outcome (or dependent) variable.

The regression analysis assumes that the outcome of the dependent variable is 'predicted' by the independent variable (Altman 1991).

Logistic regression

Many epidemiological studies have used logistic regression where the outcome variable of interest is the presence or absence of an event, such as the occurrence of an ADR as in this chapter of this thesis. In such an instance, where the dependent variable has a categorical binary outcome (e.g. no/yes, expressed as 0/1 respectively), logistic regression should be used as a means for describing the relationship between the dependent variable and independent variable(s). The basic principle of logistic regression is similar to linear regression. The main difference is that in logistic regression a transformation of the dependent variable is predicted, which is called the logit transformation of the odds of developing the outcome. In the case of an ADR as an outcome, if P is the probability of a subject having an ADR, then 1-P is the probability that they will not have one. The ratio P/(1-P) is called odds and thus

$\text{Logit}(P)=\log_e (P/(1-P)$ is the log of the odds (Altman 1991).

If we compare the prediction for a subject with or without a particular characteristic, such as gender, then the odds for female as logit(Pf) and for male as logit(Pm) will be estimated and the odds ratio (OR) will obtained as follows;

$$\text{Logit}(Pf) - \text{logit}(Pm) = \log[Pf/(1-Pf)] - \log[Pm/(1-Pm)] = \log (OR)$$

OR is an important method for relating the outcome (such as an ADR) to exposure (such as a drug or disease). For example to investigate the probability of paediatric patients on medications developing an ADR, the OR for children prescribed five or more drugs developing an ADR is 4.7 (section 2.2.2.3.2).

However, in observational pharmacoepidemiological studies, the way one variable is influenced by several variables is of interest. Therefore, multivariable logistic models are particularly useful where different variables can be added or removed from the model in order to get the best fit model using maximum likelihood. Such complex statistical models are developed by statistical programmes such as STATA which has been used for the analyses in this thesis (Altman 1991; STATA-11 2009).

Therefore, in the present study, to control potential associations and to determine independent associations between ADRs and the risk factors for ADRs, the univariable and multivariable logistic regression models at patient level were used.

Potential risk factors associated with ADRs were identified using ADR occurrence as the outcome. Univariable odds ratios (OR) with 95% confidence intervals (CI) were calculated for each independent variable. Those factors which showed a significant association with the occurrence of ADRs in the univariable analysis were included in the multivariable regression analysis. The final model included; age (in groups; 0-≤2 years, >2-≤11 years, >11-≤18 years), gender, number of low risk drugs per patient (in groups; 1-4 drugs, 5-10 drugs, >10 drugs), number of high risk drugs per patient (in groups; one drug, 2-3 drugs, >3 drugs), 'diseases of the blood or blood-forming organs and certain

disorders involving the immune mechanism' (D50-D89), 'diseases of the nervous system' (G00-G99), 'certain conditions originated in the perinatal period' (P00-P96), 'endocrine, nutritional and metabolic diseases' (E00-E90), 'certain infectious and parasitic diseases' (A00-B99). The final model was adjusted by country.

In addition, Gender and younger age (0-≤2 years, >2-≤11 years) were included in the full model despite their non-significance in the univariable analysis because previous studies had identified age and gender as risk factors for ADRs (Kanneh 2004; Martinez-Mir et al. 1999; Davies et al. 2009).

Data are presented as percentages, median with interquartile range [IQR (Q1-Q3)], and ORs with 95% CIs unless otherwise specified.

2.1.4.12 ADR incidence

The overall proportion of patients experiencing an ADR was defined as the number of patients with at least one ADR during the study period divided by the total number of patients in the study cohort. The proportion of patients experiencing an ADR in each country was defined as the number of patients with at least one ADR during the study period divided by the total number of patients in the individual country cohort.

The calculation of the proportion of patients experiencing an ADR can be expressed as:

$$\text{Proportion} = \frac{\text{Number of patients with ADR}}{\text{Total number of patients in the cohort}} \times 100$$

The incidence of ADRs was calculated by including only patients receiving medications in the denominator; the overall incidence of patients with ADRs was defined as the number of patients with an ADR divided by the number of patients receiving medications in either the total study cohort or in each country cohort.

The calculation of ADR incidence can be expressed as:

$$\text{Incidence} = \frac{\text{Number of patients with an ADR}}{\text{Total number of patients receiving medications in the cohort}} \times 100$$

The incidence of patients with ADRs during hospitalisation was defined as the number of patients with at least one ADR during their hospital stay divided by the total number of patients receiving medications. Similarly, the incidence of serious ADRs was defined as the number of patients suffering at least one serious ADR divided by the total number of patients receiving medications.

The proportion of all patients admitted to hospital due to an ADR that resulted from a drug taken prior to admission was calculated using the number of patients admitted due to an ADR divided by the total number of patients in the cohort receiving medications.

All results were multiplied by 100 and stratified by country. For calculation of incidence and number of ADRs per patient, only the first admission for each patient was considered.

We also calculated the number of ADRs per 100 admissions, per 100 days of hospital stay and per 100 prescriptions to allow comparison with the existing literature.

2.1.5 Ethical Approval

The study protocol was approved by the local research ethics committee in each participating country (Appendices 3-7: Ethics approvals).

2.1.6 Results

2.1.6.1 Study population

A total of 1278 paediatric patients (1340 admissions) were included in the cohort [Australia n=146 (149), Germany n=376 (407), HK n=143 (149), Malaysia n=300 (314), and UK n=313 (321)]. Of 1278 children 705 (55.2%) were male. The median age of the study population was two years (IQR 0-7, range 0-18 years). The total length of hospital stay in the whole cohort was 8347 days with a median of 4 days (IQR 3-7 days, range 1-150 days). Of the 1278 hospitalised children 1140 (89.2%) received 5367 drugs during their hospitalisation (median 3 drugs per patient, IQR 2-5 drugs, range 1-36 drugs). Demographic characteristics of children included from each country are shown in **Table 2.8**. There was a significant difference between countries in regard to patient age, length of hospital stay, and number of drugs prescribed per patient ($p<0.05$).

The number of drugs prescribed per patient in the UK was found to be significantly higher than in the other countries ($p<0.001$). There was no significant difference in gender among countries ($p=0.63$).

Table 2.8: Demographic characteristics of study population

Patients Characteristics	Country					Total
	Australia	Germany	UK	HK[a]	Malaysia[a]	
	[b](~250/36)	[b](120/24)	[b](180/40)	[b](1200/30)	[b](620/28)	
Number of patients (admissions)	146 (149)	376 (407)	313 (321)	143 (149)	300 (314)	1278 (1340)
Number of patient by age groups, No. (%)						
0 - ≤2y	81 (55.5)	133 (35.4)	176 (56.2)	62 (43.4)	225 (75.0)	677 (53.0)
>2y - ≤11y	51 (34.9)	156 (41.5)	102 (32.6)	43 (30.1)	72 (24.0)	424 (33.2)
>11y - ≤18y	14 (9.6)	87 (23.1)	35 (11.2)	38 (26.6)	3 (1.0)	177 (13.8)
Age, years: median (IQR)[c]	2 (0-8)	5 (1-10.5)	2 (0-6)	4 (0-13)	1 (0-2.5)	2 (0-7)
Gender, No. (%):						
Female	64 (43.8)	164 (43.8)	142 (45.4)	69 (48.2)	134 (44.7)	573 (44.8)
Male	82 (56.2)	212 (56.4)	171 (54.6)	74 (51.7)	166 (55.3)	705 (55.2)
Length of stay, days: median (IQR)[c]	4 (3-7)	4 (3-6)	4 (3-6)	6 (4-8)	5 (4-8)	4 (3-7)
Number of patients who received medications (%)	140 (95.9)	293 (77.9)	303 (96.8)	116 (81.1)	288 (96.0)	1140 (89.2)
Total number of drugs prescribed	753	1343	2010	357	904	5367
Number of drugs prescribed per patient: median (IQR)[c]	4 (2-7)	2 (1-4)	5 (3-8)	2 (1-3)	3 (2-3)	3 (2-5)
Number of drugs prescribed per patient (only those with medication): median (IQR)[c]	4 (3-7)	3 (2-5)	5 (3-8)	2 (2-4)	3 (2-4)	3 (2-5)
Number of patients with high risk drugs (%)	124 (88.6)	237(80.9)	290 (95.7)	75 (64.7)	275 (95.4)	1001 (87.9)

[a]General hospital, [b]Total No. of beds/No. of beds on study ward, [c]IQR=Inter-Quartile Range (Q1-Q3)

Based on the ICD-10 classification system, 'respiratory system' diseases were the most common diagnosis in all countries, followed by 'infectious and parasitic' diseases in Australia, Germany, the UK, and Malaysia. Although in HK there were few infectious diseases reported. Diseases of the nervous system were a common diagnosis in Germany, Malaysia, and the UK. 'Endocrine, nutritional and metabolic' diseases occurred more frequently in Germany than Australia but none were reported in Malaysia and the UK. **Table 2.9** shows the most frequent underlying diseases that the patients in each country had when they were admitted with in each country and overall.

Table 2.9: Most frequent main diagnosis recorded for children in total study cohort and in each country cohort

Diagnosis	ICD-10 code	Number of patients with diagnosis (%)					Total no. of patients [a](n=1278)
		Australia [a](n=146)	Germany [a](n=376)	UK [a](n=313)	HK [a](n=143)	Malaysia [a](n=300)	
Diseases of the respiratory system	J00-J99	45 (30.8)	89 (23.7)	83 (26.5)	23 (16.1)	184 (61.3)	424 (33.2)
Certain infectious and parasitic diseases	A00-B99	11 (7.5)	85 (22.6)	29 (9.3)	4 (2.8)	19 (6.3)	148 (11.6)
Diseases of the nervous system	G00-G99	6 (4.1)	27 (7.2)	19 (6.1)	8 (5.6)	35 (11.7)	95 (7.4)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	R00-R99	9 (6.2)	20 (5.3)	28 (8.9)	20 (14)	16 (5.3)	93 (7.3)
Diseases of the genitourinary system	N00-N99	14 (9.6)	24 (6.4)	14 (4.5)	17 (11.9)	11 (3.7)	80 (6.3)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	5 (3.4)	6 (1.6)	23 (7.3)	5 (3.5)	4 (1.3)	43 (3.4)
Certain conditions originating in the perinatal period	P00-P96	3 (2.1)	2 (0.5)	16 (5.1)	9 (6.3)	5 (1.7)	35 (2.7)
Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99	6 (4.1)	4 (1.1)	12 (3.8)	2 (1.4)	1 (0.3)	25 (2)
Injury, poisoning and certain other consequences of external causes	S00-T98	2 (1.4)	40 (10.6)	20 (6.4)	12 (8.4)	-	74 (5.8)

Data presented as number (%); [a]n=total number of patients

2.1.6.2 Drug prescriptions

A total of 5367 prescribed drugs were recorded in the study cohort. The most frequently prescribed drug groups, classified by ATC therapeutic level, are presented in **Table 2.10**. The highest number of prescriptions was for 'antibacterials for systemic use' (n=1355, 25.3%), followed by 'analgesic' drugs (n=903, 16.8%), 'drugs for obstructive airway diseases' (n=472, 8.8%), 'anti-inflammatory and antirheumatic products' (n=269, 5.0%), 'corticosteroids for systemic use' (n=238, 4.4%), 'drugs for acid related disorders' (n=176, 3.3%), and 'anti-epileptics' (153, 2.9%).

Table 2.10: Most frequently prescribed drug groups in each country

Therapeutic level (Level T)	[a]ATC code	Number of prescriptions (%)					Total no. of prescriptions [b](n=5367)
		Australia [b](n=753)	Germany [b](n=1343)	UK [b](n=2010)	HK [b](n=357)	Malaysia [b](n=904)	
Antibacterials for systemic use	J01	189 (25.1)	291 (21.7)	397 (19.8)	61 (16.8)	417 (46.1)	1355 (25.3)
Analgesics	N02	123 (16.3)	225 (16.8)	346 (17.2)	51 (14.3)	158 (17.5)	903 (16.8)
Drugs for obstructive airway diseases	R03	45 (6)	60 (4.5)	174 (8.7)	28 (1.4)	165 (18.3)	472 (8.8)
Anti-inflammatory and antirheumatic products	M01	16 (2.1)	119 (8.9)	130 (6.5)	2 (0.6)	2 (0.2)	269 (5)
Corticosteroids for systemic use	H02	52 (6.9)	54 (4)	73 (3.6)	1 (0.3)	58 (6.4)	238 (4.4)
Antiepileptics	N03	9 (1.2)	53 (4)	45 (2.2)	23 (6.4)	23 (2.5)	153 (2.9)
Blood substitutes and perfusion solutions	B05	8 (1.1)	23 (1.7)	87 (4.3)	21 (5.9)	-	139 (2.6)
Drugs for acid related disorders	A02	32 (4.3)	28 (2.1)	90 (4.5)	18 (5)	8 (0.9)	176 (3.3)
Psycholeptics	N05	21 (2.8)	23 (1.7)	64 (3.2)	17 (4.8)	1 (0.1)	126 (2.4)
Laxatives	A06	16 (2.1)	34 (2.5)	67 (3.3)	7 (2)	1 (0.1)	125 (2.3)
Antianemic preparations	B03	12 (1.6)	26 (1.9)	37 (1.8)	1 (0.3)	4 (0.4)	80 (1.5)
Antihistamines for systemic use	R06	6 (0.8)	12 (0.9)	38 (1.9)	11 (3.1)	6 (0.7)	73 (1.4)
Diuretics	C03	11 (1.5)	11 (0.8)	32 (1.6)	1 (0.3)	12 (1.3)	67 (1.3)
Cough and cold preparations	R05	7 (0.9)	22 (1.6)	32 (1.6)	3 (0.8)	2 (0.2)	66 (1.2)
Drugs for functional gastrointestinal Disorders	A03	9 (1.2)	9 (0.7)	38 (1.9)	2 (0.6)	6 (0.7)	64 (1.2)
Anesthetics	N01	5 (0.7)	2 (0.2)	54 (2.7)	2 (0.6)	-	63 (1.2)
Antidiarrheals, Intestinal anti-inflammatory/anti-infective agents	A07	13 (1.7)	17 (1.3)	25 (1.2)	1 (0.3)	6 (0.7)	62 (1.2)
Antivirals for systemic use	J05	7 (0.9)	21 (1.6)	19 (0.9)	4 (1.1)	3 (0.3)	54 (1.0)
Muscle relaxants	M03	3 (0.4)	5 (0.4)	37 (1.8)	2 (0.6)	1 (0.1)	48 (0.9)
Immunosuppressive agents	L04	5 (0.7)	36 (2.7)	4 (0.2)	-	-	45 (0.8)

Data presented as number (%); [a]ATC=Anatomical Therapeutic Chemical; [b]n=number of prescriptions

The three most frequently prescribed drug groups were similar in all countries. Details on the number of prescriptions and individual drugs in these three drug groups are given in **Table 2.11**.

Table 2.11: Most frequently prescribed drugs for the three most common drug groups by country

Drug group (ATC)	Australia		Germany		UK		HK		Malaysia	
	Drug (No. of prescriptions)	Total No. of prescriptions (%)[a]	Drug (No. of prescriptions)	Total No. of prescriptions (%)[a]	Drug (No. of prescriptions)	Total No. of prescriptions (%)[a]	Drug (No. of prescriptions)	Total No. of prescriptions (%)[a]	Drug (No. of prescriptions)	Total No. of prescriptions (%)[a]
Systemic Antibacterials (J01)	Gentamicin (36), tobramycin (9)	45 (23.8)	Cefaclor (20), cefotiam (44), cefuroxime (2)	66 (22.7)	Amoxicillin & enzyme inhibitor (78), piperacillin & enzyme inhibitor (2)	80 (20.2)	Ampicillin (11), amoxicillin (2)	13 (21.3)	Cefuroxime (152)	152 (36.5)
	Benzylpenicillin (26), phenoxymethyl-penicillin (1)	27 (14.29)	cefixime (3), cefotaxime (54), ceftazidime (6)	63 (21.6)	Cefotaxime (21), ceftriaxone (49), ceftazidime (3)	73 (18.4)	Cefuroxime (13)	13 (21.3)	Clarithromycin (69), azithromycin (6)	75 (17.99)
	Cefotaxime (21), ceftazidime (2), ceftriaxone (3)	26 (13.8)	Amoxicillin and enzyme inhibitor (34), piperacillin & enzyme inhibitor (1)	35 (12.0)	Azithromycin (12), clarithromycin (27), clindamycin (4), erythromycin (13)	56 (14.1)	Gentamicin (9), amikacin (1)	10 (16.4)	Cefotaxime (45), ceftazidime (3), ceftriaxone (14), cefoperazone-combinations (4)	66 (15.8)
	Others	91 (48.1)	Others	127 (43.6)	Others	189 (47.6)	Others	25 (40.9)	Others	124 (29.7)
Analgesics (N02)	Paracetamol (92)	92 (74.8)	Metamizole sodium (115)	115 (51.1)	Paracetamol (257)	257 (74.3)	Paracetamol (35)	35 (68.6)	Paracetamol (156)	156 (98.7)
	Morphine (12)	12 (9.8)	-	-	Morphine (53)	53 (15.3)	-	-	-	-
Obstructive airways drugs (R03)	Salbutamol (25)[b]	25 (55.6)	Salbutamol (33)[b]	33 (55.0)	Salbutamol (65)[c]	65 (37.4)	Salbutamol (17)[b]	17 (60.2)	Salbutamol (86)[b]	86 (52.1)

[a]Percentages are calculated using number of prescriptions of each drug group in each country (Table 2.10); [b]Route of administration: inhalation; [c]Route of administration: inhalation and parenteral

2.1.6.3 ADR incidence

211 of the 1278 patients experienced 380 ADRs. The overall proportion of patients experiencing an ADR in the study cohort was 16.5% (95% CI, 14.5-18.7). 129 patients experienced one ADR, 45 patients experienced two ADRs, 21 patients had three ADRs, and 16 patients developed more than three ADRs. The overall incidence of patients with an ADR was 18.5% (95% CI, 16.3-20.9). In the total cohort, there was no significant difference in gender with regards to ADR occurrence [female: n=97/573 (16.9%); male: n=114/705 (16.2%), p=0.717].

Table 2.12 shows the incidences of ADRs based on different denominators.

The incidence of patients experiencing an ADR was similar in Australia (7.9%), Germany (9.2%), and HK (10.3%), (p=0.889). The incidence was found to be significantly higher in Malaysia (19.1%) and in the UK (34.9%), ($p<0.001$) compared with Germany, Australia and HK.

In the overall study cohort the proportion of patients with ADRs was found to be higher in older children (>11y - ≤18 y) but not significantly so, however, in each country cohort the age group with the highest ADR incidence was different (**Table 2.12**).

The incidence of patients admitted to hospital due to an ADR was 1.8% (95% CI, 1.1-2.7) in the total study cohort, varying between 1.0% (95% CI, 0.21-2.9) in Germany and 2.6% (95% CI, 1.1-5.1) in the UK. 189 of the 1140 patients on medications (16.6%; 95% CI,

14.5-18.9) experienced at least one ADR during their hospitalization. Of the 380 ADRs, 26 (7.0%) were responsible for the admission of 20 patients (**Table 2.12**).

In the total cohort 380 ADRs were related to 488 drugs (9.1% of all drug prescriptions). 272 ADRs were due to single drugs and 108 reactions had multiple drug involvement.

The number of ADRs per 100 admissions was highest in the UK (69.5%, 95% CI; 64.1-74.5) and lowest in HK (8.7%, 95% CI; 4.7-14.5). Similarly, the number of ADRs per 100 days in hospital and number of ADRs per 100 prescriptions was highest in the UK (**Table 2.12**).

Table 2.12: Proportions of patients with ADRs, ADRs incidences, and frequency of ADRs based on different denominators

	Country					Total
	Australia	Germany	UK	HK	Malaysia	
Overall proportion of patients with ADRs (95% CI)	(N=11) 7.5 (3.8-13.1)	(N=27) 7.2 (4.8-10.2)	(N=106) 33.8 (28.6-39.0)	(N=12) 8.4 (4.4-14.2)	(N=55) 18.3 (14.1-23.2)	(N=211) 16.5 (14.5-18.7)
0 - ≤2years	(N=3) 3.7 (0.77-10.4)	(N=6) 4.5 (1.7-9.6)	(N=53) 30.1 (23.4-37.5)	(N=7) 11.3 (4.7-21.9)	(N=43) 19.1 (14.2-24.9)	(N=112) 16.5 (13.8-19.6)
>2 - ≤11years	(N=7) 13.7 (5.7-26.3)	(N=10) 6.4 (3.1-11.5)	(N=32) 31.4 (22.5-41.3)	(N=2) 4.6 (0.57-15.8)	(N=10) 13.9 (6.9-24.1)	(N=61) 14.4 (11.2-18.1)
>11y - ≤18y	(N=1) 7.1 (0.18-33.9)	(N=11) 12.6 (6.5-21.5)	(N=21) 60.0 (42.1-76.1)	(N=3) 7.9 (1.7-21.4)	(N=2) 66.7 (9.4-99.2)	(N=38) 21.5 (15.7-28.3)
†Overall ADR incidence (95% CI),	N=11 7.9 (3.9-13.6)	N= 27 9.2 (6.2-13.1)	N=106 34.9 (29.6-40.6)	N=12 10.3 (5.5-17.4)	N=55 19.1 (14.7-24.1)	N=211 18.5 (16.3-20.9)
†Incidence of patients admitted due to ADRs (95% CI)	N=2 1.4 (0.17-5.1)	N=3 1.0 (0.21-2.9)	N=8 2.6 (1.1-5.1)	N=2 1.7 (0.21-6.1)	N=5 1.7 (0.57-4.0)	N=20 1.8 (1.1-2.7)
†Incidence of ADRs during hospitalisation (95% CI)	N=10 7.1 (3.5-12.7)	N=25 8.5 (5.6-12.3)	N=101 33.3 (28.0-38.9)	N=7 6.0 (2.5-12.0)	N=46 16.0 (11.9-20.7)	N=189 16.6 (14.5-18.9)
†Incidence of serious ADRs (95% CI)	N=3 2.1 (0.4-6.1)	N=11 3.8 (1.9-6.6)	N=19 6.3 (3.8-9.6)	N=6 5.2 (1.9-10.9)	N=22 7.6 (4.8-11.3)	N=61 5.4 (4.1-6.5)
No of ADRs/ 100 admissions	n=21 14.1 (8.9-20.7)	n=53 13.0 (9.9-16.7)	n=223 69.5 (64.1-74.5)	n=13 8.7 (4.7-14.5)	n=70 22.3 (17.8-27.3)	n=380 28.4 (26.0-30.9)
No of ADRs/ 100 days in hospital	n=21 1.7 (1.0-2.5)	n=53 2.6 (2.0-3.4)	n=223 12.3 (10.8-13.9)	n=13 1.3 (0.68-2.2)	n=70 3.1 (2.4-3.9)	n=380 4.5 (4.1-5.0)
No of ADRs/ 100 prescriptions	n=21 2.8 (1.7-4.2)	n=53 3.9 (3.0-5.1)	n=223 11.1 (9.7-12.5)	n=13 3.6 (1.9-6.1)	n=70 7.7 (6.1-9.7)	n=380 7.1 (6.4-7.8)

N=Number of patients with ADRs; n=number of ADRs; †Incidence calculated taken into account patients on drugs only as the denominator (Table 2.8)

2.1.6.4 ADR characteristics

The five 'WHO' system-organ classes most commonly involved in the 380 identified ADRs were 'gastro-intestinal system disorders' (n=183; 48.2%), 'skin and appendages disorders' (n=59; 15.5%), 'metabolic and nutritional disorders' (n=47; 12.4%), 'heart rate and rhythm disorders' (n=41; 10.8%), and 'psychiatric disorders' (n=28; 7.4%), (**Figure 2.5**).

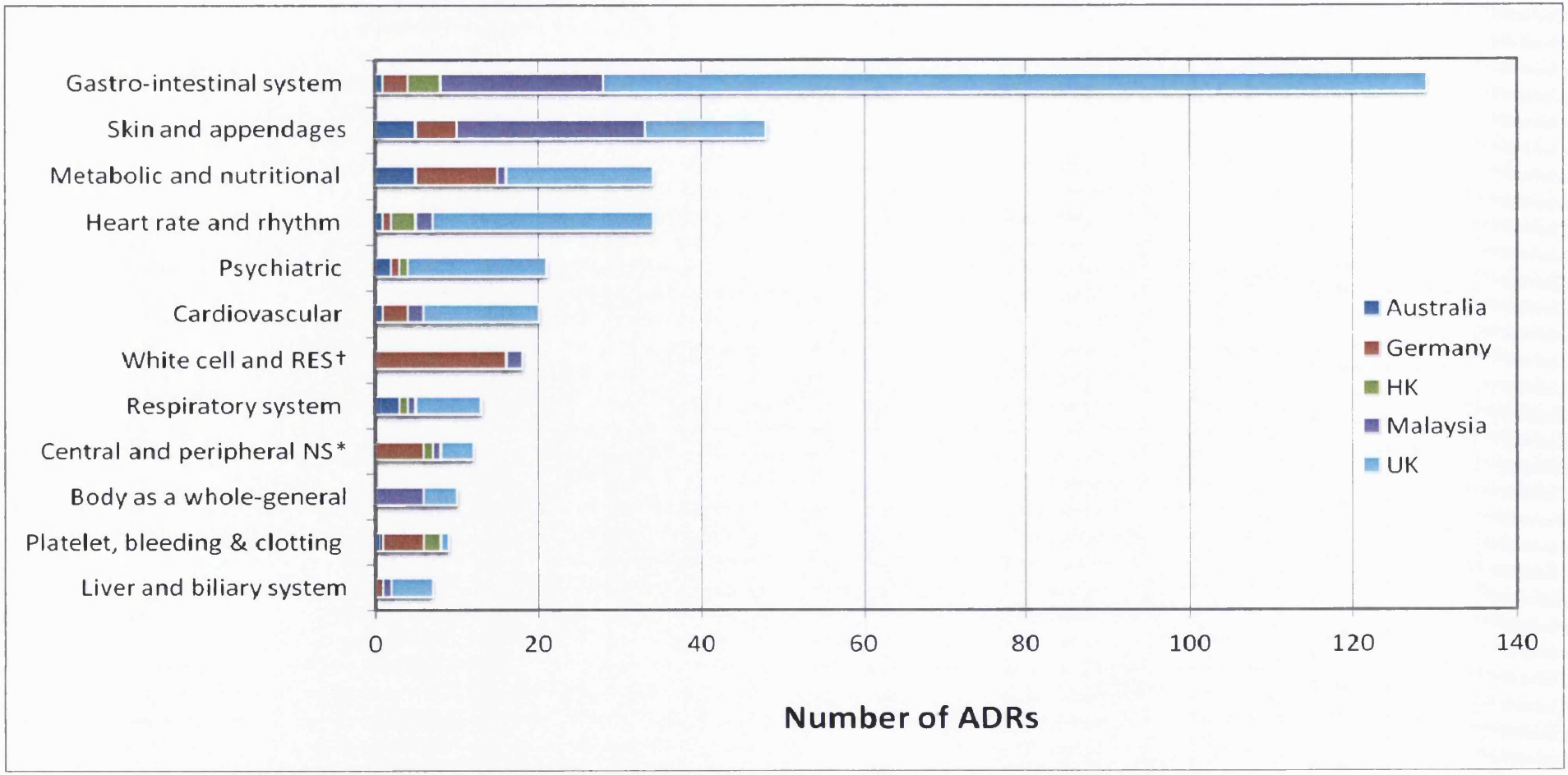
By comparing the most frequent clinical manifestations of ADRs between countries, we found that 'gastro-intestinal system disorders' (such as diarrhoea, vomiting, nausea) occurred similarly in all countries, while 'heart rate and rhythm disorders' (such as tachycardia) were reported more frequently in the UK (34 cases out of 41 total cases) compared to other countries.

Antibacterials were the drugs most frequently involved (n=200) in ADRs, mainly causing 'gastro-intestinal system disorders' (n=103) and 'skin and appendages disorders' (n=40). In particular, second- and third-generation cephalosporins (n=64), penicillins (n=70) and macrolides (n=41) were the antibacterials most frequently causing ADRs.
The second most frequently involved group of drugs were analgesics (n=83 ADRs), of which morphine and clonidine (n=64, n=13, respectively) were the drugs most often causing ADRs.

Heart rate and rhythm disorders (n=41) were mainly caused by respiratory drugs with salbutamol (n=32) being the causative drug most often.

Looking at the proportion of number of prescriptions involved in ADRs, immunosuppressants, antivirals and diuretics were the three groups most frequently associated with ADRs (33.3%, 20.4% and 14.9% of prescriptions, respectively), (**Table 2.13**).

Figure 2.5: Number of ADRs in major WHO system-organ classes affected, in each country



*NS: Nervous System, †RES: Reticuloendothelial System

Table 2.13: Drugs most frequently associated with ADRs

Drug group (ATC)	Total no. of prescriptions	No. of patients with ADRs	No ADRs [a](%)	Drugs (no of ADRs for each causative drug)	Examples of ADRs
Immunosuppressents (L04)	45	4	15 (33.33)	Azathioprine (2), ciclosporin (2), mycophenolic acid (1), tacrolimus (9)	Conjunctivitis (Azathioprin), hypertrichosis (ciclosporin) colitis (mycophenolic acid), hyperkalaemia (tacrolimus)
Antivirals (J05)	54	8	11 (20.37)	Aciclovir (6), foscarnet (2), ganciclovir (1)	Bradycardia (foscarnet), nephropathy toxic (aciclovir), neutropenia (ganciclovir)
Diuretics (C03)	67	6	10 (14.93)	Furosemide (7), spironolactone (3)	Hypokalaemia (furosemide), hyperkalaemia (spironolactone)
Antibacterials (J01)	1355	113	200 (14.76)	Penicinllins (70),macrolides (41), aminoglycosides (8), ciprofloxacin (1), cephalosporins (67), carbapenems (2), vancomycin (3), Sulphonamides and trimethoprim (7), linezolid (1)	Diarrhoea (amoxicillin), renal function abnormal (gentamicin), erythema multiforme (cefuroxime); alanine aminotransferase increased (clarithromycin), haemolysis (sulfamethoxazole & trimethoprim), leukocytosis (vancomycin)
Corticosteroids (H02)	238	16	34 (14.29)	Systemic corticosteroids (34)	Hyperglycaemia (methylprednisolone), cushing's syndrome (prednisone)
Anaesthetics (N01)	63	6	8 (12.70)	General anesthetics (5), local anesthetics (3)	Airways obstruction (propofol), respiratory distress (bupivacaine, combinations), allergic reactions (lidocaine, combination)
Antiepileptics (N03)	153	13	19 (12.42)	Antiepileptics (19)	Thrombocytopenia (valproic acid), nystagmus (phenytoin), leukocytosis (topiramate), rash (gabapentin)
Cough and Cold preparations (R05)	66	7	7 (10.61)	Bromhexine (1), codeine (6)	Constipation (codeine), cyanosis (bromhexine)
Analgesics (N02)	903	41	83 (9.19)	Acetylsalicylic acid (4), clonidine (13), metamizole sodium (1), morphine (64), tramadol (1)	Hypoventilation (morphine), pulmonary oedema (acetylsalicylic acid), bradycardia (clonidine), thrombocytopenia (metamizole)
Drugs for obstructive airway disease (R03)	472	31	45 (9.53)	Salbutamol (44), epinephrine (1)	Tachycardia, hypokalaemia and tremor (salbutamol)
Psycholeptics (N05)	126	4	7 (5.56)	Midazolam (2), diazepam (1), clobazam (3), chloral hydrate (1)	Bradycardia (midazolam), drowsiness (clobazam), respiratory disorder (chloral hydrate)
Others	789	32	49 (6.21)	Others	Others

[a]Percentages calculated using total number of prescriptions of each drug group as denominator

2.1.6.4.1 Seriousness

Applying the outcome criteria defined by ICH/CIOMS (ICH Guideline 1995) we found that 24% (n=91) of the ADRs were serious and, of these, one ADR had a fatal outcome, four were life-threatening and one led to persistent incapacity, (**Tables 2.14 and 2.15**). Of the 91 serious ADRs, 18.7% (n=17) were preventable. The incidence of patients with serious ADRs in the study cohort was 5.4% (95% CI, 4.1-6.5), being highest in Malaysia (7.6%; 95% CI, 4.8-11.3) and lowest in Australia (2.1%; 95% CI, 0.4-6.1), (**Table 2.12**).

Table 2.14: Number of ADRs with serious outcome[a] in each country

ADR outcome	Australia ([b]n=21)	Germany ([b]n=53)	UK ([b]n=223)	HK ([b]n=13)	Malaysia ([b]n=70)	Total ([b]n=380)
	[b]n (%)					
Fatal	1 (4.8)	-	-	-	-	1 (0.3)
Involved persistence or significant disability or incapacity	-	-	1 (0.4)	-	-	1 (0.3)
Involved or prolonged inpatient hospitalisation	3 (14.3)	18 (34.0)	24 (10.8)	6 (46.2)	34 (48.6)	85 (22.4)
Life threatening	-	1 (1.9)	3 (1.3)	-	-	4 (1.1)
Total serious ADRs	4 (19.0)	19 (35.8)	28 (12.6)	6 (46.2)	34 (48.6)	91 (23.9)

[a]ICH/CIOMS criteria (ICH Guideline 1995), [b]n=number of ADRs

Table 2.15: Fatal and life threatening ADRs

ADR	ADR causative drug	Outcome
Hypotension	Morphine	Life threatening
Hypoventilation	Morphine	
Liver Cell Damage	Clarithromycin	
Pseudotumor Cerebri	Immunoglobulins, normal human, for intravascular administration	
Hypomagnesaemia	Tacrolimus	Fatal

2.1.6.4.2 Severity

Using the severity scale reported by Dorman et al (2000), most of the ADRs (63.4%, n=241) were found to be mild, 35.5% (n=135) were moderate and 1.1% (n=4) severe. In four countries the majority were mild; whereas in Malaysia the majority of the ADRs (54.3%, n=38) were assessed as moderate, (**Table 2.16**).

2.1.6.4.3 Causality

Regarding causality, using the Naranjo score algorithm (Naranjo et al. 1981), 7.9% (n=30) of the identified ADRs were assessed as 'definite', 65.3% (n=248) were assessed as 'probable' and 26.8% (n=102) were assessed as 'possible', (**Table 2.16**). Most of the ADRs were judged to be 'probable' in three countries; the exception is HK where all ADRs identified were classified 'possible' and Australia where the majority were 'possible'. The percentage of ADRs assessed as definite was particularly high in Malaysia (24.3%, n=17), followed by Germany (18.9%, n=10). Only one case in the UK was assessed as 'definite'.

2.1.6.4.4 Preventability

Using the preventability system published by Schumock and Thornton (1992), we found that 16.6% (n=63) of identified ADRs were classified as preventable. The highest number of preventable ADRs was in Germany (n=10; 18.9%) and the UK (n=40; 17.9%), (**Table 2.16**).

2.1.6.4.5 Predictability

Using the Rieder (1994) classification for ADR predictability, overall we found that 66.3% (n=252) of the identified ADRs were predictable and 65.5% (165/252) of them were classified as listed side effects of the causative drugs. While 33.7% (n=128) of the ADRs were unpredictable; of these with idiosyncratic ADRs were the most frequent group of ADRs, (**Table 2.16**).

At a country level the pattern was similar in all countries except Malaysia where more ADRs (55.7%, n=39) were classified as unpredictable than as predictable.

Table 2.16: Classification of ADRs identified in the study cohort

ADR characteristics	Number of ADRs (%)					Total (n=380)
	Australia (n=21)	Germany (n=53)	UK (n=223)	HK (n=13)	Malaysia (n=70)	
[a]**Severity: n (%)**						
Mild	15 (71.4)	48 (90.6)	136 (60.9)	10 (76.9)	32 (45.7)	241 (63.4)
Moderate	5 (23.8)	4 (7.6)	85 (38.1)	3 (23.1)	38 (54.3)	135 (35.5)
Severe	1 (4.8)	1 (1.9)	2 (0.9)	-	-	4 (1.1)
[b]**Causality: n (%)**						
Definite	2 (9.5)	10 (18.9)	1 (0.45)	-	17 (24.3)	30 (7.9)
Probable	6 (28.6)	27 (50.9)	167 (74.9)	-	48 (68.6)	248 (65.3)
Possible	13 (61.9)	16 (30.2)	55 (24.7)	13 (100)	5 (7.1)	102 (26.8)
[c]**Preventability: n (%)**						
Preventable	7 (33.3)	10 (18.9)	40 (17.9)	3 (23.1)	3 (4.3)	63 (16.6)
Not Preventable	14 (66.7)	43 (81.1)	183 (82.1)	10 (76.9)	67 (95.7)	317 (83.4)
[d]**Predictability: n (%)**						
Yes: Predictable;	*13 (61.9)*	*29 (54.7)*	*170 (76.2)*	*9 (69.2)*	*31 (44.3)*	*252 (66.3)*
Toxicity	-	1 (1.9)	6 (2.7)	2 (15.4)	1 (1.4)	10 (2.6)
Side effect	3 (14.3)	23 (43.4)	119 (53.4)	7 (53.9)	13 (18.6)	165 (43.4)
Interaction	-	5 (9.4)	1 (0.5%)	-	-	6 (1.6)
Secondary effect	10 (47.6)	-	44 (19.7)	-	17 (24.3)	71 (18.7)
No: Unpredictable;	*8 (38.1)*	*24 (45.3)*	*53 (23.8)*	*4 (30.8)*	*39 (55.7)*	*128 (33.7)*
Intolerance	2 (9.5)	-	18 (8.1)	-	5 (7.1)	25 (6.6)
Idiosyncratic	5 (23.8)	23 (43.4)	28 (12.6)	4 (30.8)	2 (2.9)	62 (16.3)
Immuno-allergic	1 (4.8)	1 (1.9)	7 (3.2)	-	32 (45.7)	41 (10.8)

a Severity scale according to Dorman et al (2000)

b Causality according to Naranjo algorithm (Naranjo et al. 1981)

c Preventability according to Schumock and Thornton (1992)

[d] Predictability according to Rieder (1994)

2.1.6.5 Inter-rater reliability analysis

The inter-rater agreement between the original and second reviewers for identifying patients with ADRs was found to be 'almost perfect' with κ=0.89 (95% CI, 0.75-1.0) and the agreement on the number of ADRs per patient was 'substantial' with κ=0.77 (95% CI (0.60-0.94) (Landis & Koch 1977).

The inter-rater agreement between the four raters for ADR causality assessment using the Naranjo algorithm was found to be 'fair' with κ=0.30, while the agreement on ADR severity based on the scale reported by Dormann et al (2000) was 'moderate' with κ=0.55.

However, it needs to be mentioned that only four raters from the five countries were involved in the reliability test for the assessment of ADRs. We randomly selected 20 ADRs cases from the study cohort to assess the inter-rater reliability between the four raters, which might be an inadequate number for the reliability analysis and have an impact on the obtained kappa values for both causality and severity assessment.

Another possible explanation, which was given in section 2.1.7.3 (page 129), is that currently available ADR assessment scales are subjective and dependent, at least in part, on the knowledge and experience of assessors.

2.1.7 Discussion

In this study we found that 211 of the 1278 (16.5%) children observed in the study cohort experienced at least one ADR during the study period. The overall incidence of ADRs in hospitalised children from five European and non-European countries is 18.5% (95% CI,

16.3-20.9). This number is higher than in the previously reported meta-analyses (9.5%; 10.9%, respectively), (Impicciatore et al. 2001; Clavenna & Bonati 2009).

2.1.7.1 ADR Incidences

One reason for the higher ADR incidence found in our study compared to previous research may be the use of intensive chart review as the detection method. This method is said to be the gold standard in pharmacoepidemiology, however, because it is very time and resource intensive it has been reported that it is of limited use in clinical research projects (Thurmann 2001; Weiss et al. 2002; Murff et al. 2003). Also, not all of the studies included in the previous meta-analyses used this method for ADR identification which may explain their lower ADR incidences (Impicciatore et al. 2001; Clavenna & Bonati 2009). Previous studies using intensive chart review have reported ADR incidences of up to 20% (Haffner et al. 2005; Weiss et al. 2002; Neubert et al. 2004).

In our study, the ADR incidence was highest in the UK compared to that in the other participating countries. The number of drugs prescribed per patient was also the highest in the UK, and this may be a major contributing factor to the higher incidence of ADRs. Furthermore, one of the drugs frequently associated with ADRs in the UK was morphine; 28.2% (63/223) of all the ADRs in the UK cohort were caused by morphine prescriptions and 17.5% (53/303) of the UK patients receiving medications, were prescribed morphine. Morphine was prescribed in only two countries, the UK and Australia and the majority of the morphine prescriptions (81.5%; n=53/65) were issued in the UK. Whereas in Australia, morphine was prescribed much less frequently [18.5% (n=12/65) of all morphine prescriptions for 12 (8.6%) patients of all patients receiving medications].

Higher use of opioids in the UK compared to other European Union (EU) countries has been reported previously (Neubert et al. 2010). Morphine prescribing in hospitalised children is also common in other western countries such as United States (US). A recent study conducted in the US by Lasky et al (2011) reported that morphine was among the top 10 drugs administered to children during hospitalisation. Nevertheless, the question remains, as to whether the guidelines for using morphine in children and adolescents in UK hospitals are appropriate or not and whether these guidelines should be investigated.

The frequent use of this high risk drug may be another factor contributing to the higher ADR incidence in the UK. Other studies in hospitalised children from the UK and the US also showed that morphine was among the drugs most commonly associated with ADRs (Gill et al. 1995; Temple et al. 2004).

A very recent evaluation of voluntary safety reports in a paediatric hospital in Canada revealed that about 10% of all reports were related to opioids with morphine being the drug most often involved (McDonnell 2011).

Another drug frequently prescribed in the UK was salbutamol which was given to 18.2 % (n=55) of all UK patients and related to 15.2% (n=34/223) of the ADRs observed in the UK. Although, in Malaysia 27.8% (n=80) of patients received salbutamol, only two ADRs (3.6%, n=2/70) were associated with this drug. Salbutamol was also frequently prescribed in the other participating countries; i.e in Germany prescribed to 9.9% (n=29) of patients, in Australia 17.8% (n=25), and in HK 14.6 % (n= 17), but rarely related to ADRs. One reason for the higher number of ADRs seen in the UK may be that salbutamol was not only administered by inhalation but also intravenously (about 11% of

all salbutamol prescriptions in the UK; for 7 (12.7%) out of 55 patients receiving salbutamol; while in other countries it was only administered by inhalation.

Of the total number of ADRs, 58.7% (n=223/380) occurred in the UK and 43.5% (n=97/223) of them, in 56 patients, were associated with morphine and salbutamol. Excluding these ADRs (n=97) from the incidence calculation, the number of patients with ADRs in the UK decreased from 106 to 83 and the proportion decreased from 33.8% to 26.5% (83/313) which was still higher than in the other countries in the study (7.5% to 18.3%).

Another possible explanation of the high incidence of ADRs in the UK is the inclusion of observations reported by the parents in the nursing notes. Similar information was not found in the nursing notes of other countries. Patient reporting of potential ADRs has been found to be an enhancement for ADR detection and reporting (Jarernsiripornkul et al. 2002). In paediatric patients the parents pay close attention to their children and any troublesome symptoms. Documentation of this information in the patient medical notes may have led to increased observation of ADRs in the UK cohort. This might also explain the high percentage of non-serious ADRs reported in the UK.

Previous studies from the UK reported lower ADR incidences which, however, may be the result of the less intensive ADR monitoring. Gill et al (1995) and Turner et al (1999), used an intensified volunteering reporting system where hospital staff were encouraged to report any suspected ADR by completing green card, and this resulted in an overall ADRs incidence of 11%. Intensified spontaneous reporting systems are more efficient than

national spontaneous reporting such as the yellow card system in the UK but still suffer from under-reporting.

To our knowledge there are no previously published data, in the international literature, on the occurrence of ADRs in hospitalised children in Australia, HK and Malaysia. In Australia, paediatric medication safety research has been conducted previously, but the studies investigated drug related problems or adverse events identified by spontaneous reporting (Easton et al. 1998; Runciman et al. 2003; Dunn et al. 2006).

Malaysia had the second highest ADR incidence (19.1%). Malaysia is a tropical country and infectious diseases are common in children. Consequently, almost 50% of the prescribed drugs were antibacterials for systemic use and 75.7% of the reported ADRs were related to this drug group which is known to be frequently associated with ADRs (Turner et al. 1999; Fattahi et al. 2005; Temple et al. 2004).

In our study the ADR incidences were similar for Australia, Germany and HK (7.9%, 9.2%, 10.3%, respectively). For Germany, previously reported incidences using a comparable method were 21.9%, 17.4%, and 14.1% which are all above the incidence found in our study (Weiss et al. 2002; Neubert et al. 2004; Haffner et al. 2005). However, the length of hospital stay and the number of drugs prescribed were lower in our study which may explain the lower ADR incidence. Furthermore, the study by Weiss et al was conducted on an infectious disease ward where the use of more high risk drugs such as antibiotics was apparent (Turner et al. 1999; Weiss et al. 2002; Fattahi et al. 2005; Temple et al. 2004).

Another explanation for the lower incidence in Germany in our study compared to the study conducted by Weiss et al (2002) ten years earlier, might be due to changes in the pharmacological treatment strategies in Germany during these ten years which may have influenced the incidence of ADRs. For example, the anti-inflammatory indomethacin was the drug most often associated with ADRs in the Weiss et al study, however, this drug has been replaced by ibuprofen and indomethacin was not prescribed in our study. Schramm et al (*accepted*) has discussed the reasons for the differences between Weiss et al study and ADVISE study regarding to ADRs incidence in Germany. The authors concluded that the lower number of prescribed drugs per patient and the improvement of treatment strategies led to enhanced medication safety in children in Germany.

Similar to the findings in our paediatric study, data reported from the adult population in previous studies suggest that between 10% and 20% of patients suffer an ADR (Dormann et al. 2000; Thuermann et al. 2002; Davies et al. 2006). A more recent study from the UK in adults which used a similar approach to that which we used in our study reported that 14.7% (95% CI, 13.6-15.9%) of 3695 adult patient episodes experienced one or more ADRs during hospitalisation (Davies et al. 2009). Previously the same authors observed at least one ADR in 19% of their patients (Davies et al. 2006). Much higher rates of up to 60% are seen in geriatric patients (Egger et al. 2003; Passarelli et al. 2005). Although in the adult literature there is evidence that ADRs are more common in women compared to men (Sánchez Muñoz-Torrero et al. 2010; Zopf et al. 2008a), our study did not show a difference in proportion of girls and boys who had an ADR (16.9% vs 16.2%).

2.1.7.2 ADRs leading to hospital admission

In this study we found that 1.8% (95% CI, 1.1-2.7) of patients were admitted to hospital as a consequence of an ADR. This means that almost one in every 60 admissions was due to an ADR. This proportion is similar to that in other paediatric studies whereas higher proportions have been reported in the adult population (Moore et al. 1998; Dormann et al. 2003; Pirmohamed et al. 2004; van der Hoof et al. 2006; Clavenna & Bonati 2009).

2.1.7.3 Severity and sseriousness of ADRs

In this study the majority of ADRs were classified as mild (63.4%). This is in line with many previously published studies which all found that about half of the ADRs were mild (Gill et al. 1995; Martines-Mir et al. 1999; González-Martin et al. 1998; Weiss et al. 2002). However, it has to be acknowledged that the assessment scales used in previous studies are heterogeneous and therefore findings are difficult to compare (Macedo et al. 2003; Agbabiaka et al. 2008). Also, in our study the results of the inter-rater analysis with respect to the severity assessment varied between countries and achieved moderate agreement only. This is consistent with the currently available ADR assessment scales are subjective and no single algorithm is accepted universally.

Using the ICH/CIOMS criteria, in our study, serious ADRs accounted for 24% of ADRs identified. Other paediatric studies by Buajordet et al (2002) reported a similar percentage of ADRs (19%) as serious whereas a higher percentage (37.5%) was reported by Temple et al (2004). Among the serious ADRs in our study 18.7% were classified as preventable which underlines the fact that treatment strategies need to be optimised in order to improve patient outcome.

One ADR had a fatal outcome which accounted for 0.3% (95% CI, 0.01-1.5) of the ADRs in our study. Similar proportions have been reported previously for children and adults (Lazarous et al. 1998; Clarkson & Choonara 2002) although higher numbers were reported in more recent studies in both the adult (2.7%) and paediatric populations (1.1%) (van der Hooft et al. 2006; Temple et al. 2004).

2.1.7.4 Economic impact

In our study the economic impact of ADRs on the healthcare systems was not investigated as this was outside the scope of the study. However, we have shown that about 2% of patients were admitted because of ADRs, accounting for a total of 114 days of hospital stay. 22.4% (85/380) of ADRs resulted in a prolonged hospital stay. Thus, this clearly indicates that, not only in adults but also in children, ADRs have an economic burden since they lead to additional days of hospitalisation and therefore treatment costs (Classen et al. 1997; Pirmohamed et al. 2004).

2.1.7.5 Study strengths and limitations

2.1.7.5.1 Strengths

To our knowledge this is the first multinational study to include European and Asian countries and also Australia to investigate ADR incidence in hospitalised children. The study used the gold-standard method for ADR detection of intensive chart review and a standard protocol across five countries. The inter-rater agreement for ADR detection was 'almost perfect' indicating good and homogeneous ADR detection across the countries. Hence, variances in reported ADR incidences are unlikely to be due to the detection of

the ADRs and may reflect population differences and/or prescribing practices, and the role of parental reporting.

2.1.7.5.2 Limitations

However, this study has several limitations. The sample size of two sites (Malaysia and UK), although slightly less than 350, was acceptable based on the statistical power of the sample size according to advice received from the statistician (Personal communication). However, the sample size from two hospitals, Australia and HK, was smaller than recommended. This was due to resource limitations in Australia which resulted in only one month of data collection. The spread of pandemic flu (Influenza A H1N1) during the second half of 2009 in HK led to restrictions in ward visits for research, thus a smaller number of patients were reviewed. Consequently, variation in the number of the patients from each country makes comparison between countries more difficult.

Differences in the documentation in patients' medical records may have had an influence on the detection of ADRs in our study. If important information is not documented adequately, ADRs are unlikely to be identified by the research team reviewing patients' records. This might apply mainly to mild and clinically less serious ADRs, however, these may indicate an early sign of a potentially serious ADR.

Our descriptive analysis has shown that the most common diagnoses were similar in all countries, with respiratory system diseases being the most frequent. The next section (2.3) of this chapter will further investigate the possible relation between underlying disease(s) and ADR occurrences using more in-depth statistical analysis.

2.2 Risk factors associated with ADRs in hospitalised children

In the previous section (2.2) of this chapter descriptive results on the incidence of patients with ADRs in the study cohort and in each participated country were reported. In this section the results of an in-depth statistical analysis of potential risk factors associated with ADRs in hospitalised children in the five countries are presented.

Patients who only had an ADR before admission or were admitted due to an ADR and did not experience another ADR during hospitalisation were excluded from the cohort for the analysis of risk factors.

This section has been published (online first: 14 December 2011) by European Journal of Clinical Pharmacology (EJCP), paper entitled "Risk factors associated with adverse drug reactions in hospitalised children: international multicentre study".

2.2.1 Methods

Study design including study population, sample size calculation, data collection methodology, statistical methods used, and ethical approval of the study have been discussed in section 2.1.4.

2.2.1.1 ADR incidence

The overall incidence of patients with ADRs during admission in the risk factor cohort and in each country cohort was defined as the number of patients with at least one ADR during their hospitalisation divided by the total number of patients receiving medications multiplied by 100.

For the calculation of the incidence of patients with ADRs included in the cohort for risk factors analysis, only patients with at least one drug prescription during admission were included. Also, only the first admission was considered for calculating ADR incidence and investigating the association between the incidence and the potential risk factors.

2.2.1.2 Risk factors

Risk factors investigated were; age, gender, number of low risk drugs, number of high risk drugs, diagnoses, length of stay.

2.2.2 Results

2.2.2.1 Patient characteristics

1253 paediatric patients fulfilled the inclusion criteria and were included in the cohort, for risk factor analysis, [Australia (n=145), Germany (n=372), Malaysia (n=291), HK (n=138), and UK (n=307)]. Of 1253 children, 693 (55.3%) were male. The median age of the study population was 2 years (IQR 0-7, range 0-18 years). The total length of hospital stay in the whole cohort was 8198 days with median 4 days (IQR 3-7, range 1-150 days). Of the 1253 hospitalised children 1115 (89.0%) received 5013 prescribed drugs during

their hospitalisation (median 3 drugs per patient, IQR 2-5, range 1-36 drugs). 980 (87.9%) of the 1115 children received at least one of the high risk drugs (median 2, IQR 1-3).

Demographic characteristics of the children, from each country, included in the cohort for analysis of risk factors are shown in **Table 2.17**. There was a significant difference between countries in regards to patient age, length of hospital stay, number of drugs prescribed per patient, and the number of high risk drugs prescribed per patient ($p<0.001$).

The number of drugs prescribed per patient in the UK was found to be significantly higher than in the other countries ($p<0.001$) There was no significant difference in gender between countries ($p=0.899$).

Table 2.17: Risk factors cohort; patients' demographic characteristics

Patients Characteristics	Country					Total
	Australia	Germany	UK	HK	Malaysia	
Number of patients	145	372	307	138	291	1253
Number of patient by age groups, No. (%)						
0 - ≤2y	81 (55.9)	132 (35.5)	173 (56.4)	60 (43.5)	218 (74.9)	664 (53.0)
>2y - ≤11y	52 (35.9)	154 (41.4)	100 (32.6)	42 (30.4)	70 (24.1)	417 (33.3)
>11y - ≤18y	13 (9.0)	86 (23.1)	34 (11.1)	36 (26.1)	3 (1.0)	172 (13.7)
Age, years: median (IQR)[a]	2 (0-7)	4.5 (1-10.5)	2 (0-6)	4 (0-12)	1 (0-3)	2 (0-7)
Gender, No. (%):						
Female	64 (44.1)	162 (43.5)	138 (45.0)	67 (48.6)	129 (44.3)	560 (44.7)
Male	81 (55.9)	210 (56.5)	169 (55.0)	71 (51.4)	162 (55.7)	693 (55.3)
Length of stay, days: median (IQR)[a]	4 (3-7)	4 (3-6)	4 (3-6)	6 (4-8)	5 (4-8)	4 (3-7)
Number of patients who received medications (%)	139 (95.9)	289 (77.7)	297 (96.7)	111 (80.4)	279 (95.9)	1115 (89.0)
Total number of drugs prescribed	731	1158	1907	341	876	5013
Number of drugs prescribed per patient: median (IQR)[a]	4 (3-7)	3 (2-5)	5 (3-8)	2 (2-4)	3 (2-4)	3 (2-5)
Number of patients with high risk drugs (%)[b]	123 (88.5)	234 (81.0)	284 (95.6)	72 (64.9)	267 (95.7)	980 (87.9)
Total number of high risk drugs prescribed	371	576	827	130	634	2538
Number of high risk drug prescribed per patient: median (IQR)[a]	3 (1-4)	2 (1-3)	2 (1-4)	1 (0-2)	2 (1-3)	2 (1-3)

[a]IQR: Interquartile range (Q1-Q3), [b]percentage calculated using patients on drugs as the denominator

'Respiratory system diseases' were the most common diseases in all countries, followed by 'infectious and parasitic diseases' in Australia, Germany, UK, and Malaysia. In the HK cohort only a few patients were reported with infectious diseases. 'Diseases of the nervous system' were common in Germany, Malaysia, and the UK. Germany was the country in which 'endocrine, nutritional and metabolic diseases' occurred most frequently, followed by Australia but none were reported in Malaysia and the UK. **Table 2.18** shows the main diagnoses most frequently recorded in the risk factors cohort, stratified by country.

Table 2.18: Risk factors cohort; number of patients with main diagnoses

Diagnosis (ICD-10 code)	Total no. of patients (%)	Total no. of patients on drugs (%)	Number of patients with diagnoses (%)				
			Australia	Germany	UK	HK	Malaysia
Diseases of the respiratory system (J00-J99)	415 (33.1)	408 (36.6)	45 (31)	88 (23.7)	81 (26.4)	23 (16.7)	178 (61.2)
Certain infectious and parasitic diseases (A00-B99)	147 (11.7)	120 (10.8)	11 (7.6)	85 (22.8)	29 (9.4)	4 (2.9)	18 (6.2)
Diseases of the nervous system (G00-G99)	94 (7.5)	85 (7.6)	6 (4.1)	26 (7)	19 (6.2)	8 (5.8)	35 (12)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	92 (7.3)	74 (6.6)	9 (6.2)	20 (5.4)	28 (9.1)	20 (14.5)	15 (5.2)
Diseases of the genitourinary system (N00-N99)	77 (6.1)	75 (6.7)	13 (9)	24 (6.5)	13 (4.2)	16 (11.6)	11 (3.8)
Injury, poisoning and certain other consequences of external causes (S00-T98)	74 (5.9)	44 (4.0)	2 (1.4)	40 (10.8)	20 (6.5)	12 (8.7)	-
Diseases of the digestive system (K00-K93)	56 (4.5)	45 (4.0)	7 (4.8)	22 (5.9)	16 (5.2)	4 (2.9)	7 (2.4)
Endocrine, nutritional and metabolic diseases (E00-E90)	50 (4.0)	39 (3.5)	19 (13.1)	22 (5.9)	-	9 (6.5)	-
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	38 (3.0)	38 (3.4)	5 (3.4)	5 (1.3)	22 (7.2)	3 (2.2)	3 (1)
Certain conditions originating in the perinatal period (P00-P96)	35 (2.8)	30 (2.7)	3 (2.1)	2 (0.5)	16 (5.2)	9 (6.5)	5 (1.7)
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	25 (2.0)	24 (2.2)	6 (4.1)	4 (1.1)	12 (3.9)	2 (1.4)	1 (0.3)
Other diseases	150 (12.0)	133 (11.9)	19 (13.1)	34 (9.1)	51 (16.6)	28 (20.3)	18 (6.2)
Total	1253 (100)	1115 (100)	145 (100)	372 (100)	307 (100)	138 (100)	291 (100)

2.2.2.2 ADR characteristics

A total of 328 ADRs were identified in the cohort for risk factors analysis. Overall ADR incidence during hospitalisation was found to be 16.7% (95% CI, 14.5-19.0). **Table 2.19** gives details of the incidence, preventability, and seriousness of ADRs in the total study cohort and in each country.

Table 2.19: Risk factors cohort; incidence, preventability, and seriousness of ADRs stratified by country

Country	Incidence of patients with ADRs (95% CI)	Number of ADRs (%)	Number of preventable ADRs (%)[b]	Number of serious ADRs (%)[b]
Australia ([a]n=10/139)	7.2% (3.5-12.8)	18 (5.5)	7 (38.9)	2 (11.1)
Germany ([a]n=23/289)	8.0% (5.1-11.7)	37 (11.3)	5 (13.5)	12 (32.4)
HK ([a]n=7/111)	6.3% (2.6-12.6)	8 (2.4)	2 (25.0)	1 (12.5)
Malaysia ([a]n=46/279)	16.5% (12.3-21.4)	60 (18.3)	1 (1.7)	26 (43.3)
UK ([a]n=100/297)	33.7% (28.3-39.4)	205 (62.5)	39 (19.0)	21 (10.2)
Overall ([a]n=186/1115)	16.7% (14.5-19.0)	328 (100)	54 (16.5)	62 (18.9)

[a]n=total number of patient with ADRs/total number of patients on drugs. [b]Percentage of serious and preventable ADRs related to total number of ADRs in each county.

Table 2.20 shows identified ADRs in the study cohort classified according to WHO-ART classification.

Table 2.20: Risk factors cohort; identified ADRs classified according to WHO-ART classification

System-organ class	Frequency (% of 328[a])	Examples
Gastro-intestinal system	118 (36)	Diarrhoea, constipation, vomiting, nausea
Skin and appendages	43 (13.1)	Rash macula-papular, angioedema, itching
Heart rate and rhythm disorders	34 (10.4)	Bradycardia, tachycardia
Metabolic and nutritional disorders	30 (9.2)	Hypokalaemia, hyperglycaemia, hyponatraemia
Cardiovascular disorders, general	16 (4.9)	Hypertension, hypotension
Psychiatric disorders	15 (4.6)	Appetite lost, hallucination
White cell and [b]RES disorders	14 (4.3)	Leukocytosis, eosinophilia
Central & peripheral nervous system disorders	10 (3.1)	Headache, tremor, convulsions
Respiratory system disorders	10 (3.1)	Respiratory distress, hypoventilation
Body as a whole, general disorders	9 (2.7)	Fever, odema peripheral
Liver and biliary system	8 (2.4)	[c]ALT increased, bilirubin increased, [d]GGT increased
Resistance mechanism disorders	7 (2.1)	Candidiasis, thrush
Platelet, bleeding & clotting disorders	3 (0.9)	Bruise, thrombocytopenia
Urinary system disorders	3 (0.9)	Nephropathy toxic, urine discolouration
Vascular (extracardiac) disorders	3 (0.9)	Thrombophlebitis
Vision disorders	2 (0.6)	Conjunctivitis, vision blurred
Endocrine disorders	1 (0.3)	Cushing's syndrome
Red blood cell disorders	1 (0.3)	Haemoglobin decreased
Reproductive disorders, female	1 (0.3)	Genital ulceration

[a]Total number of ADRs in risk factors' cohort; [b]RES=Reticuloendothelial system; [c]ALT= Alanine aminotransferase; [d]GGT= gamma-glutamyltransferase

2.2.2.3 Potential risk factors associated with ADRs

2.2.2.3.1 Descriptive statistics

In the risk factors cohort, children with ADRs were hospitalised longer compared to those without ADRs (median 6 days, IQR 4-11 vs 4 days IQR 3-6, $p<0.001$). Overall, age and gender were found not to be associated with the incidence of ADRs ($p=0.117$, $p=0.776$, respectively). However, on a country level; in Australia, Germany, Malaysia, and the UK; patients with an ADR were significantly older compared to those without an ADR ($p<0.05$). The total number of drugs prescribed per patient for children with ADRs was significantly higher compared to children without ADRs (median 6 drugs, IQR 4-10 vs median 3 drugs, IQR 2-5, $p<0.001$). On a country level this was significant for all countries except HK where most of the patients with ADRs had less than five drugs prescribed. Moreover, the number of high risk drugs prescribed per patient was found to be significantly higher in children with ADRs than in children without ADRs (median 3 drugs, IQR 2-5 vs 2 drugs IQR 1-3, $p<0.001$). This was the case in the overall study cohort and in three country cohorts; the exceptions being Australia and HK.

2.2.2.3.2 Statistical modelling

The univariable analysis showed that 9 of the 15 variables were significantly associated with the occurrence of ADRs. In the multivariable modelling only seven variables remained statistically significant.

The use of five or more low risk drugs per patient and the use of three or more high risk drugs were strong predictors for the occurrence of ADRs (OR 4.7, 95% CI, 2.4-9.3; OR 6.5, 95% CI, 2.7-16.0; respectively, $p<0.001$).

In the full model adjusted by country, diagnoses on admission which were significantly associated with an ADR, were diseases of the 'nervous system' or of 'blood and blood-forming organs and certain disorders involving the immune mechanisms' or 'certain conditions originating in the perinatal period'.

The univariable analysis showed that older children aged between >11 and 18 years were more likely to experience ADRs than younger children aged less than 11 years (OR 1.7, 95% CI, 1.0-2.8; $p = 0.031$). This remained significant in the full model adjusted by country.

The univariable analysis for the association between ADR occurrence and the potential risk factors and also the results of the full model of multivariable analysis are shown in **Table 2.21**.

Table 2.21: Risk factors[c] of ADRs in hospitalised children in the study cohort adjusted by country

Risk factors	Univariable OR (95%CI)	*p*-value	Full model[d] OR (95%CI)	*p*-value
Age (years)				
0-≤2y	1.1 (0.79-1.6)	0.498	1.2 (0.80-1.9)	0.351
>2y-≤11y	1.00 (reference)		1.00 (reference)	
>11y-≤18y	1.7 (1.0-2.8)	0.031	2.1 (1.1-3.8)	0.020
Gender (female vs male)	0.96 (0.70-1.3)	0.776	0.94 (0.65-1.4)	0.739
Number of low risk drugs prescribed				
0[a]	1.00 (reference)		1.00 (reference)	
1-4	1.4 (0.91-2.2)	0.129	2.3 (1.4-4.0)	0.002
5-10	4.8 (2.8-8.2)	<0.001	4.7 (2.4-9.3)	<0.001
>10	18.4 (7.6-44.5)	<0.001	11.5 (3.6-36.3)	<0.001
Number of high risk drugs prescribed				
0[b]	1.00 (reference)		1.00 (reference)	
1	1.2 (0.48-3.0)	0.690	0.91 (0.35-2.4)	0.855
2-3	3.5 (1.6-7.7)	0.002	2.4 (1.0-5.6)	0.045
>3	12.1 (5.4-27.3)	<0.001	6.5 (2.7-16.0)	<0.001
A00-B99 (Yes/No)	0.33 (0.15-0.68)	0.003	0.61 (0.30-1.4)	0.225
D50-D89 (Yes/No)	3.9 (2.0-7.5)	0.001	2.3 (1.0-5.1)	0.043
G00-G99 (Yes/No)	2.2 (1.4-3.7)	0.001	2.3 (1.3-4.2)	0.006
P00-P96 (Yes/No)	2.2 (1.0-4.9)	0.053	2.6 (1.0-6.5)	0.049
E00-E90 (Yes/No)	0.13 (0.02-0.93)	0.042	0.20 (0.02-1.6)	0.132

[a]Patients have no low risk drug prescribed; [b]Patients have no high risk drug prescribed. A00-B99: certain infections and parasitic diseases (e.g. enteroviral meningitis, Tuberculosis); D50-D89: diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms (e.g. Sickle-cell anaemia, agranulocutosis); G00-G99: diseases of the nervous system (e.g. epilepsy, sleep apnoea); P00-P96: certain conditions originating in the perinatal period (e.g. congenital hypotonia, bacterial sepsis of newborn); E00-E90: endocrine, nutritional and metabolic diseases (e.g. nutritional deficiency, insulin-dependent diabetes mellitus). [c]Risk factors are presented as crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CI); [d]Full model adjusted for possible confounding factors (age, gender, number of drugs prescribed, and above disease groups)

Table 2.22 summarises the independent factors which were statistically significant in the univariable and multivariable analysis.

Table 2.22: Independent risk factors

Predicator	OR (95% CI)
Age (>11y-≤18y)	2.1 (1.1-3.8)
Number of low risk drugs prescribed; 5-10 >10	 4.7 (2.4-9.3) 11.5 (3.6-36.3)
Number of high risk drugs prescribed 2-3 >3	 2.4 (1.0-5.6) 6.5 (2.7-16.0)
[a]D50-D89	2.3 (1.0-5.1)
[b]G00-G99	2.3 (1.3-4.2)

[a]D50-D89: diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms; [b]G00-G99: diseases of the nervous system

We also considered another regression model including the above predictors plus length of hospital stay to see the influence of hospital stay as a predictor. We obtained the same conclusion from the model for the statistical significance of the included variables except for the diseases variables ("D50-D89" and "P00-P96") which became not significant. Therefore we chose to report the model without length of stay.

2.2.3 Discussion

Data from a large prospective multicentre international cohort study were utilised to investigate risk factors associated with ADRs in hospitalised paediatric patients. The overall ADR incidence in this cohort was 16.7% (95% CI, 14.5-19.0). The previous section (2.1) of this chapter discussed the differences between countries with regards to ADR incidences as well as the characteristics of identified ADRs.

The early detection of ADRs is important to prevent unnecessary harm to the patients. Knowledge of factors predisposing a patient to ADRs is important to develop appropriate prevention strategies.

This study shows that the occurrence of ADRs depends on several factors, which healthcare professionals should consider as key points for identifying potential ADRs; a greater awareness of such factors should minimise patients' risk of ADRs. This is particularly important because the early detection of an ADR is most likely to depend on the clinical observation of patients.

2.2.3.1 Risk factors

2.2.3.1.1 Polypharmacy

Undoubtedly polypharmacy is an important risk factor for ADRs. Previous data have shown that it is significantly associated with the occurrence of ADRs in adults and children (Impicciatore et al. 2001; Weiss et al. 2002; Fattinger et al. 2000; Zopf et al. 2008a). Our study confirmed these findings showing a statistically significant relationship

between the number of drugs prescribed and the occurrence of ADRs. This relationship remained statistically significant in the multivariable analysis in the overall study cohort as well as in each individual country cohort except for HK where the total number of prescribed drugs per patient was very small compared to other countries. The majority of patients with ADRs in HK had less than five drugs prescribed.

Patients with five or more drugs prescribed during their hospital stay had the highest risk of developing an ADR; three times higher compared to patients receiving between one and four drugs, as shown in the multivariable analysis. Similar findings of polypharmacy as a risk factor for ADR occurrence were reported in a study by Zopf et al (2008a), conducted in an adult population.

The use of many drugs (polypharmacy), which was associated with ADRs in the present study, is commonly seen in all types of paediatric wards. For example, antibacterials, analgesics, and drugs for obstructive airway diseases were most often associated with ADRs and most commonly prescribed together.

2.2.3.1.2 Age

When looking into the predefined age groups in the univariable logistic regression analysis, the ORs indicated that older children were more prone to have ADRs than younger children. This was confirmed in the multivariable analysis which showed that the age group "$>11y$-$\leq 18y$" was an independent risk factor. A previous study by Gonzalez-Martin et al (1998) showed that, although there was no statistically significant difference

between age groups, older age children (10 to 16 years) had a tendency to have a higher ADR frequency.

Similar findings have been reported in other published studies (McKenzie et al. 1973; Mitchell et al. 1979). However, these findings should be interpreted with caution. Human physiology is constantly changing from birth to adolescence, resulting in varying responses to drugs among age groups. These differences in pharmacokinetics are particularly significant in neonates and very young children (Kearns et al. 2003). Thus, a higher ADR incidence would be expected in very young children such as neonates. The question remains as to whether this association is because more high risk drugs are given to older children causing more ADRs or because of the nature of the drugs.

2.2.3.1.3 Gender

Some studies in adults have shown that female patients are more prone to develop ADRs than male patients whereas other studies do not (Fattinger et al. 2000; Bates et al. 1999; Sánchez Muñoz-Torrero et al. 2010; Zopf et al. 2009). However, a recent paediatric study which used the WHO VigiBase database found that a high proportion of ADR reports among children were for boys (Star et al. 2011). In our study, we found that almost equal proportions of ADRs were identified for female and male patients (17.0%, 16.4%, respectively). Also, univariable and multivariable analyses showed that gender was not a predisposing factor in either the overall study cohort or in any country cohort. However, our results could be explained by the fact that due to the unique physiology and immature systems in children, especially young children, gender might not be a predisposing factor

for ADRs in children. A study by Zopf et al (2008b) found that females were at higher ADR risk compared to males except for children and young adults.

Although the impact of other socioeconomic factors on the occurrence of ADRs has been reported in adults and children (Caamaño et al. 2005; Major et al. 1998), they were not investigated in our study because it would have been very difficult to get comparable information on such risk factors from the different countries and hence a bias could be introduced. Nevertheless, it is an interesting area for further research.

A study by Knopf and Du (2010) showed that there was no significant difference in the occurrence of ADRs between boys and girls with regards to their social status (defined by parents' education level, household incomes, and profession). However, another study looking for drug-related hospitalisation in both adults and children in Lebanon found that socioeconomic status was a risk factor for increased ADR incidence in children (Major et al. 1998). But it did not comment on any difference between males and females with regard to socioeconomic status. Though one hypothesis might be that less education might led to more medicines being taken because the patients are less cautious and therefore more ADRs might have occurred due to polypharmacy. However, an alternative hypothesis could be that having low income could lead to less access to prescribed medicines which in turn could result in greater use of either non-prescribed or traditional medicines.

2.2.3.1.4 Drugs involved in ADRs

Another factor we investigated as a potential risk factor for ADRs was the use of certain drug groups which we had pre-defined as high risk drugs. There was a significant association between the use of high risk drugs (analgesics; antiepileptics; systemic corticosteroids; immunosuppressive agents; systemic antibacterials and antimycotics, drugs for obstructive airway diseases) and the risk of ADRs. Bates et al (1999) using univariable analysis, reported that in adults, diuretics, electrolyte concentrates, antitumor agents and anticoagulants are associated with the occurrence of ADRs. However, the majority of drugs identified in this study as risk factors in adults were not commonly prescribed in our paediatric study cohort. Therefore, data from adults are not necessarily applicable to children.

In our study antibacterials, analgesics and 'drugs for obstructive airways diseases' were most often reported to be associated with ADRs. This is in line with what has been reported by Turner et al (1999) and Neubert et al (2006). Gill et al (1995) also reported similar drugs (morphine, salbutamol) as being most frequently involved in ADRs. Anti-infective and respiratory drugs were found to be the medications most commonly prescribed to children in primary care in the UK, Italy and the Netherlands (Sturkenboom et al. 2008), therefore, it is important for both primary care and secondary care physicians and pharmacists to be vigilant and to be aware of the risks associated with the use of these medications and monitor patients for potential ADRs.

2.2.3.1.5 Associated diagnosis

In this study, the univariable analysis showed that the risk of ADRs is higher if the patient has one of the following four ICD diagnoses on admission; 'certain infections and parasitic diseases' (A00-B99), 'diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms' (D50-D89), 'diseases of the nervous system' (G00-G99), 'endocrine, nutritional and metabolic diseases' (E00-E90). However, in the multivariable regression model only two types of disease were shown as independent variables and remained statistically significant (D50-D89, G00-G99).

These two disease groups which were independently associated with the occurrence of ADRs, involve an impairment of biological defence mechanisms which may predispose patients to the development of ADRs as the body has less capacity to compensate. This is especially applicable to patients with suppressed immune systems and metabolic diseases (Bennett & Brown 2003). On the other hand these findings could be because healthcare professionals/caregivers use one or more of the high risk drugs to treat such conditions which in turn predispose a patient to an ADR. Comparisons with previous studies are not possible to make as none has investigated disease as a potential predictor for ADRs.

2.2.3.2 Length of hospital stay (LOS)

We considered the length of stay in hospital (LOS) as a consequence of having an ADR though not as a risk factor to predispose to an ADR. Many previous studies have considered length of hospital stay as a risk factor for ADRs (Weiss et al. 2002). However, the fact of being hospitalised is not necessarily associated with the occurrence of ADRs. By comparing the length of hospital stay for patients with an ADR with patients who did

not experience an ADR (median 6 days vs 4 days, $p<0.05$) we could not exclude the possibility that a longer hospital stay could be the consequence of an ADR rather than a risk factor predisposing to an ADR. Previous studies conducted in adults, showed that ADRs could be a cause of a longer LOS for patients with an ADR (Sánchez Muñoz-Torrero et al. 2010; Fattinger et al. 2000).

Extended hospital stays due to ADRs lead to an increase in costs for hospitalisations, which in turn increases the economic burden on the healthcare system. Previous studies conducted in adults have shown that ADRs occurring during hospitalisation increase the length of hospital stay, as well as increase the cost of hospitalisation (Classen et al. 1997; Pirmohamed et al. 2004).

2.2.3.3 Strengths and Limitations

2.2.3.3.1 Strengths

This study used multiple logistic regression which allows us to better understanding of the relationship between independent ADR predictors. This study was conducted on an international level and involved five hospitals from five countries in Europe, Asia and Australia which, we believe, overcomes variations reported in previous studies (Impicciatore et al. 2001), such as study settings, patient group, and also standardised methods were used to identify ADRs, for statistical analysis, and for ADR definition. This makes the results of our study more generalizable to other healthcare settings in other countries and/or hospitals. Moreover, this study also allowed us to get a clear

picture regarding the effect of different treatment strategies and different study populations on the occurrence of ADRs.

2.2.3.3.2 Limitations

A limitation of this study is that the effect of unlicensed and off-label use of medications as potential risk factors for ADRs was not analysed. Another limitation was that the duration of data collection in Australia was only one month due to resource limitations which resulted in a small sample size from Australia. Other limitations are described in detail in section 2.1.7.5.2 of this chapter.

2.3 Conclusions

This international paediatric study provides important information about the nature of ADRs in hospitalised paediatric populations across different countries around the world. Collecting data from five countries in Europe, Asia and Australia shows that there is great variation between countries (e.g. frequency and nature of ADRs) which were likely to be due to different populations and treatment strategies. However, the highest incidence of ADRs in children was reported in the UK.

The present study found that 1.8% of children were admitted to a hospital over the study period as a result of an ADR. Furthermore, it also confirmed that ADRs are a considerable risk for hospitalised children, i.e. on average every sixth child in hospital experiences an ADR and every 18th has an ADR with serious consequences. Also the number of drugs per patient is a major contributor to the occurrence of ADRs in all

countries. The use of morphine and IV salbutamol contributed to the higher ADR incidence in the UK.

Furthermore, the in-depth statistical analysis for the potential risk factors in this study showed that the following were independent predictors of ADRs: number of drugs prescribed per patient, older children, presence of 'diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms'; or 'diseases of the nervous system'; or 'certain conditions originating in the perinatal period'. Gender, however, did not appear to play such an important role in paediatric ADR epidemiology in this study as has been reported in adult populations.

2.3.1 Implications for healthcare

- Opioids were found to be of particular concern regarding their use in hospitalised children as well as the number of drugs prescribed per patient. Therefore, optimising treatment strategies and reducing drug use (polypharmacy) are important to maximise patient safety.

- The findings of the risk factors analysis indicate that to minimize the risk of ADRs, healthcare professionals including pharmacists should keep the number of prescribed drugs as low as possible, pay particular attention to children prescribed five drugs or more, to those children at high risk such as immuno-compromised patients, and also to children prescribed certain categories of drugs (high risk drug groups). Improvements in the education of prescribers emphasising identification of risk factors for ADRs and the importance of risk benefit assessments before any

medicine is prescribed could help to implement such practices in paediatric hospital departments.

- To facilitate the earlier identification of ADRs in the paediatric setting, documentation in hospitals needs to be improved to include all potential data sources such as relevant information given by parents.

- Sharing safety information is essential to enhance the benefit-risk profile of drugs used in children. The findings from this study could act as baseline to which other paediatric services around the world could compare their practice. Furthermore, these data could be used to support evidence-based protocols for healthcare professionals and policy makers to improve the awareness of the safety of drugs used in children.

Chapter THREE: Drug-related problems in children

The ADVISE study in the previous chapter (chapter 2) showed that ADRs were common in hospitalised paediatric populations at international level and also that there were variations in the ADR incidence across the five countries included in the ADVISE study (7.9% - 34.9%). The overall incidence of ADRs was 18.5% for hospitalised children on medication which is higher than was reported in previous ADR research in paediatric populations. In addition, it was noted during the study that there seemed to be variation in the treatment strategies used by healthcare professionals in different countries. Therefore, a research study investigating this further in the wider context involving all types of problems related to the medication process, including ADRs, considered to be one of the most important drug-related problems (DRPs) as they are common and may cause serious harm to hospitalised children, and also to establish whether there is a difference in the safety culture within the healthcare profession treating paediatric patients in different countries.

This chapter describes a pharmacoepidemiological study of DRPs problems, including ADRs, that was conducted in hospitalised children and/or those attending the accident and emergency department (A&E) in two hospitals, one in the UK and one in the Kingdom of Saudi Arabia (KSA).

3.1 Drug-related problems in children in United Kingdom and Saudi Arabia

The work in this chapter has been submitted as a paper to 'BMJ Quality and Safety in Health Care'.

3.1.1 Introduction

The use of medications can result in significant problems which might be associated with morbidity and mortality (Johnson & Bootman 1995).

Drug-related problems (DRPs) are defined as "an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcome" (Pharmaceutical Care Network Europe "PCNE" 2006). DRPs encompass adverse drug reactions (ADRs), inappropriate drug choice, medication errors, and untreated conditions all these are common in adults and in children (Koh et al. 2005; Eichenberger et al. 2010; Rashed et al. 2011). Previous studies have shown that DRPs are of major concern in the adult population and the incidence of DRPs leading to hospitalisation has been reported to be high as 24% in previous studies (Zed 2005; Koh et al. 2003; Zargarzadeh et al. 2007).

Hospitalisations, long-term care admissions, emergency department visits, additional physician office visits, and additional prescriptions are some of the consequences associated with DRPs (Howard et al. 2008; Zed 2005; Easton et al. 1998; Roughead, 1999; Major et al. 1998; van den Bemt et al. 2000a; Bednall et al. 2003). Therefore, the economic burden of DRPs is extensive and this has been demonstrated in several studies (Einarson 1993; Ernst & Grizzle 2001). It was found that drug-related morbidity and

mortality could cost between $30.1 billion and $136.8 billion annually in the United States (Johnson & Bootman 1995).

However, epidemiological and economic data on DRPs in the paediatric population are limited as most of the published studies were conducted in adults. Studies in the paediatric population focused mainly on one aspect of DRPs such as ADRs, non-compliance or medication errors. Consequently the results of these studies are limited and only partially reflect the wider picture of DRPs (Gallagher et al. 2011; Ghaleb et al. 2010; Clavenna & Bonati 2009; Neubert & Rascher 2007; dos Santos & Coelho 2006; Classen et al. 1997; Einarson 1993; Yosselson-superstine & Weiss 1982).

Data from Australia indicate that 4.3% (n=127/2933) of paediatric hospital admissions and 3.3% (n=280/8601) of A&E visits are related to DRPs and 51.3% were found to be preventable (Easton et al. 2004, Easton et al. 2003). We have not been able to identify any other studies which reported on all types of DRPs in hospitalised paediatric patients in other countries. In the United Kingdom (UK), the extent of DRPs in children is not well known and there have been no studies conducted on the hospitalised paediatric population in regard to DRPs in the Kingdom of Saudi Arabia (KSA). Only two previous studies have been conducted in KSA on DRPs; one was conducted in both adult and paediatric populations (Al-Olah & Al Thiab 2008), focusing mainly on DRPs causing admission (Ahmed 1997, Al-Olah & Al Thiab 2008) and one of them (Ahmed 1997) was limited to two types of DRPs.

Recently at King Abdulaziz Medical City, Saudi Arabia, and in collaboration with the Institute for Safe Medication Practices (ISMP), a system to improve medication safety practice was established. Whilst in the United Kingdom (UK), as in many other European countries, medication safety research and practice has been established for a long time. Therefore, conducting drug safety projects such as investigating DRPs in these two countries would help them to define opportunities for practice improvement and further collaboration.

Given this background, the aim of this study was to determine the epidemiology of and to identify the characteristics of DRPs in children admitted to hospital or attending an A&E department in two teaching hospitals, one in KSA and the other in the UK. Furthermore, areas of most concern were to be identified. This is particularly important to determine opportunities for improving the practice of pharmacological treatment.

Originally, the plan was to include the same countries for the DRPs study that participated in the ADVISE study. However, due to resource limitations and time constraints this was not feasible, so the DRPs study was conducted in two countries; the UK and the KSA. It had not been possible to collect ADR data for the ADVISE study from the KSA site because they joined the team very late, however, the KSA team are planning to conduct an ADR study later. Moreover, the German team are now applying for a grant to conduct a DRP study, but due to time constraints it was not possible to include their study in this thesis.

Although, HK which was involved in the ADVISE study also conducted a study on DRPs but the assessment of the DRP cases for severity and preventability was not completed in time to be included in the analysis for this thesis, hence the HK data were excluded from this thesis. However, the HK team are working to complete the assessment and their data will be analysed and submitted for publication later.

The data collection at the UK site was funded by the Neonatal and Paediatric Pharmacists Group (NPPG) ManMed award 2009 (NPPG 2009).

3.1.2 Aim and objectives

The aim of this study was to determine the epidemiology of and to identify the characteristics of DRPs in children admitted to hospital or attending an A&E department in two teaching hospitals, one in the KSA and the other in the UK.

The objectives were to identify:

- The incidence of DRPs at each study site.
- The types and causes of DRPs in children.

3.1.3 Method

3.1.3.1 Study setting

An observational study conducted in two large teaching hospitals (King Abdul-Aziz Medical City in Jeddah and Evelina Children's Hospital based at St Thomas' Hospital in London) in two countries (KSA & UK). The study was conducted in the paediatric medical ward, the paediatric intensive care unit (PICU), the neonatal intensive care unit (NICU), and/or in those attending the A&E department in each hospital.

King Abdul-Aziz Medical City, in Jeddah, is a tertiary teaching hospital providing services for the Saudi Arabian population in the western region of KSA. It has over 500 beds in total and the paediatric wards have a capacity of 83 beds but there are no special beds for paediatric patients in A&E, although it receives on average 3000 children per month (36,000 per year).

The Evelina Children's hospital has 180 beds in total (Chapter 2, section 2.2.4.2, **Table 2.2**) and it has a specified paediatric A&E area located within St Thomas' Hospital A&E department. The A&E receives on average 1750 children per month (21,000 per year).

3.1.3.2 Study design

The aim was to collect data over a three-month period in each hospital between 1st April 2010 and 30th September 2010. Data were collected over a three-month period for all wards in KSA. In the UK, data were collected over a three-month period for the medical ward, but only over a one-month period for PICU and NICU due to shortage of pharmacy's staff. However, data were collected for one month period only for A&E in both hospitals due to resource limitations. **Table 3.1** shows the data collection period in each ward in both countries.

All study wards were overseen on a daily basis (excluding weekends) by a staff pharmacist except the A&E department which does not have regular pharmacist support in either of the two countries, therefore, a researcher (research pharmacist/resident doctor) collected the data.

Table 3.1: Data collection period in each ward

Country	Ward			
	A&E	Medical	NICU	PICU
KSA	1st – 30th September	1st June – 1st September	1st June – 1st September	1st June – 1st September
UK	15th July - 15th August	1st April – 1st July	15th June – 15th July	15th July – 15th August

3.1.3.3 Study Population

Patients included were children aged 0-18 years admitted to the study wards or A&E during the study period.

Children were grouped into five age groups modified from the International Conference of Harmonization Guideline (ICH) E11 as following; ≤1 month, >1 month -to- ≤2 years, >2 years - ≤6 years, >6 years - ≤12 years, and >12 years - ≤18 years (ICH guideline 2001).

3.1.3.3.1 Exclusion criteria

- Patients not on medication either on admission or during their stay were not included in the study cohort.
- Patients whose records were not available for the pharmacist during the ward visit were not included in the study cohort.

3.1.3.4 Data collection

The staff pharmacists and the researchers visited the participating wards and the A&E departments on a daily basis (excluding weekends) and reviewed all patients' drug charts (prescriptions), medical records, and laboratory data for potential DRPs. A DRP was defined as;

> "*an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcome*" (PCNE 2006).

Patients' demographics and clinical details including age, gender, and principal diagnosis were recorded for all patients included in the study. Details of potential DRPs including type of DRP, causes (reasons for), action taken (intervention) and outcome of the interventions were identified and recorded.

The data collection form was modified from the DRP-Registration Form version 5.01 designed by the PCNE (2006), (Appendix 8). The adapted collection form allowed documentation of who identified the DRP and who took action to resolve it, as well as the time spent per DRP.

For standardisation, established international terminologies were used;

- Anatomical Therapeutic Chemical (ATC) classification (WHO 2011) for drugs,
- International Classification of Diseases 10th (ICD-10) revised version (WHO 2007) for diagnoses.

3.1.3.5 Classification of DRPs

3.1.3.5.1 Types of DRPs

PCNE developed a hierarchically structured system which contains codes for problems, their causes, interventions and the outcome of the intervention. As previously shown in **Table 1.4** in chapter one (section 1.2.2) of this thesis, the PCNE classification system for DRPs was the only system among the systems evaluated that has a clear clinical definition and hierarchical classification for types of DRP, their related causes, and the interventions taken. In addition, this system has a published validation, evidence of usability in practice, and focuses on the medicines' use process (van Mil et al. 2004).

We adapted the PCNE classification system (version 5.01) by adding subcategories to classify the DRPs identified in our study. This modified PCNE classification system for DRPs has six main categories and 25 subcategories (original version contains 21 subcategories). The main categories are; adverse drug reactions (ADRs), drug choice problem, dosing problem, drug use problem, interactions, and 'others' (**Table 3.2**).

Table 3.2: Type of DRPs based on the adapted PCNE[a] classification system (V5.01)

Main category	Code	Subcategory
Adverse Reactions	P1	
	P1.1	Side effect suffered (non allergic)
	P1.2	Side effect suffered (allergic)
	P1.3	Toxic effect suffered
Drug Choice Problem	P2	
	P2.1	Inappropriate drug
	P2.2	Inappropriate dosage form
	P2.3	Inappropriate duplication of drug group
	P2.4	Contra-indication for drug
	P2.5	No clear indication for drug
	P2.6	No drug but clear indication
Dosing Problem	P3	
	P3.1	Drug dose too low or dosing interval too long
	P3.2	Drug dose too high or dosing interval too short
	P3.3	Duration of treatment too short
	P3.4	Duration of treatment too long
	[b]P3.5	Inappropriate infusion rate
	[b]P3.6	Inappropriate concentration
Drug Use Problem	P4	
	P4.1	Drug not taken/administered at all
	P4.2	Wrong drug taken/administered
	[b]P4.3	Admixture incompatible or unstable drugs
Interaction	P5	
	P5.1	Potential interaction
	P5.2	Manifest interaction
Others	P6	
	[b]P6.1	Wrong patient
	P6.2	Illegible writing and inappropriate abbreviation
	P6.3	Patient dissatisfied with therapy
	P6.4	Insufficient awareness of health and disease
	P6.5	Therapy failure (unknown reason)

[a]PCNE = Pharmaceutical Care Network Europe; [b]Subcategories that have been added

3.1.3.5.2 Causes and interventions

The adapted PCNE form (V 5.01) classified the reasons (causes for) which may have lead to the problem into six main categories; drug or dose selection (C1), drug use process (C2), information (C3), patient/psychological (C4), and logistic (C5) (including: prescribed drug not available, other prescribing error "information written wrong or missing on the prescription", dispensing error), 'others' (C6) and 36 subcategories (original version contains 34 subcategories), (**Table 3.3**).

Table 3.3: DRP causes based on the adapted PCNE[a] classification system (V5.01)

Main category	Code	Subcategory
Drug or Dose Selection	C1	
	C1.1	Inappropriate drug selection
	C1.2	Inappropriate dosage selection
	C1.3	More cost-effective drug available
	C1.4	Pharmacokinetic problems
	C1.5	Synergistic/preventive drug required
	C1.6	Deterioration/improvement of disease state
	C1.7	New symptom/indication revealed
	C1.8	Manifest side effect, no other cause
Drug Use Process	C2	
	C2.1	Inappropriate timing of dosing
	C2.2	Drug underused/ under-administered
	C2.3	Drug overused/ over-administered
	C2.4	No therapeutic drug monitoring
	C2.5	Drug abused
	C2.6	Patient unable to use drug/form as directed
Information	C3	
	C3.1	Instructions for use/taking not known
	C3.2	Caregiver unaware of reason for drug treatment
	C3.3	Caregiver has difficulties reading/understanding drug label
	C3.4	Caregiver unable to understand local language
	C3.5	Lack of communication between health professionals
	[b]C3.6	Poor documentation of drug history
	[b]C3.7	Misinterpretation of computer drug record
Patient/Psychological	C4	
	C4.1	Caregiver forgets to use drug
	C4.2	Caregiver has concerns with drugs
	C4.3	Caregiver suspects side-effects
	C4.4	Caregiver unwilling to carry financial costs
	C4.5	Caregiver unwilling to bother physician
	C4.6	Caregiver unwilling to change drugs
	C4.7	Caregiver unwilling to adapt life-style
	C4.8	Burden of therapy
	C4.9	Treatment not in line with health beliefs
	C4.10	Patient takes food that interacts with drug
Logistics	C5	
	C5.1	Prescribed drugs not available
	C5.2	Other prescribing error (information wrong/missing on the prescription)
	C5.3	Dispensing error
Others	C6	
	C6.1	Other cause
	C6.2	No obvious cause

[a]PCNE = Pharmaceutical Care Network Europe; [b]Subcategories that have been added

Potential interventions to solve the problem were classified into four main categories (at prescriber level (I1), patient/carer level (I2), drug level (I3), and 'others' (I4), and 21 subcategories (original version contains 17 subcategories), (**Table 3.4**). For each DRP a maximum of three causes and three interventions could be allocated.

Table 3.4: Type of interventions based on the adapted PCNE[a] classification system (V5.01)

Main category	Code	Subcategory
No Intervention	I0	
At Prescriber Level	I1	
	I1.1	Prescriber informed only
	I1.2	Prescriber asked for information
	I1.3	Intervention proposed, approved by prescriber
	I1.4	Intervention proposed, not approved by prescriber
	I1.5	Intervention proposed, outcome unknown
At Patient/Carer level	I2	
	I2.1	Patient (medication) counselling
	I2.2	Written information provided only
	I2.3	Patient referred to prescriber
	I2.4	Spoken to family member/caregiver
At Drug Level	I3	
	I3.1	Drug changed
	I3.2	Dosage changed
	I3.3	Formulation changed
	I3.4	Instructions for use changed
	[b]I3.5	Route of administration changed
	[b]I3.6	Duration of treatment changed
	I3.7	Drug Stopped
	I3.8	New drug started
	[b]I3.9	Recommend monitoring of drug concentration
	[b]I3.10	Recommend monitoring of related laboratory data
Others	I4	
	I4.1	Other intervention
	I4.2	Side effect reported to authorities

[a]PCNE = Pharmaceutical Care Network Europe; [b]Subcategories that have been added

3.1.3.5.3 Outcome of DRPs which had intervention(s)

The adapted PCNE form (V 5.01) classifies the outcome of the interventions into four main categories; unknown (O0), totally solved (OI), partially solved (O2), not solved (O3) [with 4 subcategories]. The subcategories of the outcome of the interventions remained unchanged. Only one outcome could be selected for each DRP that had intervention(s) (**Table 3.5**).

Table 3.5: Outcome for a DRP which had intervention(s) based on the adapted PCNE[a] classification system (V5.01)

Main category	Code	Subcategories
0. Not known	O0.0	Outcome of intervention not known
1. Solved	O1.0	Problem totally solved
2. Partially solved	O2.0	Problem partially solved
3. Not solved	O3.1	Problem not solved, lack of cooperation of patient
	O3.2	Problem not solved, lack of cooperation of prescriber
	O3.3	Problem not solved, intervention not effective
	O3.4	No need or possibility to solve problem[b]

[a]PCNE = Pharmaceutical Care Network Europe; [b]If the patient had transferred or was discharged or died.

3.1.3.6 Validation and analysis of DRPs

3.1.3.6.1 Validation of DRPs

All potential DRPs detected by the staff pharmacists or researchers were validated by an expert panel in the individual country. The panel in each country consisted of a consultant paediatrician, clinical pharmacist, and a researcher. The panel reviewed the cases and validated whether it was a DRP as defined by PCNE (2006). Once a DRP was validated by the panel, they assessed it for severity and preventability.

3.1.3.6.2 Severity

As there is no established measure of severity of DRPs, we adopted the validated scale for medication errors published by Dean and Barber (1999). The members of the panel scored the validated DRPs independently in terms of potential patient outcome on a scale of 0 to 10, where 0 represents a case with no potential adverse effect and 10 a case that would result in death. The mean score for each DRP was used as an index of severity, a mean score of less than 3 was considered to be a minor outcome (very unlikely to have adverse effects), a mean score between 3 and 7 was considered to be moderate (likely to cause some adverse effects or interfere with therapeutic goals but very unlikely to result in death or lasting impairment), and a mean score greater than 7 was considered to be a severe outcome (likely to cause death or lasting impairment).

3.1.3.6.3 Preventability

In each country, the preventability of each identified DRP was assessed by two members of the panel, using the criteria provided by Schumock and Thornton (1992) which have been used in previous studies conducted on DRPs in paediatric populations (Baena et al. 2001; Easton et al. 1998; Easton et al. 2003; Easton et al. 2004). Schumock and Thornton's (1992) algorithm criteria have been given in Chapter two of this thesis (Section 2.2.4.7, **Table 2.6**).

3.1.3.6.4 DRP incidence during study period

The incidence of patients with a DRP was defined as the number of patients with at least one DRP during the study period divided by the total number of patients in the study cohort and multiplied by 100, or by the number in each country or ward, as appropriate. The incidence was calculated with 95% CIs.

3.1.3.7 Sample size calculation

As this is a descriptive study, assuming the incidence of DRP is approximately 3% of patients; a sample size of 500 will be able to detect a DRP incidence with 95% CI between 1.8% and 4.8%, using a spreadsheet based on Wilson's method (Wilson 1927).

3.1.3.8 Statistical analysis

The data were entered into a database designed for this study using Microsoft Access 2007 and analysed using Stata 11 (StataCorp, College Station, Texas, USA). Descriptive statistics were performed on all data. Generally, data are presented as number, percentage, median, Inter-Quartile Range [IQR (Q1-Q3)] unless otherwise specified. The Chi-

Squared test was used to detect significant differences for categorical variables. As the data did not exhibit a normal distribution, the Kruskal-Wallis rank test and the Wilcoxon rank-sum test (Mann-Whitney U) were used to determine significant differences between numerical variables. For all tests $p<0.05$ was selected as the level for statistical significance.

3.1.4 Ethical consideration

The study was approved by the local NHS Ethics Committee as an amendment to the ADVISE study in the UK and by the Research Committee at King Abdulaziz Medical City, National Guard Health Affairs, Jeddah, KSA (Appendices 9 & 10).

3.1.5 Results

3.1.5.1 Characteristics of study population

A total of 990 patients were included in this study from the two countries (KSA n=507, UK n=483). Their ages ranged from 0 to 18 years (median 3 years, IQR 10 months – 8 years) and 58.6% (n=580) were male. There was a significant difference in age between patients from the two countries ($p<0.01$), while there was no statistical difference with regards to gender ($p=0.364$). Overall, 281 patients experienced one DRP, 72 patients experienced two DRPs, 22 patients had three DRPs, and 13 patients had more than three DRPs. **Table 3.6** gives details of patients' characteristics and frequency of DRPs in the study cohort as well as in each country cohort.

Table 3.6: Patients demographics and frequency of DRPs in each ward

	KSA					UK					Study cohort (n=990)
	A&E (n=143)	Medical (n=302)	NICU (n=45)	PICU (n=17)	Total (n=507)	A&E (n=110)	Medical (n=273)	NICU (n=50)	PICU (n=50)	Total (n=483)	
Gender; n (%)											
Female	59 (41.3)	129 (42.7)	22 (48.9)	7 (41.2)	217 (42.8)	42 (38.2)	104 (38.1)	24 (48.0)	23 (46.0)	193 (40.0)	410 (41.4)
Male	84 (58.7)	173 (57.3)	23 (51.1)	10 (58.8)	290 (57.2)	68 (61.8)	169 (61.9)	26 (52.0)	27 (54.0)	290 (60.0)	580 (58.6)
Median age[a] (IQR: Q1-Q3)	3.7 (1.3-8.3)	5.0 (2.0-8.0)	1 d (1.0d-7.0d)	5.0 (1.0-9.0)	4.0 (1.0-8.0)	4.8 (2.0-9.0)	3.0 (11.0m-10.0y)	1 d (1.0d-2.0d)	7.5 m (3.0m-2.3y)	2.2 (6.0m-8.0y)	3.0 (10.0m-3.0y)
Age in group; n (%)											
0-1m	3 (2.1)	5 (1.7)	40 (88.9)	0	48 (9.5)	1 (0.9)	15 (5.5)	50 (100)	8 (16.0)	74 (15.3)	122 (12.3)
>1m-≤2y	43 (30.1)	97 (32.1)	5 (11.1)	8 (47.1)	153 (30.2)	26 (23.6)	109 (39.9)	0	28 (56.0)	163 (33.7)	316 (31.9)
>2y-≤6y	51 (35.7)	91 (30.1)	0	1 (5.9)	143 (28.2)	41 (37.3)	52 (19.0)	0	11 (22.0)	104 (21.5)	247 (25.0)
>6y-≤12y	36 (25.2)	89 (29.5)	0	5 (29.4)	130 (25.6)	33 (30.0)	46 (16.8)	0	1 (2.0)	80 (16.6)	210 (21.2)
>12y-≤18y	10 (7.0)	20 (6.6)	0	3 (17.6)	33 (6.5)	9 (8.2)	51 (18.7)	0	2 (4.0)	62 (12.8)	95 (9.6)
Frequency of DRPs and of patients with DRPs in each ward											
No. of DRPs (%)[b]	51 (16.5)	210 (68.0)	27 (8.7)	21 (6.8)	309 (100)	17 (7.2)	143 (60.3)	28 (11.8)	49 (20.7)	237 (100)	546
No. of patients with DRP (%)[c]	41 (28.7)	159 (52.6)	17 (37.8)	10 (58.8)	227 (44.8)	14 (12.7)	93 (34.1)	24 (48.0)	30 (60.0)	161 (33.3)	388 (39.2)
No. of patients with DRP by gender: n(%)											
Female	18 (30.5)	64 (49.6)	9 (40.9)	3 (42.9)	94 (43.3)	3 (7.1)	34 (32.7)	14 (58.3)	14 (60.9)	65 (33.7)	159 (38.8)
Male	23 (27.4)	95 (54.9)	8 (34.8)	7 (70.0)	133 (45.9)	11 (16.2)	59 (34.9)	10 (38.5)	16 (59.3)	96 (33.1)	229 (39.5)
No. of patients with DRPs, stratified by DRP type; n (%)[d]											
ADRs	1 (2.4)	11 (6.9)	2 (11.8)	3 (30.0)	17 (7.5)	8 (57.1)	21 (22.6)	10 (41.7)	16 (53.3)	55 (34.2)	72 (18.6)
Drug choice problem	2 (4.9)	26 (16.4)	-	3 (30.0)	31 (13.7)	1 (7.1)	43 (46.2)	-	9 (30.0)	53 (32.9)	84 (21.6)
Dosing problem	39 (95.1)	135 (84.9)	12 (70.6)	10 (100)	196 (86.3)	2 (14.3)	41 (44.1)	11 (45.8)	12 (40.0)	66 (41.0)	262 (67.5)
Drug use problem	1 (2.4)	3 (1.9)	2 (11.8)	-	6 (2.6)	4 (28.6)	13 (14.0)	2 (8.3)	4 (13.3)	23 (14.3)	29 (7.5)
Interactions	-	14 (8.8)	1 (5.9)	1 (10.0)	16 (7.0)	-	-	-	-	-	16 (4.1)
Others	-	4 (2.5)	5 (29.4)	-	9 (4.0)	1 (7.1)	11 (11.8)	3 (12.5)	2 (6.7)	17 (10.6)	26 (6.7)

[a]Age calculated in years (y) unless otherwise specified, d=day, m=month, IQR=Inter-Quartile Range; [b]% calculated out of total number of DRPs in each country; [c]% calculated using total number of patients (in each ward, country cohort, and study cohort) as denominator; [d]number of children with various DRP types does not add up to total number in each ward, as one child can contribute to more than one DRP type, % calculated out of total number of patients with DRPs in each ward, each country or the overall study cohort.

Using the WHO-ICD 10 classification, overall the most frequently reported diagnoses of the conditions that the children had when they attended the hospitals were: "symptoms, signs and abnormal clinical laboratory findings, not elsewhere classified" (n=157), followed by "diseases of the respiratory system" (n=87), and "neoplasm disease" (n=79), though the pattern differed by country. **Table 3.7** shows the diagnoses most frequently reported from each country and overall.

Table 3.7: Top ten diagnoses using WHO-ICD10 classification

Diagnosis	KSA n=507 (%)	UK n=483 (%)	Study cohort n=990 (%)
Symptoms, signs and abnormal clinical and laboratory findings (NOS)[a] (e.g. wheezing, fever)	34 (6.7)	123 (25.5)	157 (15.9)
Diseases of the respiratory system (e.g. bronchitis, asthma)	37 (7.3)	50 (10.4)	87 (8.8)
Neoplasms (e.g. Leukaemia, severe combined immunodeficiency [SCID] with reticular dysgenesis)	63 (12.4)	16 (3.3)	79 (8.0)
Injury, poisoning and certain other consequences of external causes (e.g. superficial injury of head, venom of scorpion)	31 (6.1)	42 (8.7)	73 (7.4)
Factors influencing health status and contact with health services (e.g. presence of ontological and audiological implants, attention to tracheostomy)	49 (9.7)	20 (4.1)	69 (7.0)
Congenital malformations, deformations (e.g. cleft palate, patent ductus arteriosus)	36 (7.1)	29 (6.0)	65 (6.6)
Certain conditions originating in the perinatal period (e.g. respiratory distress of newborn, bacterial sepsis of newborn)	34 (6.7)	30 (6.2)	64 (6.5)
Diseases of the digestive system (e.g. gatro-oesophageal reflux disease, constipation)	50 (9.9)	11 (2.3)	61 (6.2)
Certain infectious and parasitic diseases (e.g. septicaemia, chickenpox)	28 (5.5)	31 (6.4)	59 (6.0)
Diseases of the blood and blood-forming organ and certain disorders involving the immune mechanism (e.g. sickle-cell anaemia, anaemia due to G6PD[b] deficiency	22 (4.3)	27 (5.6)	49 (5.0)

[a]NOS = not elsewhere classified; [b]G6DP = glucose-6-phosphate dehydrogenase

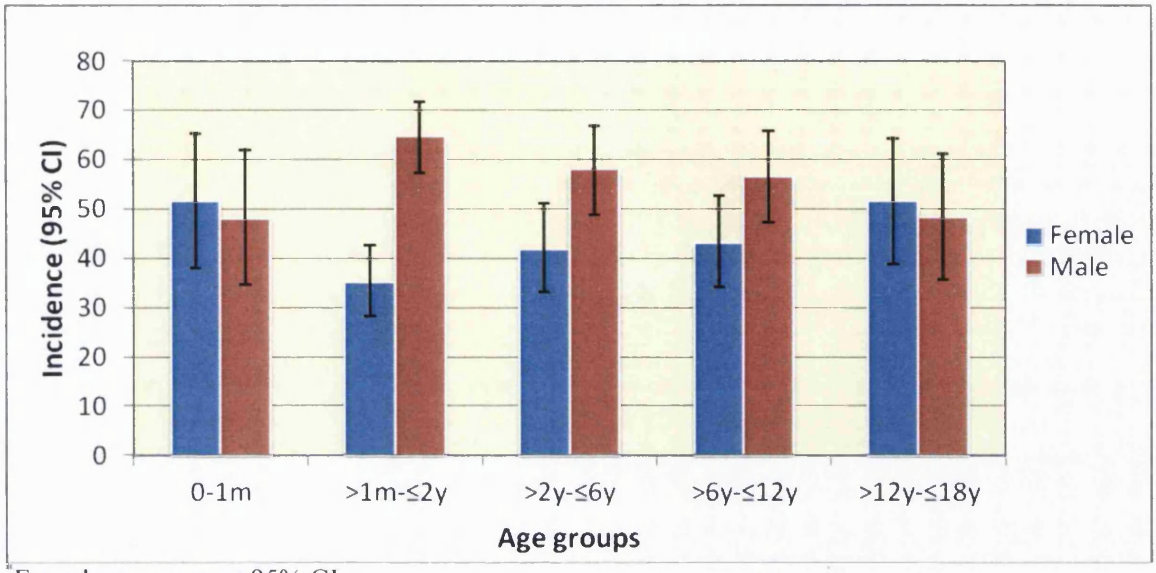
3.1.5.2 Incidence of DRPs during the study period

A total of 546 confirmed DRPs (KSA n=309, UK n=237) were identified for 388 children (KSA n=227, UK n=161), (**Table 3.6**). In the total cohort, the median for the number of DRPs per patient was one (min 1, max 5, IQR 1-2). The difference in the number of DRP per patient between KSA (median 1) and the UK (median 1) was not significant (p=0.088).

The overall DRP incidence in the study cohort was 39.2% (95% CI, 36.1-42.3). The incidence was significantly higher in KSA (44.8%; 95% CI, 40.4-49.2) compared to UK (33.3%, 95% CI, 29.1-37.7), p<0.001, (**Table 3.8**). Overall, no significant difference in DRP incidence was found between age groups and gender (p=0.567), (**Figure 3.1**).

The study found no association between gender and the occurrence of DRPs either in the overall study cohort or within in each country. Also, no statistical association was found between the patients' age and DRP occurrence. However, in this study the median age of the patients who experienced DRPs was three years which is the same as the overall cohort and more than half of the patients with at least one DRP were aged older than two years (**Table 3.6**).

Figure 3.1: DRP incidence in each age group stratified by gender in the study cohort



*Error bars represent 95% CIs.

In the overall study cohort there is a significant difference in the DRP incidence between wards and also between the wards within each hospital (p<0.001). Overall, the highest incidence was reported in the PICU (59.7%; 95% CI, 47.0-71.5) and the lowest in A&E (21.7%; 95% CI, 16.8-27.3). **Table 3.8** shows DRP incidences stratified by ward, age group and gender.

Table 3.8: DRP incidences stratified by ward, age group and gender[a]

	KSA %(95% CI)	UK %(95% CI)	Study cohort %(95% CI)
Overall	44.8 (40.4-49.2)	33.3 (29.1-37.7)	39.2 (36.1-42.3)
Ward:			
A&E	28.7 (21.4-36.8)	12.7 (7.1-20.4)	21.7 (16.8-27.3)
Medical	52.6 (46.9-58.4)	34.1 (28.5-40.0)	43.8 (39.7-48.0)
NICU	37.8 (23.8-53.5)	48.0 (33.7-62.6)	43.2 (33.0-53.7)
PICU	58.8 (32.9-81.6)	60.0 (45.2-73.6)	59.7 (47.0-71.5)
Age group:			
0-1m	31.3 (18.7-46.3)	43.2 (31.8-55.3)	38.5 (29.9-47.8)
>1m-≤2y	43.8 (35.8-52.0)	37.4 (30.0-45.3)	40.5 (35.0-46.1)
>2y-≤6y	44.8 (36.4-53.3)	26.0 (17.9-35.5)	36.8 (30.8-43.2)
>6y-≤12y	47.7 (38.9-56.6)	27.5 (18.1-38.6)	40.0 (33.3-47.0)
>12y-≤18y	57.6 (39.2-74.5)	30.6 (19.6-43.7)	40.0 (30.1-50.6)
Gender:			
Female	43.3 (36.6-50.2)	33.7 (27.1-40.8)	38.8 (34.0-43.7)
Male	45.9 (40.0-51.8)	33.1 (27.7-38.8)	39.5 (35.5-43.6)

[a]The total number of patients and patients with DRPs are given in Table 3.6

3.1.5.3 Type of DRPs

Overall, dosing problems had the highest frequency of the reported DRPs (n=303, 55.5% of 546), followed by drug choice problems (n=91, 16.7% of 546). This was the case in both countries. ADRs (n=76, 13.9% of 546) were the third most frequently reported type of DRP, being higher at the UK site than at the KSA hospital (n=59, 24.9% of 237 vs. n=17, 5.5% of 309). The overall incidence of patients with ADRs was 7.3% (n=72/990; 95% CI, 5.7-9.1).

Interaction problems (n=17) were identified in KSA only; while most of the problems in the 'others' category of the DRP classification were reported from the UK (n=18/27). A summary of the most common DRPs, according to the six main categories and related subcategories of the adapted PCNE classification, from the two countries are given in **Table 3.9**.

Table 3.9: Most common type of DRPs identified from the two countries classified according to the adapted PCNE classification (V5.01)

Main category	Code	Subcategory	KSA n (% of 309)	UK n (% of 237)	Study cohort n (% of 546)
Adverse reactions	P1	***Total***	***17 (5.5)***	***59 (24.9)***	***76 (13.9)***
	P1.1	Side effect suffered (non-allergic)	13 (4.2)	44 (17.3)	57 (10.4)
	P1.2	Side effect suffered (allergic)	2 (0.6)	5 (2.1)	7 (1.3)
	P1.3	Toxic effects suffered	2 (0.6)	10 (4.2)	12 (2.2)
Drug choice problem	P2	***Total***	***32 (10.4)***	***59 (24.9)***	***91 (16.7)***
	P2.1	Inappropriate drug	4 (1.3)	7 (3.0)	11 (2.0)
	P2.2	Inappropriate dosage form	9 (2.9)	20 (8.4)	29 (5.3)
	P2.3	Inappropriate duplication of drug or drug group	9 (2.9)	9 (3.8)	18 (3.3)
	P2.6	No drug but clear indication	5 (1.6)	19 (8.0)	24 (4.4)
Dosing problem	P3	***Total***	***225 (72.8)***	***78 (32.9)***	***303 (55.5)***
	P3.1	Drug dose too low or dosing interval too long	135 (43.7)	38 (16.0)	173 (31.7)
	P3.2	Drug dose too high or dosing interval too short	80 (25.9)	34 (14.3)	114 (20.9)
	P3.6	Inappropriate concentration	9 (2.9)	3 (1.3)	12 (2.2)
Drug use problem	P4	Total	9 (2.9)	23 (9.7)	32 (5.9)
	P4.1	Drug not taken/administered at all	7 (2.3)	22 (9.3)	29 (5.3)
	P4.2	Wrong drug taken/administered	2 (0.6)	1 (0.4)	3 (0.5)
Interactions	P5	Total	17 (5.5)	-	17 (3.1)
	P5.1	Potential interaction	17 (5.5)	-	17 (3.1)
Others	P6	Total	9 (2.9)	18 (7.6)	27 (4.9)
	P6.1	Wrong patient	7 (2.3)	-	7 (1.3)
	P6.2	Illegible writing and inappropriate abbreviation	-	6 (2.5)	6 (1.1)
	P6.3	Patient dissatisfied with therapy	-	8 (3.4)	8 (1.5)
	P6.4	Insufficient awareness of health and disease	2 (0.6)	3 (1.3)	5 (0.9)

*bold italics represent the most frequent DRPs.

In the study cohort, a statistically significant association was found between the occurrence of a DRP and certain disease categories that patients were admitted with; 'diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism' (D50-D89), $p<0.01$, also 'injury, poisoning and certain other consequences of external causes' (S00-T98), $p<0.001$, (using the Chi-Square test).

On a country level, statistically significant associations were found only in the UK between six types of disease category and DRP incidence (**Table 3.10**). While no significant associations between the diseases and DRP incidence were found in KSA.

Table 3.10: Diseases associated with DRP incidence in the UK

Disease category (ICD-10 code)	*p*-value[a]
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	0.036
Diseases of the respiratory system (J00-J99)	0.045
Diseases of the digestive system (K00-K93)	0.031
Diseases of the skin and subcutaneous tissue (L00-L99)	0.005
Diseases of the musculoskeletal system and connective tissue (M00-M99)	0.035
Injury, poisoning and certain other consequences of external causes (S00-T98)	0.001

[a]Chi-Square test

3.1.5.4 Causes of DRPs

Overall, 762 causes were reported for the 546 identified DRPs using the modified PCNE classification system. The majority (n=319, 41.9%) were related to the selection of the drug and/or dosage (C1). The next most frequently reported causes involved the drug use

process (n=219, 28.7%) (C2), followed by logistics problems (C5) (n=84, 11%). **Table 3.11** shows the most frequently reported causes of DRPs in the two countries and overall.

There were statistically significant differences between the two countries for the three main categories of causes; 'drug use process', 'information', and 'logistics', ($p<0.001$). In the KSA, the causes of the DRPs, 'drug under-used/under–administered' and 'drug-over-used/over-administered' causes were more frequently given compared to the UK [n=101 (21.8%) vs. n=7 (2.3%), n=53 (11.4%) vs. n=6 (2%), $p<0.001$, respectively]. Whilst, 'poor documentation of drug history' and 'other prescribing error' causes were more frequent in the UK than in the KSA [n=26 (8.7%) vs. n=2 (0.4%); n=40 (13.4%) vs. n=9 (1.9%), $p<0.001$, respectively].

Table 3.11: The most frequently reported causes of DRPs classified according to the adapted PCNE classification (V5.01)

Main category	Code	Subcategory	KSA n (% of 464[a])	UK n (% of 298[a])	Study cohort n (% of 762[a])
Drug or dose selection	C1	***Total***	***184 (39.7)***	***135 (54.3)***	***319 (41.9)***
	C1.2	Inappropriate dosage selection	148 (31.9)	49 (16.4)	197 (25.8)
	C1.8	Manifest side effect	13 (2.8)	48 (16.1)	61 (8.0)
	C1.1	Inappropriate drug selection	11 (2.4)	15 (5.0)	26 (3.4)
	C1.4	Pharmacokinetic problems	6 (1.3)	8 (2.7)	14 (1.8)
Drug use process	C2	***Total***	***185 (39.9)***	***34 (11.4)***	***219 (28.7)***
	C2.2	Drug underused/under-administered	101 (21.8)	7 (2.3)	108 (14.2)
	C2.3	Drug overused/over-administered	53 (11.4)	6 (2.0)	59 (7.7)
	C2.1	Inappropriate timing of dosing	30 (6.5)	8 (2.7)	38 (5.0)
Information	C3	Total	32 (6.9)	43 (14.4)	75 (9.8)
	C3.6	Poor documentation of drug history	2 (0.4)	26 (8.7)	28 (3.7)
	C3.1	Instructions for use/taking not known	10 (2.1)	7 (2.3)	17 (2.2)
	C3.5	Lack of communication between health professionals	11 (2.4)	4 (1.3)	15 (2.0)
Patient/ Psychological	C4	Total	14 (3.0)	14 (4.7)	28 (3.7)
	C4.2	Caregiver has concerns with drugs	-	7 (2.3)	7 (0.9)
	C4.1	Caregiver forgets to use drug	4 (0.9)	1 (0.3)	5 (0.6)
	C4.3	Caregiver suspects side-effects	2 (0.4)	3 (1.0)	5 (0.6)
Logistics	C5	***Total***	***27 (5.8)***	***57 (19.1)***	***84 (11.0)***
	C5.2	Other prescribing error (information wrong/missing on the prescription)	9 (1.9)	40 (13.4)	49 (6.4)
	C5.3	Dispensing error	16 (3.4)	4 (1.3)	20 (2.6)
	C5.1	Prescribed drugs not available	2 (0.4)	10 (3.3)	12 (1.6)
Others	C6	Total	22 (4.7)	15 (5.0)	37 (4.8)
	C6.1	Other causes	21 (4.5)	11 (3.7)	32 (4.2)
	C6.2	No obvious cause	1 (0.2)	4 (1.3)	5 (0.6)

[a]Total number of causes reported. Bold italics represent the most frequent categories

3.1.5.5 Interventions

Overall 711 interventions were carried out to manage the 451 of the 546 identified DRPs (median one intervention per DRP, min 1, max 3). A total of 302 (42.5% of all interventions) were at drug level, followed by interventions at prescriber level (n=268, 37.7%), and only 84 (11.8%) interventions were at patient/caregiver level.

In total, for 95 of the 546 DRPs there was no intervention. A high number of the problems (n=78/309, 25.2%) that had no intervention were in KSA and more than half (57.6%, n=45/78) of these problems were from the A&E department. **Table 3.12** shows the most frequently reported interventions classified according to the adapted PCNE classification (V5.01).

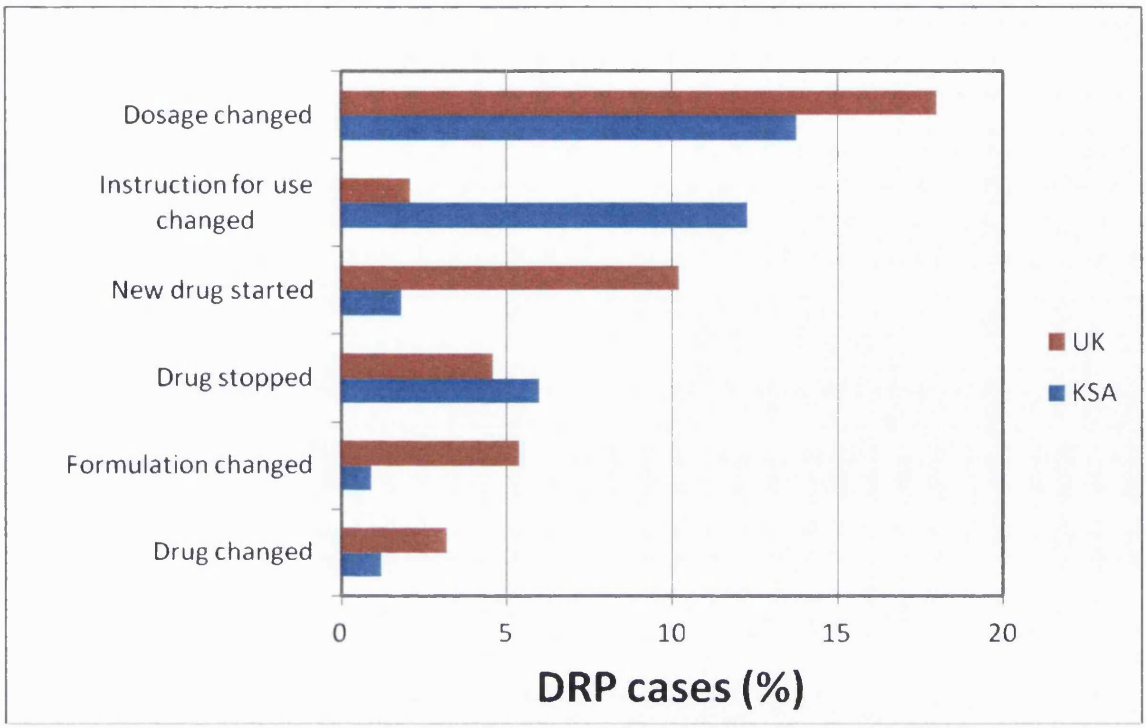
Table 3.12: The most frequently reported interventions classified according to the adapted PCNE classification (V5.01)

Main category	Code	Subcategory	KSA n (% of 337[a])	UK n (% of 374[a])	Study cohort n (% of 711[a])
At prescriber level	I1	***Total***	***147 (43.6)***	***121 (32.3)***	***268 (37.7)***
	I1.1	Prescriber informed only	73 (21.7)	22 (5.9)	95 (13.4)
	I1.3	Intervention proposed, approved by prescriber	57 (16.9)	90 (24.1)	147 (20.7)
	I1.4	Intervention proposed, not approved by prescriber	14 (4.1)	5 (1.3)	19 (2.7)
At patient/ Carer level	I2	Total	43 (12.7)	41 (11)	84 (11.8)
	I2.2	Written information provided	29 (8.6)	2 (0.5)	31 (4.4)
	I2.4	Spoken to family member/caregiver	5 (1.5)	25 (6.7)	30 (4.2)
	I2.1	Patient (medication) counselling	5 (1.5)	10 (2.7)	15 (2.1)
	I2.3	Patient referred to prescriber	4 (1.2)	4 (1.1)	8 (1.1)
At drug level	I3	***Total***	***124 (36.8)***	***178 (47.6)***	***302 (42.5)***
	I3.2	Dosage changed	46 (13.6)	67 (17.9)	113 (15.9)
	I3.4	Instruction for use changed	41 (12.2)	8 (2.1)	49 (6.9)
	I3.8	New drug started	7 (2.1)	38 (10.2)	45 (6.3)
	I3.7	Drug stopped	20 (6.0)	18 (4.8)	38 (5.3)
	I3.3	Formulation changed	3 (0.9)	20 (5.4)	23(3.2)
	I3.1	Drug changed	4 (1.2)	12 (3.2)	16 (2.3)
Others	I4	Other interventions	23 (6.8)	34 (9.1)	57 (8.0)

[a]Total number of interventions reported. Bold italics represent the most frequent categories

Figure 3.2 shows the most common interventions carried out at drug level.

Figure 3.2: Most common interventions at drug level



Of the 147 interventions approved by the prescriber, 80.3% (n=118) were proposed by pharmacists. The median time spent by a pharmacist per intervention for a DRP was five minutes (IQR 5-10 minutes) compared to ten minutes (IQR 5-15 minutes) by other healthcare professionals. 74.7% (n=221) of the 296 DRPs that totally resolved, were due to pharmacists' interventions. Pharmacists intervened in relation to dosing and drug choice problems [77.2% (n=234/303) cases, 80.2% (n=73/91) cases, respectively] more often than other professionals [6.6% (n=20/303) cases, 14.3% (n=13/91) cases, respectively]. Also, pharmacists more frequently intervened in relation to drug use problems compared to other professionals [59.4% (n=19/32) cases, 40.6% (n=13/32), respectively]. Pharmacists intervened in all the interaction problems (n=17). However,

other healthcare professionals intervened more frequently in relation to ADRs, 75% (n=57/76) compared to 6.6% (n=5/76) by pharmacists.

3.1.5.6 Outcome of DRPs which had intervention(s)

Overall most of the interventions resulted in resolution of the DRPs (65.6%, n=296/451). Similarly in each country [KSA 57.6% (n=133/231); UK 74.1% (n=163/220)], the majority of the DRPs resolved following the intervention(s). The percentage of problems that were not solved was higher in KSA (13.9%, n=32/231) than in the UK (5.5%, n=12/220). **Table 3.13** gives details of the outcome of the interventions in both countries as well as in the overall cohort.

Table 3.13: Most frequent reported outcome of DRPs which had interventions

Outcome of intervention	KSA n (% of 231[a])	UK n (% of 220[a])	Overall n (% of 451[a])
Problem totally solved	133 (57.6)	163 (74.1)	296 (65.6)
Problem partially solved	13 (5.6)	16 (7.3)	29 (6.4)
Outcome not known	53 (22.9)	29 (13.2)	82 (18.2)
Problem not solved, lack of cooperation of physician	17 (7.3)	7 (3.2)	24 (5.3)
Problem not solved, intervention not effective	10 (4.3)	2 (0.9)	12 (2.7)

[a]Total number of DRPs that had an intervention

3.1.5.7 Severity classification

Overall, the majority of DRPs were found to be minor (71.4%, n=390/546,) and 27.8% (152/546) DRPs were assessed as moderate, similarly at ward level in each country except in A&E in the UK, where 11 (64.7% of 17 cases) were assessed as moderate. Severe cases were only identified in KSA (n=4, 1.3% of 309). However, neither severe nor any other DRPs caused actual harm to patients.

Overall there was no significant difference between the countries with respect to severity (p=0.098). **Table 3.14** shows the severity of DRPs stratified by ward in each country and overall.

Table 3.14: DRP severity stratified by ward

Ward	KSA n (% of 309)			UK n (% of 237)		Overall n (% of 546)		
	Minor	Moderate	Severe	Minor	Moderate	Minor	Moderate	Sever
A&E	39 (12.6)	12 (3.9)	-	6 (2.5)	11 (4.6)	45 (8.2)	23 (4.2)	-
Medical	152 (49.2)	57 (18.4)	1 (0.3)	125 (52.7)	18 (7.6)	277 (50.7)	75 (13.7)	1 (0.2)
NICU	12 (3.9)	13 (4.2)	2 (0.6)	19 (8.0)	9 (3.8)	31 (5.7)	22 (4.0)	2 (0.4)
PICU	10 (3.2)	10 (3.2)	1 (0.3)	27 (11.4)	22 (9.3)	37 (6.8)	32 (5.9)	1 (0.2)
Total	213 (68.9)	92 (29.8)	4 (1.3)	177 (74.7)	60 (25.3)	390 (71.4)	152 (27.8)	4 (0.7)

3.1.5.8 Preventability

Using the Schumock and Thornton (1992) preventability criteria, overall and in both countries, most of the identified DRPs (n=437, 80.0%) were found to be preventable. The highest percentage of preventable DRPs was identified in the medical wards (54.8, n=299/546) while the lowest percentage was found in NICU (7.1%, n=39/546). **Table 3.15** shows preventability data stratified by ward in the two countries and overall.

Table 3.15: DRP preventability stratified by ward in the two countries

Ward	KSA n (% of 309)		UK n (% of 237)		Overall n (% of 546)	
	Yes	No	Yes	No	Yes	No
A&E	50 (16.2)	1 (0.3)	3 (1.3)	14 (5.9)	53 (9.7)	15 (2.7)
Medical	193 (62.5)	17 (5.5)	106 (44.7)	37 (15.6)	299 (54.8)	54 (9.9)
NICU	24 (7.8)	3 (1.0)	15 (6.3)	13 (5.5)	39 (7.1)	16 (2.9)
PICU	18 (5.8)	3 (1.0)	28 (11.8)	21 (8.9)	46 (8.4)	24 (4.4)
Country cohort	285 (92.2)	24 (7.8)	152 (64.1)	85 (35.9)	437 (80.0)	109 (20.0)

An example of a DRP deemed to be severe and preventable is given in Box 3.1

Box 3.1 Case vignette for a severe drug-related problem

Case history: **Study ID:** 603-3

A boy aged 1 year admitted to medical ward as case of bronchial asthma.

Drugs:

Dompridone PO 2.2mg Q6H syrup

Piperacillin & enzyme inhibitor (Tazocin) IV 440mg Q8H

Ranitidine PO 8.4mg Q8H

Budesonide nebulizer 250mcg Q12H

Ipratopium bromide (Atrovent) nebulizer 250mcg Q6H

Sulfamethoxazole & trimethoprim (Bactrim) PO 20mg suspension Q12H twice weekly

Paracetamol PO 65mg syrup Q4-6HR PRN

Immunoglobulims, IV 1.2g 1 dose

Epinephrine IM **4mg** 1 Dose

Description of the DRP:

Epinephrine was prescribed as a stand-by order for an anaphylactic reaction as patient received immunoglobulin IV. Epinephrine was prescribed as 4mg IM (1 dose) which is a high dose for this patient. The pharmacist contacted the prescriber to change the order to 0.04mg IM. The prescriber agreed and wrote a new prescription.

DRP classification based on PCNE classification:

Type of problem:

Dose too high.

Cause:

Inappropriate dosage selection

Intervention:

Intervention proposed by pharmacist and approved by prescriber, dosage changed

Outcome:

Problem solved

Severity classification (using Dean and Barber (1999) scale):

Severe

Preventability (using Schumock and Thornton (1992) criteria):

Preventable

3.1.5.9 Drugs involved in the DRP occurrence

Using the WHO-ATC classification system for medications, the ATC anatomical group (first level) most often involved in DRPs in the overall cohort was 'systemic anti-infectives' (J) (n=207/546, 37.9%), followed by 'alimentary tract and metabolism' (A) (n=115/546, 21.1%), and 'nervous system' drugs (N) (n=81/546, 14.8%). Overall, 122 different drugs were involved in the 546 DRPs.

At the ATC chemical level (fifth level) 'amoxicillin & enzyme inhibitor' was most frequently associated with DRPs (n=56 cases) [KSA n=49/309 cases (15.9%), UK n=7/237 cases (2.9%)]. The second most frequently involved antibacterial was gentamicin (n=32 cases) [KSA n=19/309 cases (6.1%); UK n=13/237 cases (5.5%)]. Morphine and salbutamol were more frequently involved in DRPs in the UK than in KSA [n=17/237 (7.2%); n=15/237 (6.3%) vs. n=5/309 (1.6%), n=2/309 (0.6%); respectively].

Table 3.16 shows the anatomical groups, based on the WHO-ATC classification, most frequently associated with DRP cases.

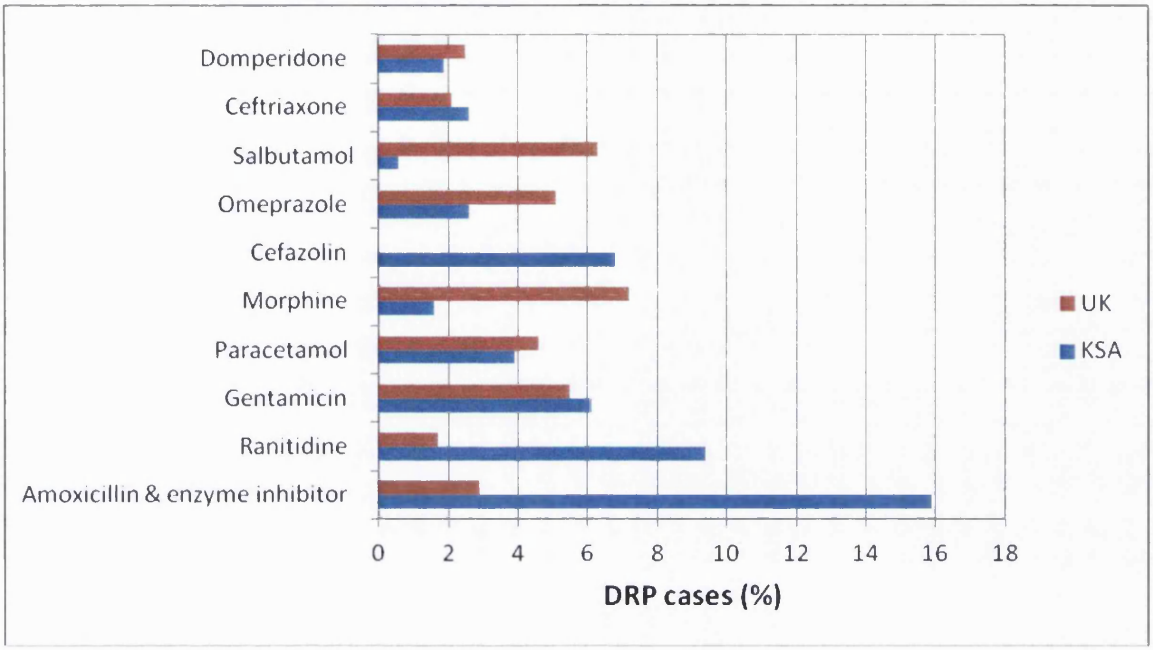
Table 3.16: Drug groups most frequently associated with DRPs, stratified by country

Anatomical level (ATC[a])	KSA [b]n (% of 309)	UK [b]n (% of 237)	Overall [b]n (% of 546)
Systemic anti-infective (J)	148 (47.9)	59 (24.9)	207 (37.9)
Alimentary tract and metabolism (A)	76 (24.6)	39 (16.5)	115 (21.1)
Nervous system (N)	29 (9.4)	52 (21.9)	81 (14.8)
Respiratory system (R)	20 (6.5)	34 (14.3)	54 (9.9)
Blood and blood forming organs (B)	11 (3.6)	19 (8.0)	30 (5.5)
Cardiovascular system (C)	5 (1.6)	7 (3.0)	12 (2.2)
Musculo-skeletal system (M)	4 (1.3)	8 (3.4)	12 (2.2)
Systemic hormonal preparations (H)	4 (1.3)	8 (3.4)	12 (2.2)
Anti-neoplastic and (L)	3 (1.0)	3 (1.3)	6 (1.1)
Dermatologicals (D)	4 (1.3)	2 (0.8)	6 (1.1)

[a]ATC= Anatomical Therapeutic Chemical classification, [b]n=number of DRPs

Figure 3.3 shows the ten drugs (chemical level) most frequently associated with DRP cases.

Figure 3.3: Top ten drugs most frequently causing DRPs



At the therapeutic level of the WHO-ATC classification, 'Systemic antibacterials' was the drug group that was involved in most of the categories (five categories) of DRPs, and was the drug group most frequently associated with dosing problems (46.2%, n=140/303). Drugs for 'acid related disorders' were involved in four of the categories of DRPs and were frequently involved in dosing problems (11.6%, n=35/303), while analgesics were involved in three DRPs categories and were involved in a high number of the dosing problems (8.3%, n=25/303). Drugs for obstructive airway diseases were also involved in three of the DRP categories and were associated with a high number of ADR cases (17.1%, n=13/76), mainly in the UK (92.3%, 12/13) (**Table 3.17**).

Table 3.17: DRP types with the drug groups (LT)[a] most frequently implicated; stratified by country

DRP Type	Involved drug (total No. of cases)	KSA (no. of cases)	UK (no. of cases)
ADRs	Analgesics (15)	2	13
	Systemic antibacterials (22)	-	22
	Drugs for obstructive airway diseases (13)	1	12
Drug choice problem	Systemic antibacterials (24)	13	11
	Drugs for acid related disorder (21)	10	11
Dosing problem	Systemic antibacterials (140)	123	17
	Drugs for acid related disorder (35)	31	4
	Analegesics (25)	12	13
	Drugs for obstructive airway diseases (7)	3	4
	Drugs for functional gastrointestinal disorders (12)	6	6
	Systematic antihistamines (10)	8	2
	Antiepileptics (9)	4	5
Drug use problem	Drugs for obstructive airway diseases (5)	1	4
	Systemic antibacterials (3)	2	1
	Antianemic preparations (3)	-	3
Interactions	Mineral supplements (6)	6	-
	Drugs for acid related disorders (3)	3	-
	Other alimentary tract and metabolism products (3)	3	-
	Antiepileptics (2)	2	-
Others	Analgesics (4)	2	2
	Drugs for acid related disorders (4)	-	4
	Systemic antibacterials (3)	-	3
	Systemic corticosteroids (3)	-	3

[a]LT= Therapeutic level according to WHO-ATC classification

3.1.6 Discussion

The extent of DRPs in hospitalised children or children attending an A&E department has not previously been studied in the two countries (UK and KSA) included in this study. Our study shows that DRPs are a frequent healthcare issue in the hospitalised paediatric populations in these two countries and also that most of the DRPs could be prevented by healthcare professionals. The combined data from the two countries showed that 39.2% (388/990; 95% CI, 36.1-42.3) of the children included in the study, from the three wards (medical, NICU, PICU) and the A&E departments, experienced at least one DRP; dosing and drug choice problems were the most common.

Comparable data from other studies investigating DRPs in hospitalised paediatric population are limited. A retrospective US study investigating the rate of pharmacists' clinical interventions in adult and paediatric inpatients concluded that the rate of DRPs was 19 times greater in the paediatric patients than in the adults (Chan & Kotzin 1998). Other studies on paediatric populations have mainly addressed drug-related admissions to hospitals (Yosselson-Superstine & Weiss, 1982; Easton et al. 2004; Easton et al. 1998). The reported incidences of DRPs associated with paediatric admissions from these studies ranged from 3.4% to 18%.

The majority of the published studies on hospitalised children have focused on one aspect of DRPs, for example ADRs or medication errors, or exclusively focused on the interventions of pharmacists for the purpose of justification of the clinical pharmacy services (Munzenberger et al. 1972; Koren et al. 1991; Falck et al. 1997; Blix et al. 2006; Virani & Crown 2003; Fattinger et al. 2000, Chua et al. 2010, Krupicka et al. 2002).

Previous studies from the UK were conducted to identify the interventions and the impact of pharmacists in relation to medication errors (Guy et al. 2003; Krupicka et al. 2002).

3.1.6.1 Types and causes of DRPs

Our study shows that the majority of DRPs in both countries were related to dosing and drug selection. Other studies on medication errors have shown that dosing errors are the most common medication error affecting the paediatric population (Blum et al. 1988; Ghaleb et al. 2010; Chua et al. 2010; Ghaleb et al. 2006a; Wong et al. 2004; Kaushal et al. 2001; Al-Jerasiy et al. 2011).

One reason for the high frequency of dosing problems identified in study cohorts might be related to the difficulties in calculating the dosage for paediatric patients, as the dose for a child is dependent on several factors such as the child's age, weight, body surface area, and their associated clinical condition (Wong et al. 2009). Thus the medication process in the paediatric population is complex which may explain why dosing errors are the most common DRP. Electronic prescribing systems have been shown to be effective in optimising the prescribing process in children (Jani et al. 2008; Jani et al. 2010; Conroy et al. 2007), however, evidence based rules and paediatric information (including dosing information) are essential for the successful implementation of electronic prescribing systems. At the time the study was conducted there was no electronic prescribing system in none of the two hospitals.

ADRs were the third most frequent type of DRP in both countries accounted for 14% (n=76/546) of all DRPs with an incidence of 7.3% (n=72/990, 95% CI, 5.7-9.1) in the

overall study population. This is similar to the incidence (9.5%; 95% CI 6.8-12.3) reported in a previous meta-analysis (Impicciatore et al. 2001).

However, in the current study, looking at the individual countries, more ADR cases were reported in the UK (24.9%, n=59/237) than in the KSA (5.5%, n=17/309). There is no clear explanation for this difference, but it might be explained by the fact that in KSA healthcare professionals (i.e physicians and nurses) tend not to record all ADRs in the medical notes. In other words, differences in documentation between countries might be an explanation, as the ADVISE study showed that in the UK, healthcare professionals tend to document more information including parental concerns (Rashed et al. *In press*). Another explanation might be that the UK team were also involved in the ADVISE study, thus the team was already trained to detect ADRs and probably more focused on this problem than the KSA team. However, the percentage of ADRs (24.9%) in the UK in this study was less than that (34.9%) reported from the UK in the ADVISE study (Chapter 2, section 2.1.6.3, **Table 2.12**).

Among the reported causes for the DRPs identified in this study, using the PCNE classification system, 'inappropriate dosage selection' and 'under-using/under-administering the prescribed drug' were the most frequent causes in the two countries. This could be explained by the fact that many drug formulations that are used in children are used either unlicensed or off-label and as shown in previous studies that data on medication use in children are not well established in different countries (Neubert et al. 2004).

Also, among the logistics causes, the study showed that 'other prescribing errors' were more frequently involved in DRP cases in the UK (n=40/298 cases, 13.4%) compared to cases in the KSA (n=9/546 cases, 1.9%), while 'dispensing errors' involved in DRPs were more in KSA (n=16/546 cases, 3.4%) than in the UK (n=4/298 cases, 1.3%). Moreover, the problems occurring because of unavailability of prescribed drugs were more frequent in the UK (n=10/298 cases; 3.3%) compared to the KSA (n=2/464 cases, 0.4%).

Problems related to drug choice were also higher in the UK (n=59/237, 24.9%) than in KSA (n=32/309, 10.4%). However, problems related to drug dosing were more frequently reported in KSA (n=225/309 cases, 72.8%) compared to UK (n=78/237 cases, 32.9%). This study was not designed to justify the differences, however it might be explained by the fact that pharmacists and other healthcare professionals use different data sources, hence there is heterogeneity in the information sources used in practice, in each country. In KSA information sources are not standardised among healthcare professionals (pharmacist and physicians) with more variety of sources are available. They tend to use American references (such as Micromedx electronic version, Lexi-Com Pediatric Dosage Handbook, Harriet Lane, and Neofax) in addition to the British National Formulary for Children (BNFC) and the hospital's formulary. Whilst, in the UK more standardised sources are used, they depend more on BNFC and the hospital's own formulary.

DRP cases related to potential interactions (n=17) and problems related to drug treatment being given to the wrong patient (n=7 cases) were identified in KSA only and all of them were deemed preventable. However, problems related to 'illegible writing and

inappropriate abbreviations' (n=6 cases) which were also assessed to be preventable were identified in the UK only. All of the cases (n=8) of patients dissatisfied with therapy were reported in the UK; seven of them were found to be preventable.

The DRP classification used in this study was adapted from PCNE (V5.01) and covers the entire range of DRPs. This classification takes into account the basic characteristics and differences between DRPs, and, we believe, it is generally applicable to be used by both healthcare professionals and researchers as a structure for a good understanding of the wide-range of problems related to drug therapy. Moreover, this system may help to improve systematic documentation of such problems and also communication between healthcare providers. This may in turn lead to further studies concerning specific types of drugs. Lampert et al (2008) conducted a study to evaluate the use of the PCNE classification system as tool to evaluate a clinical pharmacy service in identifying and minimising DRPs in a hospital setting. The authors concluded that this system is an 'easy-to-use' tool which could be used in daily practice at a hospital and help in reducing drug costs.

In another study conducted by Eichenberger et al (2010), in which they used the same version (V5.01) of the PCNE classification, and also made modifications to the categories. They collected data from primary care and hospital discharge prescriptions for adults with DRPs. In this study the author asked the observers (n=64) eight questions regarding their opinion about the practicality and usability of the modified PCNE classification system used in the study, and found that 33% (21/64) of them agreed that it

is easy and practical means to use for identifying and documenting DRPs, while 34% (22/64) were 'neutral' in their opinion but 29% (19/64) disagreed.

However, the two above studies were conducted in the same European country (Switzerland) and one of the authors was involved in the assessment of both studies which may have been a source of bias regarding the assessment of usefulness and practicality of this classification. There is a draw-back to this system as it gives the opportunity to choose several interventions for a DRP, which may led to some over coding. Though, we believe, the use of this classification system in daily practice can provide reasonable data on the impact of pharmacists on drug use management. In our study we calculated the acceptance of pharmacists' interventions at prescriber level based on one subcategory (I1.3), which may have resulted in a lower percentage than in other studies where they included all other subcategories to show the acceptance of the pharmacists' interventions to reduce or manage a DRP (Lampert et al. 2008). Therefore, additional modifications and rules for the use of this classification system are needed to achieve consistent classification based on one choice only for the intervention taken.

3.1.6.2 Drugs involved in DRPs

The ATC drug classes most frequently implicated in DRP cases were 'systemic anti-infective', 'alimentary tract and metabolism', and 'nervous system' in both countries. This is consistent with published data (Chan & Kotzin 1998; Easton et al. 2004; Koh et al. 2005; Rashed et al. 2011). However, when making comparisons between the two countries using the chemical level (fifth level) of WHO-ATC classification system, 'amoxicillin & enzyme inhibitors' were mostly involved in DRPs in KSA (15.9%,

n=49/309) compared to the UK (3.0%, n=7/237) whilst morphine and salbutamol were more frequently reported to be associated with DRPs in the UK [7.2% (n=17/237); 6.3% (n=15/237) vs. 1.6% (n=5/309); 0.6% (n=2/309), respectively). The ADVISE study in Chapter two (section 2.1) showed that morphine and salbutamol were more frequently involved in the ADRs in the UK compared to the other countries involved in the study (Rashed et al. *In press*). Neubert et al's study (2010) also showed that morphine was prescribed more frequently in the UK than in Italy and the Netherlands. Moreover, a report published in 2009 by the National Patient Safety Agency (NPSA) in the UK, 'Safety in Doses', indicated that morphine was among the five drugs most frequently implicated in the reported medication incidents involving children from different NHS sectors in 2007 (NPSA 2009). Our study's results from the UK are in line with this report and these other studies.

Whether the above differences between the two countries occurred because certain drugs were prescribed more often in one country than the other could not be determined from this analysis of this study. Further analysis of medications usage in the two countries would be required and exceeds the scope of the current study. Additional work on this area would be of great interest.

3.1.6.3 Interventions

In both countries pharmacists detected more DRPs than other health professionals, particularly problems at drug level. This probably reflects the fact that pharmacists are primarily focused on the use of pharmacological treatments in terms of safety and efficacy due to their specialised knowledge of drugs. Recommending a change to the dose

and/or starting a new drug were the most common interventions in the UK, whilst changing the instructions for using the prescribed drug was the intervention cited more frequently in the KSA than in the UK.

Of the 81.4% (367/451) of cases had an intervention where pharmacists intervened, 60.2% of them (n=221/367) were totally resolved and 90.5% (n=200/221) of these DRPs were deemed to be preventable. This was similar in each country which shows the importance of hospital pharmacists in improving the safety of drug therapy in children. The findings are consistent with previous studies where pharmacists have been shown to be effective in intervening and resolving prescribing problems in children (Sanghera et al. 2006; Guy et al. 2003; Krupicka et al. 2002, Falck & Darsey 1997).

3.1.6.4 Preventability and severity

The majority of identified DRPs were found to be preventable (80.0%, n=437/546). This is true for all wards except at A&E in the UK where most of the reported DRPs were not preventable. This might be due to the fact that most of the identified DRPs occurred prior to the patient attending A&E, and thus were not seen as preventable by the hospital healthcare team.

Most of the preventable DRPs were associated with dosing problems (67.3%, n=294/437) and drug choice problems (18.1%, n=79/437). All the potential interaction cases (n=17) occurred in the KSA and were deemed preventable as were the cases of illegible writing and inappropriate abbreviations (n=6) which occurred in the UK.

An Australian study which used the same preventability criteria as our study, found that of children's admissions due to DRPs, 66.6% of the DRP cases were preventable which is similar to our findings (Easton et al. 1998). The same author conducted another study on paediatric attendance at A&E due to a DRP, and found that 51.3% of identified DRPs were deemed to be preventable (Easton et al. 2003). Another study conducted by Kunac and Reith (2008) in hospitalised children in New Zealand and used the same preventability criteria reported that majority (92.2%) of medication-related events were preventable. In an adult study it has also been shown that a high percentage (92%) of detected DRPs was preventable or probably preventable and most of the DRPs were associated with prescriber or patient errors (Zargarzadeh et al. 2007).

Regarding DRP severity, most of the DRPs were assessed as minor (n=390/546, 71.4%) and overall most of them (n=277/390; 71%) were from the medical wards in the study cohort as well as in each country cohort. All the DRPs assessed as severe were from the KSA (n=4/309, 1.3%) and were deemed preventable; two of the four were from the NICU. One possible explanation for the high percentage of moderate DRPs from the A&E department in the UK (64.7%, 11/17) could be that parents took their children to A&E only if they had a relatively serious disease/condition. Similar findings regarding severity of DRPs in children attending A&E department were reported previously from Australia (Easton et al. 2003). The study found that most of the identified DRPs (42.1% of 280 cases) were assessed as moderate.

Overall there is a high incidence of preventable DRPs in children; the results suggest that a better pharmaceutical care service is needed in this patient group. It has long been

acknowledged that paediatric pharmacology and pharmacotherapy training within the medical and nursing professions is limited. It is important to provide more training to these health professionals in prescribing medications and their use in the paediatric population. Furthermore, a high percentage of DRPs were identified and resolved by pharmacists; demonstrating the important role of the clinical pharmacist in optimizing pharmacotherapy in children which reflects their specialised training.

However the severity scale used in our study was originally established to assess medication errors. Although the preventability criteria used in our study were used in previous DRP studies, this classification was originally developed for ADR assessment. Therefore, the question remains as to whether this tool is adequate for DRPs or should specific tools be developed and further studies undertaken to develop more specific tools for assessing DRPs.

3.1.6.5 Strengths and limitations

3.1.6.5.1 Strengths

To our knowledge this is the first study to quantify the occurrence of DRPs in children admitted to paediatric wards or attending A&E in a tertiary teaching hospital in the KSA and to a teaching NHS paediatric hospital in the UK. Data collection by chart review has been recognised as the gold standard in pharmacoepidemiology (Murff et al. 2003).

Our study showed that DRPs are a common healthcare issue in hospitalised paediatric populations as well as in adults and most of the DRPs are preventable by healthcare

professionals. The data were collected from paediatric wards in both countries by the hospital staff and this suggests that data on DRPs could be collected by healthcare professionals as daily routine which would increase their awareness of DRPs. This in turn could lead to changes in procedures or training to minimize the incidence of DRPs.

3.1.6.5.2 Limitations

Certain limitations must be considered when interpreting our findings. The study only included two teaching hospitals and the results are not necessarily representative of other hospitals in these countries. Another limitation of our study is that data collection in NICU and PICU in the UK was done over a one month period due to shortage of staff. Also, the hospitals in the UK and the KSA, included in the study do not have pharmacy support at their paediatric A&E departments; therefore, a researcher collected the data for a one month period and was not allowed to intervene with the patients' treatment which resulted in a large number of DRPs that had no intervention. Different people collected the data from the wards and from A&E which might have impacted on the data collected, though training was done for all staff involved in the data collection to maximise consistency of these procedures. Due to time constraints, no kappa statistics (inter-rater test) were performed to evaluate the agreement on identifying DRPs, as we did in the ADVISE study for ADR detection.

Finally, unlicensed or off-label use of medication in children was not considered in the analysis of this study.

3.1.6.6 Conclusions and implications for healthcare

In summary, this study addressed an important and under-researched area in the paediatric population, that of DRPs. The study showed the magnitude of DRPs in hospitalised paediatric patients and those attending A&E and their high degree of preventability, in two countries, the UK and the KSA. These findings require healthcare providers to initiate new policy measures. This would not only improve the patients' health and quality of life, but would also enhance the efficiency of the healthcare system in the countries studied.

Dosing and drug choice problems were the most frequent DRPs, in both countries. Anti-infectives and analgesics were frequently associated with the majority of the DRPs. Thus prescribing and monitoring of these drugs needs particular attention. A focus on paediatric pharmacology and pharmacotherapy within paediatric medical and nursing education is an important step to improve prescribing practises and the involvement of clinical pharmacists in the education process should lead to better prescribing. Also, a high percentage of DRPs are resolved by pharmacist's interventions, which confirms the important role of clinical pharmacists in dealing with DRPs in hospitalised children.

Though there are differences between the KSA and the UK, for example with regard to drug choice and dosing problems, this study's results provide a basis for future studies investigating and quantifying the potential risk factors of DRPs which would give more information on the clinical and economic considerations for providing healthcare services to children. Also, this is a first step to establish further collaboration between these two countries.

Chapter FOUR: Overall discussion and conclusions

In Chapters 2 and 3 the individual studies were presented with discussion of the methods used, results and also the limitations and strengths of the studies. This chapter provides an overall discussion on the safety of the medications used in children considering the key findings of the studies described in this thesis. The overall conclusion draws attention to the original contribution made by this work. Further areas of future research are identified to build on and add to the current knowledge in this field.

4.1 Overall discussion

Medication safety in children has become a leading concern in most countries including those with western culture (e.g. United Kingdom, Germany, and Australia) and those with Middle Eastern or Asian culture (e.g. Kingdom of Saudi Arabia, Hong Kong, and Malaysia). During the last decade, improving the rational use of drugs in children is one of the recurrent topics that has influenced the activities of many paediatricians, clinical pharmacists, clinical pharmacologists, regulatory agencies, and political decision makers in different countries (Campino A et al. 2009; Takata et al. 2008; Broussard 2010; Al-Jeraisy et al. 2011; Gallagher et al. 2011).

Children and adolescents are considered a population at risk from a safety point of view concerning medication use, due to their specific characteristics as discussed in Chapter 1 (Table 1.7). Currently data from the paediatric population are often scarce and not homogenous, therefore it is difficult to evaluate the risks of DRPs such as ADRs.

Assessing the incidence and characteristics of ADRs and other DRPs at an international level will help to better characterise the risk.

Therefore, the aim of this research was to investigate and evaluate the safety of medication use in children at an international level to help in the development of strategies to improve paediatric patient safety. The objectives of the thesis were based on the knowledge that DRPs including ADRs are a significant global concern in paediatric patients (Aagaard et al. 2010; Kunac & Reith 2005; Ghaleb et al. 2006a). The work on this project began in 2008 as much of the literature in the last decade on the safety of medicines used in children, had raised concerns about the difficulties of comparing or extrapolating data from one country or hospital to another due to variation in the methods, setting, design, and the population included in the studies (Impicciatore et al. 2001). As a result, in the research reported in this thesis, a standardised methodology was used to collect data from several countries.

The aim of the studies described in this thesis was to assess the safety of medication use in paediatric populations using pharmacoepidemiological methods. A standardised methodology was used in all participating countries with data collected by intensive chart review. To achieve this aim two studies were conducted; the first was the ADVISE study (Chapter 2) which was conducted in five countries; two European countries (UK and Germany), two Asian countries (HK and Malaysia), and also in Australia to investigate the incidence and characteristics of ADRs in hospitalised children and to identify potential risk factors for ADRs. The second was the DRP study (Chapter 3) which was conducted in the UK and in a Middle-Eastern country (KSA) to investigate the incidence

and characteristics of DRPs in hospitalised children and children attending the A&E department.

The NPSA (2007) report concluded that hospitals tend to have sicker patients who need medicines that may have a small therapeutic window and such medicines may increase the risk of harm. Therefore, there is a need for close monitoring of hospitalised patients and close collaboration of all healthcare professionals to maximise safety when medicines are used. For the above reasons, we chose to conduct our studies on hospitalised children rather than children from primary care sectors or from community pharmacies as hospitalised children are likely to be more ill and might need a wide range of medicines to be used in their treatment resulting in polypharmacy. Thus there is a greater potential for harm to occur.

4.1.1 Adverse drug reactions in hospitalised children in European and non-European countries (ADVISE study)

The results of the ADVISE study given in Chapter 2 showed that 16.5% of hospitalised children to a general paediatric medical ward experienced at least one ADR. Though the current practice is to focus on severe or serious ADRs, it is important to remember that apparently non-serious or mild ADRs, for example constipation from using opioids, can have a significant impact on the patients' quality of life and require the development of preventive strategies. Furthermore, although the majority of detected ADRs were mild in severity; it is recognised that, serious outcomes may develop over time from initially mild ADRs, so early detection of ADRs, and interventions to resolve them where feasible, are important for patients' heath. The study showed that there is a strong relationship

between pharmacological treatment strategies and the occurrence of ADRs. In the UK, for example, morphine was used regularly on the ward via both oral and parenteral routes and a high percentage of the ADRs reported was in relation to the use of morphine (17% of ADRs) (Rashed et al. *In press*). This raises the question as to whether the guidelines for the use of morphine in the hospital in the UK are appropriate. On the other hand, in Malaysia which had the second highest ADR incidence, 76% of the reported ADRs were associated with systemic antibacterial drug groups which were the highest proportion of prescribed drugs in this country.

The in-depth analysis of the ADVISE data using logistic regression (Chapter 2, section 2.2) identified polypharmacy and certain drug groups (analgesics, or antibacterials, or drug for obstructive airways) as risk factors of ADRs (Rashed et al. 2011). So patients receiving these medicines and those on polypharmacy need careful monitoring by the whole healthcare team (physicians, pharmacists, and nurses), with its range of skills, to improve the safety of drugs used in children.

4.1.2 Drug-related problems in children in developed/developing countries

The results of the DRPs study given in Chapter 3 showed that DRPs are of major concern in the paediatric population in both developed and developing countries. The magnitude of the incidence of DRPs and the high percentage of preventability of them in the two countries studied, requires public policy measures to be initiated, not only to improve the paediatric patients' health and quality of life, but also to enhance the efficiency of the healthcare system.

This research found that 39.2% of children admitted to medical, PICU, NICU wards or who attended the A&E department, experienced at least one DRP. Dosing and drug choice problems were the most frequently reported in the study cohort as well as in each country cohort. This is consistent with a retrospective study conducted very recently, on medication prescribing errors in paediatric inpatients (Al-Jeraisy et al. 2011) in the KSA in KAMC in Riyadh (which is the same organisation involved in our study but in a different region of the country). A total of 1333 (56%) medication errors were found. The highest number of errors was related to dose errors (39.4%, n=526/1333) followed by route of administration errors (21.4%, n=286/1333). A study conducted by Kunac and Reith (2005), to identify and prioritise potential failures in the NICU medication use process, found that prescribing of medications and preparation of them for administration were the main stages where most errors occurred.

ADRs were the third most frequent type of DRP that occurred, with an overall proportion of 18.6% (n=72/388) of patients with DRPs, which supports the ADVISE study's results and emphasises the importance of identifying and preventing ADRs in children.

The importance of pharmacists in patient's medication safety has been acknowledged in several studies (Krupicka et al. 2002; Bedouch et al. 2008; Sanghera et al. 2006). This is confirmed in our study as the majority of DRPs were identified by pharmacists and most of them were assessed as preventable. Pharmacists have a specialised knowledge of medications and a crucial role in the medication process. Hospital pharmacists reviewing patient's medication records can identify children at risk of experiencing DRP.

Thus pharmacists are in a unique position to prevent drug-related problems particularly at drug level and at prescribing level (i.e. before an error affects a patient) and ensure appropriate use of medications.

4.1.3 Summary

The prospective nature of this research allowed a more detailed review of events leading to the occurrence of ADRs and/or other DRPs in hospitalised children. Data collected prospectively can be collected with greater confidence in its reliability and accuracy and using standardised methods.

These two studies (ADVISE & DRPs) highlight areas in the use of medicines in hospitalised children [such as poly-pharmacy, high risk drug groups, dosing and drug choice problems, (chapter 2 & 3)] that need more attention from both healthcare providers and policy makers. A good example of the impact of increased attention and effort from healthcare providers can be found in Germany, which was a participant in the ADVISE study. A similar study using the same methodology which had been conducted there, ten years earlier in 1999, by Weiss et al (2002) showed that Between 1999 and 2008, the incidence of patients with ADRs had decreased significantly from 20% to 7.8%, $p<0.01$, (Schramm et al. *submitted*). One reason for this decline could be related to a clear change in the prescribing behaviour, drugs within particular categories that were used in 2008 were often different to those used in 1999 and have been shown to have fewer side effects. For example, indomethacin which is a drug known to have many side effects (Indomethacin SPCs 2011) was replaced by ibuprofen which is considered safer than indomethacin (FDA 2002). Also, an improvement in paediatric pharmacovigilance has

been noticed in terms that the awareness of healthcare professionals towards ADRs had been increased. Furthermore, the introduction of diagnosis-related groups (DRGs) as the hospital repayment system may have resulted in decreasing the length of hospital stay (Schramm et al. *submitted*).

The work in this thesis is an original contribution to enhance the knowledge in the area of patient safety in paediatric populations. The studies described in this thesis have generated evidence on medication safety and provided quantitative data on incidence of ADRs and DRPs across a large paediatric population from Europe, Asia, the Middle-East, and Australia.

The following section summaries what is known in the field of children's medication use and the key findings of this research;

4.1.3.1 What is already known

- ADRs are a global problem for patient safety. Their significance has been shown in adults and children, but to date the data available in children are limited.
- A meta-analysis conducted in 2001 by Impicciatore et al, estimated that the incidence of ADRs in hospitalised children was 9.5% (95% CI, 6.8-12.3).
- However, differences in methodology used in the studies included in this meta-analysis for detecting ADRs made it difficult to extrapolate findings to an international level.
- Most previous studies have shown that a high number of drugs being taken is the most important factor for increasing the risk of an ADR in children.

- Other potential risk factors such as age, associated diseases, and drug prescription patterns have not been adequately studied.
- Previous studies have shown that the frequency of DRPs associated with paediatric hospital admissions ranged from 3.4% to 18%.
- Published research regarding the incidence and nature of DRPs in children is limited and none has been conducted in the UK and the KSA.

4.1.3.2 What this thesis adds

- The frequency of ADRs in hospitalised children was similar to some of the figures (15%) published for adults (Davies et al. 2009); occurring in 16.5% of children admitted to hospital and accounted for 1.8% of paediatric hospitalisations.
- ADRs are a considerable risk for children admitted to hospital, as on average one in six children in hospital experienced an ADR and one in 18 children had an ADR with serious consequences.
- There were significant differences between countries in the incidence of ADRs which may be explained by differences in treatment strategies, in the use of different drugs, in the routes of administration and also in the recording of data in the medical records.
- Data from five countries showed that polypharmacy, older children, and the presence of certain types of disease were independent risk factors for ADRs.
- Antibacterial, analgesic and drugs for obstructive airways diseases were often associated with ADRs, therefore, clinicians and pharmacists should monitor closely the children receiving these drugs.
- The number of prescribed drugs per patient should be kept as low as possible to prevent or minimize the risk of ADRs.

- The overall incidence of DRPs in children admitted to the hospital or attending A&E was 39.2% (95% CI, 36.1- 42.3).
- Dosing and drug choice problems were the most frequent DRPs.
- 80% of confirmed DRPs were deemed to be preventable.
- The high percentage of preventable DRPs emphasizes the importance of providing more training to healthcare professionals in prescribing and medication use.
- There were differences between the two countries included in the DRPs study, in the incidence, characteristic and types of DRPs, which might be due to the different treatment strategies used.

4.2 Implications for healthcare

- The studies described in this thesis have shown the importance of understanding drug safety problems in children and also that these problems frequently differ between countries. Hence there is a need for each country to carefully monitor drug use in children and to identify problems based on their particular prescribing practises so that any new strategies developed are applicable to their hospitals; as developing new strategies based on data from other countries and/or settings is unlikely to be appropriate.
- The selection and use of the best and safest medication(s) for a given child requires considerable skill for the prescriber as there are many choices available. Therefore, there should be a focus during the education of healthcare professionals to enhance their knowledge of and the skills required in the practice of paediatric medicine. This should enable them to recognise the warning signals of DRPs and minimise potential harm to the children.

- The high percentage of identified DRPs which were assessed as preventable suggested that, to prevent or reduce harm to a child, mechanisms for monitoring and evaluating the safety of medicines in clinical use are vital in each country. Such procedures would improve paediatric patients' health and should also enhance the efficiency of the healthcare system as well as the economic burden by reducing the time patients spend in hospitals. Therefore, this thesis's findings may have implications in setting policies for dispensing of drugs and their use in hospitalised children.
- The majority of the ADRs identified were assessed as of minor severity. However, it is important that healthcare professionals and carers are aware of them and recognise that they might be an early symptom or sign of a more serious adverse reaction.
- The findings of these two studies suggest that a more widespread acceptance of the role of hospital pharmacists in monitoring drug treatment would result in a decrease in the number of DRPs and an improvement in drug therapy as well as in the quality of care for paediatric patients.

4.3 Recommendations for future work

The studies described in this thesis have provided comprehensive information on DRPs and ADRs from different countries across the world. They have also added to the knowledge currently available on this topic, and provide baseline data for healthcare professionals and scientists for further research to improve safety of drugs used in children.

- From the ADVISE study (Chapter 2) in this thesis;
  - This study showed that different treatment strategies might be one of the major influences on the ADR incidence in each country, therefore, if a drug utilisation study were conducted involving the same five countries, more information about this would be obtained which could help to establish the reasons for such variations. Probably selecting a certain drug group to be studied across the five countries and investigating each country's prescribing guidelines for those drugs.
  - As the ADVISE study showed that morphine and salbutamol were associated with a high incidence of ADRs in the UK, a study on the rational use of the these two drugs in children in the UK would be worth conducting to help in improving the guidelines for using these drugs.
  - A study focusing on one of the high risk drug groups (e.g. antibacterials), identified in the ADR occurrence, in patients with specific conditions (e.g respiratory diseases) could prove very useful; such a study could help to design interventions or prevention strategies to minimise the occurrence of ADRs in this particular patient group and if successful could be applied to other drug classes and to other clinical problems.
  - In the ADVISE study (Chapter 2), the inter-rater agreements between the four raters for ADR causality and severity assessment was not high. It could be that such assessment scales might not be appropriate for use in paediatric studies. Therefore, it would be useful to undertake a study to evaluate the appropriateness of currently available paediatric assessment scales for

causality and severity and if necessary to develop specific assessment tools for paediatric populations.

- From the DRP study (Chapter 3) in this thesis;
  - It has been recognised that computerized physician order entry (CPOE) and electronic prescribing systems can reduce medication harm (Jani et al. 2010; van Rosse et al. 2009; Wong 2009, Fortescue et al. 2003). The hospital in Saudi Arabia (King Abdulaziz Medical City-Jeddah) which participated in the DRPs study is implementing a CPOE system in 2011 which could have an impact on the incidence of DRPs. Therefore, a follow-up study in this hospital post implementation of the CPOE system is recommended to investigate the impact of CPOE on the incidence and nature of DRPs. Also this study could investigate whether the CPOE system resulted in clinical benefit to the children by improving hospital care for paediatric patients. Such a study would also enable it to be established whether or not new types of DRPs could occur as a result of implementing a CPOE system. In addition, the implementation of CPOE system could impact positively on the economic cost of their healthcare system.
  - Since the DRPs study in this thesis was primarily descriptive and an in-depth statistical analysis was not conducted, future studies could identify and/or investigate possible risk factors associated with or confounders for the risk of DRPs such as co-morbidities, co-medications, ethnicity and overall therapeutics' management.

- It is clear from this work that DRPs are common in paediatric populations and pharmacists play an important role in their identification and prevention. To enlarge the study to other countries including those which do not have a pharmacist on the wards will;
    i. Increase the size of the paediatric population being studied so that an adequate sample size can be obtained to enable evaluation and statistical comparison of the interventions made.

    ii. Increase the generalisability of the results of such a study. Moreover, a large study will enable further investigation of recurrent problems and look at clinical need, for example should intravenous salbutamol be used as in current practice in the UK. In addition, there is a need to study current interventions that are used to reduce DRPs occurrence in paediatric populations, a large observational study of such interventions will be useful to explore the most effective way of reducing the incidence of DRP in children.
- The economic impact of ADRs and other DRPs in paediatric populations is still unclear. Therefore, optimisation of drug therapy in the paediatric population can be improved by targeting the medicines used and by careful monitoring of the medication process and the patients to identify and to resolve DRPs.

4.4 Overall conclusions

We have shown that the incidence of ADRs in children is at least as high as in adults. There is a great variation in the incidences between countries which was mainly due to treatment strategies and might be due to populations' differences (geographically and culturally). Clinicians and pharmacists should aim to minimise polypharmacy and be aware of the higher ADR risks associated with some drug groups. Particular attention should be given to use of opioids in hospitalised children, to reduce the risk of ADRs in these children. DRPs are a significant problem in hospitalised paediatric populations in the UK and the KSA and the majority of them are preventable.

Therefore, a focus on paediatric pharmacology and pharmacotherapy within paediatric medical and nursing education is an important step to improve prescribing practices and medication use in children.

References

't Jong GW, Stricker BH, Choonar I, van den Anker JN. (2002). Lack of effect of the European guidance on clinical investigation of medicines in children. *Acta Paediatr*, 91(11):1233-8.

Aagaard L, Christensen A, Hansen EH. (2010). Information about adverse drug reactions reported in children: a qualitative review of empirical studies. *Br J Clin Pharmacol*, 70(4): 481-91

AbuRuz SM, Bulatova NR, Yousef AM. (2006). Validation of a comprehensive classification tool for treatment-related problems. *Pharm World Sci,* 28(4): 222-32.

Ackers R, Besag FMC, Hughes E, Squier W, Murray ML, Wong ICK. (2011). Mortality rates and causes of death in children with epilepsy prescribed antiepileptic drugs. *Drug Saf*, 34(5): 403-413.

Agbabiaka TB, Savović J, Ernst E. (2008). Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf*, 31(1): 21-37.

Ahmed M el-B. (1997). Drug-related admissions to a district hospital in Saudi Arabia. *J Clin Pharm Therap*, 22: 61-66.

Al-Jeraisy MI, Alanazi MQ, Abolfotouh MA. (2011). Medication prescribing errors in a pediatric inpatient tertiary care setting in Saudi Arabia. *BMC Res Notes*, 4:297.

Allen A, Mitchell MD, Lacouture PG, Sheehan JE, Kauffman RE, and Shapiro S. (1988). Adverse Drug Reaction in Children leading to Hospital Admission. *Pediatrics*, 82 (1): 24-29.

Al-Olah YH, Al Thiab MK. (2008). Admissions through the emergency department due to drug-related problems. *Ann Saudi Med*, 28(6): 426-429.

Altman D. (1991). Practical statistics for medical research. 1st edition. London: Chapman & Hall.

Azaz-Livshits T, Levy M, Sadan B, Shalit M, Geisslinger G, Brune K. (1998). Computerized surveliance of adverse drug reactions in hospital: pilot study. *Br J Clin Pharmacol*, 45(3): 309-14.

References

Baena MI, Fajardo P, Luque FM, Marin R, Arcos A, Zarzuelo A, Jimenez J, Faus MJ. (2001). Drug related problems in hospital emergency service users: results of the validation of a questionnaire. *Pharm Care Esp*, 2: 345-357.

Baena MI, Faus MJ, Fajardo PC, Luque FM, Sierra F, Martinez-Olmos J, Cabrera A, Fernandez-Llimos F, Martinez-Martinez F, Jiménez J, Zarzuelo A. (2006). Medicine-related problems resulting in emergency department visits. *Eur J Clin Pharmacol*, 62(5): 387-93.

Barata IA, Benjamin LS, Mace SE, Herman MI, Goldman RD. (2007). Pediatric patient safety in the prehospital/emergency department setting. *Pediatr Emerg Care*, 23(6): 412-418.

Bates DW. (2002). Using information technology to screen for adverse drug events. *Am J Health Syst Pharm*, 59(23): 2317-9.

Bates DW, Miller EB, Cullen DJ, Burdick L, Williams L, Laird N, Petersen LA, Small SD, Sweitzer BJ, Vander Vliet M, Leape LL. (1999). Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. *Arch Intern Med*, 159(21): 2553-60.

Bedouch P, Charpiat B, Conort O, Rose F, Escofier L, Juste M, Roubille R, Allenet B. (2008). Assessment of clinical pharmacists' interventions in French hospitals: results of a multicenter study. *Ann Pharmacother*, 42: 1095-103.

Bednall R, McRobbie D, Hicks A. (2003). Identification of medication-related attendances at an A & E department. *J Clin Pharm Ther*, 28(1): 41-5

Bennett PN and Brown NJ. (2003). Clinical pharmacology. 9th edition, Edinburgh: Churchill Livingstone.

Blix HS, Viktil KK, Moger TA, Reikvam A. (2006). Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams. *Pharm World Sci*, 28(3): 152-8.

Blum KV, Abel SR, Urbanski CJ, Pierce JM. (1988). Medication error prevention by pharmacists. *Am J Hosp Pharm*, 45: 1902-3.

BNFC. (2011). British National Formulary for Children. Paediatric Formulary Committee. London: BMJ Publishing Group, RPS Publishing, and RCPCH Publications.

References

Bonati M, Marchetti F, Zullini MT, Pistotti V, Tognoni G. (1990). Adverse drug reactions in neonatal intensive care units. *Adverse Drug React Acute Poison Rev*, 9(2): 103-18.

Bowman L, Carlstedt BC, Hancock EF, Black CD. (1996). Adverse drug reaction (ADR) occurrence and evaluation in elderly inpatients. *Pharmacoepidemiol Drug Saf,* 5(1): 9-18.

Broussard L. (2010). Small size, big risk: preventing neonatal and paediatric medication errors. *Nurs Womens Health*, 14(5): 405-408.

Buajordet I, Wesenberg F, Brors O, Langslet A. (2002). Adverse drug events in children during hospitalization and after discharge in a Norwegian university hospital. *Acta Paediatr*, 91(1): 88-94.

Caamaño F, Pedone C, Zuccalà G, Carbonin P. (2005). Socio-demographic factors related to the prevalence of adverse drug reaction at hospital admission in an elderly population. *Arch Gerontol Geriatr*, 40(1): 45-52.

Campino A, Lopez-Herrera MC, Lopez-de-Heredia I, Valls-i-Soler A. (2009). Educational strategy to reduce medication errors in a neonatal intensive care unit. *Acta Paediatr*, 88: 782-785.

Carleton BC, Smith MA, Gelin MN, Heathcote SC. (2007). Paediatric adverse drug reaction reporting: understanding and future directions. *Can J Clin Pharmacol*, 14(1): e45-e57.

Casavant MJ, Griffith JR. (2010). Pediatric pharmacotherapy part 1: the history of pediatric drug therapy: learning from errors, not trials. AccessMedicine from McGraw-Hill, The McGraw Companies. Available from: http://www.medscape.com/viewarticle/726236 [accessed June 2011].

Chan DS, Kotzin DA. (1998). Adult vs pediatric clinical intervention trends: a four year, retrospective report. *J Pediatr Pharm Pract*, 3(3): 144-149.

Choonara I, Gill A, Nunn A. (1996). Drug toxicity and surveillance in children. *Br J Clin Pharmacol*, 42(4): 407-10.

Choonara I, Rieder MJ. (2002). Drug toxicity and adverse drug reactions in children - A Brief historical Review. *Paediatric and Perinatal Drug Therapy*, 5(1): 12-8.

Choonara I. (2006). Paediatric pharmacovigilance. *Paediatric and Perinatal Drug Therapy*, 7(2): 50-53.

References

Choonara IA, Harris F. (1984). Adverse drug reactions in medical inpatients. *Arch Dis Child,* 59(6): 578-580.

Chua SS, Chua HM, Omar A. (2010). Drug administration errors in paediatric wards: a direct observation approach. *Eur J Pediatr*, 169: 603-611.

Clarkson A, Choonara I. (2002). Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child*, 87(6): 462-466.

Clarkson A, Conory S, Burroughs K, Choonara I. (2004). Surveillance for adverse drug reactions in children: a paediatric regional monitoring centre. *Paediatric and Perinatal Drug Therapy*, 6(1):20-23.

Clarkson A, Ingleby E, Choonara I, Bryan P, Arlett P. (2001). A novel scheme for the reporting of adverse drug reactions. *Arch Dis Child*, 84(4): 337-339.

Classen DC, Pestotnik SL, Evans RS, Burke JP. (1991). Computerized surveillance of adverse drug events in hospital patients. *JAMA*, 266(20): 2847-2851.

Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. (1997). Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA*, 277(4): 301-306.

Clavenna A, Bonati M. (2009). Adverse drug reactions in childhood: a review of prospective studies and safety alerts. *Arch Dis Child*, 94: 724-728.

Clifford S, Barber N, Elliott R, Hartley E, Horne R. (2006). Patient-centred advice is effective in improving adherence to medicines. *Pharm World Sci*, 28(3): 165-70.

Conroy S. (2003). Paediatric pharmacy- drug therapy. *Hospital pharmacist*, 10 (2):49-57.

Conroy S, Sweis D, Planner C, Yeung V, Collier J, Haines L, Wong IC. (2007). Interventions to reduce dosing errors in children: a systematic review of the literature. *Drug Saf*, 30(12): 1111-25.

Conroy S. (2011). Association between licence status and medication errors. *Arch Dis Child*, 96(3): 305-306

Cunningham G, Dodd TR, Grant DJ, McMurdo ME, Richards RM. (1997). Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. *Age Ageing*, 26(5): 375-82.

Cuzzolin L, Zaccaron A, Fanos V. (2003). Unlicensed and off-label uses of drugs in paediatrics: as review of the literature. *Fundam Clin Pharmacol*, 17(1): 125-31.

Davies EC, Green CF, Mottram DR, Pirmohamed M. (2006). Adverse drug reactions in hospital in-patients: a pilot study. *J Clin Phar Ther*, 31: 335-341.

Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. (2009). Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One*, 4(2): e4439.

de Vries TW, de Langen-Wouterse JJ, van Puijenbroek E, Duiverman EJ, de Jong-Van den Berg LT. (2006). Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. *Eur J Clin Pharmacol*, 62(5): 343-6.

Dean BS, Barber ND. (1999). A validated, relaiable method of scoring the severity of medication errors. *Am J Health Syst Pharm*, 56(1): 57-62.

Dean FB, Vincent C, Schachter M, Barber N. (2005). The incidence of prescribing errors in hospital inpatients: an overview of the research methods. *Drug Saf*, 28(10): 891-900.

Denneboom W, Dautzenberg MGH, Grol R, De Smet PAGM. (2005). User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance. *J Clin Pharm Ther*, 30(3): 215-23.

Dormann H, Criegee-Rieck M, Neubert A, Egger T, Geise A, Krebs S, Schneider TH, Levy M, Hahn EG, Brune KR. (2003). Lack of awareness of community-acquired adverse drug reactions upon hospital admission: dimensions and consequences of a dilemma. *Drug Saf*, 26(5): 353-62.

Dormann H, Criegee-Rieck M, Neubert A, Egger T, Levy M, Hahn EG, Brune K. (2004a). Implementation of a computer-assisted monitoring system for the detection of adverse drug reactions in gastroenterology. *Aliment Pharmacol Ther*, 19(3): 303-309.

Dormann H, Neubert A, Criegee-Rieck M, Egger T, Radespiel-Troger M, Azaz-Livshits T, Levy M, Brune K, Hahn EG. (2004b). Readmissions and adverse drug reactions in internal medicine: the economic impact. *J Intern Med*, 255(6): 653-663.

Dormann H, Krebs S, Muth-Selbach U, Criegee-Rieck M, Radespiel-Troger M, Levy M, Hahn EG, Brune K, Scheider HT. (2001). Adverse drug reactions in patients with gastroenterological diseases: does age increase the risk? *Aliment Pharmacol Ther*, 15(2): 171-180.

References

Dormann H, Muth-Selbach U, Kerbs S, Criegee-Rieck M, Tegeder I, Schneider HT, Hahn EG, Levy M, Brune K, Geisslinger G. (2000). Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. *Drug Saf*, 22(2): 161-168.

dos Santos DB, Coelho HL. (2006). Adverse drug reactions in hospitalized children in Fortaleza, Brazil. *Pharmacoepidemiol Drug Saf*, 15(9): 635-640.

Dunn KL, Reddy P, Moulden A, Bowes G. (2006). Medical record review of deaths, unexpected intensive care unit admissions, and clinician referrals: detection of adverse events and insight into the system. *Arch Dis Child*, 91(2): 169-172.

Easton KL, Chapman CB, Brien JA. (2004). Frequency and characteristics of hospital admissions associated with drug-related problems in paediatrics. *Br J Clin Pharmacol*, 57(5): 611–615.

Easton KL, Parsons BJ, Starr M, Brien JE. (1998). The incidence of drug-related problems as a cause of hospital admissions in children. *Med J Aust*, 169(7): 356-359.

Easton CKL, Chapman CB, Brien JE. (2003). Emergency department attendances associated with drug- related problems in paediatrics. *J Paediatr Child Health*, 39(2): 124-9.

Edwards IR, Aronson JK. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Lancet*, 356(9237): 1255-1259.

Egger T, Dormann H, Ahne G, Runge U, Neubert A, Criegee-Rieck M, Gassmann KG, Brune K. (2003). Identification of adverse drug reactions in geriatric inpatients using a computerised drug database. *Drugs Aging*, 20(10): 769-776.

Eichenberger PM, Lampert ML, Kahmann IV, van Mil JWF, Hersberger KE. (2010). Classification of drug-related problems with new prescriptions using a modified PCNE classification system. *Pharm World Sci*, 32: 362-372.

Einarson TR. (1993). Drug-related hospital admissions. *Ann Pharmacother*, 27: 832-40.

EMA. 2007. European Medicines Agency: the European paediatric initiative: history of the paediatric regulation. London, UK. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003693.pdf (accessed December 2011).

References

Ernst FR, Grizzle AJ. (2001). Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc*, 41(2): 192-9.

Falck KA, Darsey EH, Naughton MJ. (1997). Pharmacy interventions in a multidisciplinary paediatric intensive care unit. *J Paediatr Pharm Pract*, 2: 162-7.

Fattahi F, Pourpak Z, Moin M, Kazemnejad A, Khotaei GT, Mamishi S, Siadati A, Tabatabaei P. (2005). Adverse drug reactions in hospitalized children in a department of infectious diseases. *J Clin Pharmacol*, 45(11): 1313-1318.

Fattinger K, Roos M, Vergères P, Holenstein C, Kind B, Masche U, Stocker DN,Braunschweig S, Kullak-Ublick GA, Galeazzi RL, Follath F, Gasser T, Meier PJ. (2000). Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol*, 49(2): 158-67.

FDA. (2002). Non-prescription use of ibuprofen and the risk of gastrointestinal and renal toxicity. Presented by the International Ibuprofen Foundation. Available from: http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882b2_06_international%20ibuprofen%20foundation.htm (accessed December 2011).

Ferranti J, Horvath MM, Cozart H, Whitehurst J, Eckstrand J. (2008). Reevaluating the safety profile of pediatrics: a comparison of computerized adverse drug event surveillance and voluntary reporting in the pediatric environment. *Pediatrics*, 121(5): e1201-e1207.

Fortescue EB, Kaushal R, Landrigan CP, McKenna KJ, Clapp MD, Federico F, Goldmann DA, Bates DW. (2003). Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. *Pediatrics*, 111(4 Pt 1): 722-9.

Gallagher RM, Bird KA, Mason JR, Peak M, Williamson PR, Nunn AJ, Turner MA, Pirmohamed M, Smyth RL. (2011). Adverse drug reactions causing admission to a paediatric hospital: a pilot study. *J Clin Pharm Ther*, 36(2): 194-199.

Gandhi TK, Seger DL, Bates DW. (2000). Identifying drug safety issues: from research to practice. *Int J Qual Health Care*, 12(1): 69-76.

Ghaleb MA, Barber N, Franklin BD, Wong ICK. (2010). The incidence and nature of prescribing and medication administration errors in paediatric inpatients. *Arch Dis Child*, 95: 113-118.

Ghaleb MA, Barber N, Franklin BD, Yeung VW, Khaki ZF, Wong IC. (2006a). Systematic review of medication errors in pediatric patients. *Ann Pharmacother*, 40(10): 1766-76.

References

Ghaleb MA, Wong ICK. Medication errors in paediatric patients. (2006b). *Ach Dis Child Educ Pract Ed,* 91: ep20–ep24

Ghaleb M A, Barber N, Dean FB, Wong IC. (2005). What constitutes a prescribing error in paediatrics? *Quality & Safety in health care*, 14(5): 352-357.

Ghose K. (1980). Hospital bed occupancy due to drug-related problems. *J R Soc Med*, 73(12): 853-6.

Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. (1995). Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr*, 84(4): 438-41.

González-Martin G, Caroca CM, Paris E. (1998). Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study. *Int J Clin Pharmacol Ther*, 36(10): 530-3.

Gordon KJ,Smith FJ, Dhillon S. (2005). The development and validation of a screening tool for the identification of patients experiencing medication-related problems. *Int J Pharm Pract*, 13(3): 187-193.

Green CF, Mottram DR, Rowe PH, Pirmohamed M. (2000). Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study. *J Clin Pharm Ther*, 25(5):355-361.

Greenall J, Santora P, Koczmara C, Hyland S. (2009). Enhancing safe medication use ofr pediatric patients in the emergency department. *CJHP*, 62(2): 150-153.

Guerreiro MP, Cantrill JA, Pisco L, Martins AP. (2005). Considerations on preventable drug-related morbidity in primary care. Part 1- Impact of preventable drug-related morbidity. *Rev Port Clin Ger*, 21: 269-279.

Gupta A, Waldhauser LK. (1997). Adverse drug reactions from birth to early childhood. *Pediatr Clin North Am*, 44(1): 79-92.

Guy J, Persaud J, Davies E, Harvey D. (2003). Drug errors: what role do nurses and pharmacists have in minimizing the risk? *J Child Health Care*, 7(4): 277-90.

Haffner S, von LN, Wirth S, Thurmann PA. (2005). Detecting adverse drug reactions on paediatric wards: intensified surveillance versus computerised screening of laboratory values. *Drug Saf*, 28(5): 453-464.

References

Hammerlein A, Griese N, Schulz M. (2007). Survey of drug-related problems identified by community pharmacies. *Ann Pharmacother*, 41(11): 1825-1832.

Hatoum HT, Hutchinson RA, Witte KW, Newby GP. (1988). Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. *Drug Intell Clin Pharm*, 22(3): 252-9.

Hepler CD, Strand LM. (1990). Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm*, 47:533- 43.

Hewitt J. (1995). Drug-related unplanned readmissions to hospital. *Aust J of Hosp Pharm*, 25: 400-403.

Holdsworth MT, Fichtl RE, Behta M, Raisch DW, Mendez-Rico E, Adams A, Greifer M, Bostwick S, Greenwald BM. (2003). Incidence and impact of adverse drug events in pediatric inpatients. *Arch Pediatr Adolesc Med*, 157(1): 60-65.

Howard R, Avery A, Bissell P. (2008). Causes of preventable drug-related hospital admissions: a qualitative study *Qual Saf Health Care*, 17: 109-116.

Hwang SH, Lee S, Koo HK, Kim Y. (2008). Evaluation of a computer-based adverse-drug-event monitor. *Am J Health Syst Pharm*, 65(23): 2265-2272.

ICH Guideline. (2001). International Conference on Harmonisation (ICH) Guideline. E 11: Clinical Investigation of Medicinal Products in the Paediatric Population. European Medicines Agency for the Evaluation of Medicinal Products (EMEA), London, UK. Available from: http://www.emea.europa.eu/pdfs/human/ich/271199en.pdf (accessed September 2011).

ICH Guideline. (1995). International Conference on Harmonisation (ICH) Guideline . Topic E 2 A: Clinical safety data management: definitions and standards for expedited reporting. European Medicines Agency (EMEA), CPMP/ICH/377/95. Available from:http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf (accessed July 2011).

Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. (2001). Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol*, 52(1): 77-83.

Impicciatore P, Mohn A, Chiarelli F, Pandolfini C, Bonati M. (2002). Adverse drug reactions to off-label drugs on a paediatric ward: an italian prospective pilot study. *Paediatric & Perinatal Drug Therapy*, 5(1): 19-24.

References

Indomethacin SPCs. (2011). Summary of product characteristics: Ativan injection. Wyeth Pharmaceuticals. Electronic Medicine Compendium (eMC), last updated June 2011, http://www.medicines.org.uk/EMC/medicine/24419/SPC/Indometacin+Capsules+BP+25mg/ (accessed December 2011).

Jacqz-Aigrain E, Choonara I. (2006). Paediatric clinical pharmacology. Chapter 3: medication errors by Cousins DH, p254. Published by FontisMedia SA and Taylor & Francis Group, New York, London.

Jani YH, Barber N, Wong ICK. (2010). Paediatric dosing errors before and after electronic prescribing. *Qual Saf Health Care*, 19: 337-340.

Jani YH, Ghaleb MA, Marks SD, Cope J, Barber N, Wong IC. (2008). Electronic prescribing reduced prescribing errors in a pediatric renal outpatient clinic. *J Pediatr*, 152:214-8.

Jarernsiripornkul N, Krska J, Capps PA, Richards RM, Lee A. (2002). Patient reporting of potential adverse drug reactions: a methodological study. *Br J Clin Pharmacol*, 53(3): 318-325.

Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, Burdick E, Seger DL, Vander Vliet M, Bates DW. (1998). Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc*, 5(3): 305-314.

Jha AK, Kuperman GJ, Rittenberg E, Teich JM, Bates DW. (2008). Identifying hospital admissions due to adverse drug events using a computer-based monitor. *Pharmacoepidemiol Drug Saf*, 10(2): 113-119.

Johnson JA, Boorman JL. (1997). Drug-related morbidity and mortality and the economical impact of pharmaceutical care. *Am J Health-Syst Pharm*, 54: 554-8.

Johnson JA, Bootman JL. (1995). Drug-related morbidity and mortality. A cost-ofillness model. *Arch. Intern. Med*, 155: 1949-56.

Jonville-Bera AP, Giraudeau B, Blanc P, Beau-Salinas F, Autret-Leca E. (2002). Frequency of adverse drug reactions in children: A prospective study. *Br J Clin Pharmacol*, 53(2): 207-210.

Kanneh AB. (2004). Adverse drug reactions (ADRs) in children: Part 1. *Paediatr Nurs*, 16(6): 32-35.

Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, Goldmann DA. (2001). Medication errors and adverse drug events in paediatric inpatients. *JAMA*, 285: 2114-2120.

Kearns GL, Abdel-Rahman DM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. (2003). Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*, 349(12): 1157-67.

Kimland E, Bergman U, Lindemalm S, Bottiger Y. (2007). Drug related problems and off-label drug treatment in children as seen at a drug information centre. *Eur J Pediatr*, 166(6): 527-32.

Kimland E, Rane A, Ufer M, Panagiotidis G. (2005). Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiol Drug Saf*, 14(7): 493-499.

Knopf H, Du Y. (2010). Perceived adverse drug reactions among non-institutionalized children and adolescents in Germany. *Br J Clin Pharmacol*, 70: 409-417.

Koh Y, Kutty FB, Li SC. (2005). Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender. *Ther Clin Risk Manag*, 1(1): 39-48.

Koh Y, Kutty FM, Li SC. (2003). Therapy related hospital admission in patients on polypharmacy in Singapore: a piloit study. *Pharm World Sci*, 25(4): 135-137.

Kongkaew C, Noyce PR, Ashcroft DM. (2008). Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother*, 42 (7): 1017-25.

Koren G, Reich A, Hales B. (1991). Use of clinical pharmacists to prevent medication errors in children. *J Pharm Technol*, 7: 219-21

Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. (2007). Drug-related problems in hospitals: a review of the recent literature. *Drug Saf*, 30(5): 379-407.

Krupicka MI, Bratton SL, Sonnenthal K, Goldstein B. (2002). Impact of a pediatric clinical pharmacist in the pediatric intensive care unit. *Critical Care Medicine*, 30(4): 919-921.

Kunac DL, Kennedy J, Austin N, Reith D. (2009). Incidence, Preventability, and Impact of Adverse Drug Events (ADEs) and Potential ADEs in Hospitalized Children in New Zealand: A Prospective Observational Cohort Study. *Paediatr Drugs*, 11(2): 153-160.

References

Kunac DL, Reith DM. (2008). Preventable medication-related events in hospitalised children in New Zealand. *N Z Med J*, 121:17-32.

Kunac DL, Reith DM. (2005). Identification of priorities for medication safety in neonatal intensive care. *Drug Saf*, 28(3): 251-261.

Kyngäs HA, Kroll T, Duffy ME. (2000). Compliance in adolescents with chronic diseases: a review. *J Adolesc Health*, 26(6): 379-88.

Lamabadusuriya SP, Sathiadas G. (2003). Adverse drug reactions in children requiring hospital admission. *Ceylon Med J*, 48(3): 86-87.

Lampert ML, Kraehenbuehl S, Hug BL. (2008). Drug-related problems: evaluation of a classification system in the daily practice of a Swiss University Hospital. *Pharm World Sci*, 30: 768-776.

Landis JR, Koch GG. (1977). The measurement of observer agreement for categorical data. *Biometrics*, 33: 159-174.

Lasky T, Ernst FR, Greenspan J, Wang S, Gonzalez L. (2011). Estimating pediatric inpatient medication use in the United States. *Pharmacoepidemiol Drug Saf*, 20: 76-82.

Lassetter JH, Warnick ML. (2003). Medical errors, drug-related problems, and medication errors: a literature review on quality of care and cost issues. *J Nurs Care Qual*, 18(3): 175-81.

Lazarous J, Pomeranz BH, Corey PN. (1998). Incidence of adverse drug reactions in hospitalised patients: a meta-analysis pf prospective studies. *JAMA*, 279(15): 1200-1205.

Le J, Nguyen T, Law AV, Hodding J. (2006). Adverse drug reactions among children over a 10-year period. *Pediatrics*, 118(2): 555-562.

Leary PM. (1991). Adverse reactions in Children. Special considerations in prevention and management. *Drug Saf*, 6(3): 171-82.

Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. (2008). Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med*, 168(17): 1890-6.

Leff RD, Roberts RJ. (1987). Problems in drug therapy for pediatric patients American *Journal of Hospital Pharmacy*, 44: 865-70.

References

Levy M, zaz-Livshits T, Sadan B, Shalit M, Geisslinger G, Brune K. (1999). Computerized surveillance of adverse drug reactions in hospital: implementation. *Eur J Clin Pharmacol*, 54(11): 887-892.

Lorazepam SPCs. (2010). Summary of product characteristics: Ativan injection. Wyeth Pharmaceuticals. Electronic Medicine Compendium (eMC), last updated September 2010. Available from: http://www.medicines.org.uk/EMC/medicine/2196/SPC/Ativan+Injection/ (accessed September 2011).

Macedo AF, Marques FB, Ribeiro CF, Teixeira F. (2003). Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, according to different levels of imputability. *J Clin Pharm Ther*, 28(2): 137-43.

Major S, Badr S, Bahlawan L, Hassan G, Khogaoghlanian T, Khalil R, Melhem A, Richani R, Younes F, Yeretzian J, Khogali M, Sabra R. (1998). Drug-related hospitalization at a tertiary teaching centre in Lebanon: incidence, associations, and relation to self-medicating behavior. *Clin Pharmacol Ther*, 64 (4): 450-61.

Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Rubio E, Morales-Olivas FJ. (1996). A prospective study of adverse drug reactions as a cause of admission to a paediatric hospital. *Br J Clin Pharmacol*, 42(3): 319-324.

Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Rubio E, Morales-Olivas FJ. (1999). A prospective study of adverse drug reactions in hospitalized children. *Br J Clin Pharmacol*, 47(6): 681-688.

McDonnell C. (2011). Opioid medication errors in pediatric practice: four years' experience of voluntary safety reporting. *Pain Res Manag*, 16(2): 93-8.

McKenzie MW, Marchall GL, Netzloff ML, Cluff LE. (1976). Adverse drug reactions leading to hospitalization in children. *J Pediatr*, 89(3): 487-490.

McKenzie MW, Stewart RB, Weiss CF, Cluff LE. (1973). A pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients. *Am J Hosp Pharm*, 30(10): 898-903.

Menson EN, Walker AS, Sharland M, Wells C, Tudor-Williams G, Riordan FA, Lyall EG, Gibb DM, for the collaborative HIV paediatric study steering committee. (2006). Underdosing of antiretrovirals in UK and Irish Children with HIV as an example of

problems in prescribing medicines to children, 1997-2005: chohort study. *BMJ*, 332(7551): 1183-7.

Meyboom RHB, Lindquist M, Egberts ACG. (2000). An ABC of drug-related problems. *Drug Saf*, 22: 415-23.

Mitchell AA, Goldman P, Shapiro S, Slone D. (1979). Drug utilization and reported adverse reactions in hospitalized children. *Am J Epidemiol*, 110(2): 196-204.

Mitchell AA, Lacouture PG, Sheehan JE, Kauffman RE, Shapiro S. (1988). Adverse drug reactions in children leading to hospital admission. *Pediatrics*, 82(1): 24-29.

Moore TJ, Weiss SR, Kaplan S, Blaisdell CJ. (2002). Reported adverse drug events in infants and children under 2 years of age. *Pediatrics* 2002; 110(5): e53.

Moore N, Lecointre D, Noblet C, Mabille M. (1998). Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol*, 45(3): 301-8.

Morkane C, Binns KG, Coleman JJ. (2007). The medic's guide to prescribing: Prescribing for children. StudentBMJ, 15: 320-321. Available from: http://archive.student.bmj.com/search/pdf/07/09/sbmj320.pdf [accessed June 2011].

Munzenberger P, Emmanuel S, Heins M. (1972). The role of a pharmacist on the paediatric unit of a general hospital. *Am J Hosp Pharm*, 29(9):755-60.

Murff HJ, Patel VL, Hripcsak G, Bates DW. (2003). Detecting adverse events for patient safety research: a review of current methodologies. *J Biomed Inform*, 36(1-2): 131-43.

Nahata MC. (2000). Pharmaceutical Care Research and Pharmacy Practice. Chair Report for the 1999/2000 Research and Graduate Affairs Committee. *American Journal of Pharmaceutical Education* (Winter supplement), 64: 24S-29S.

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecg C, Greenblatt DJ. (1981). A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*, 30(2): 239-245.

National Coordinating Council for Medication Error Reporting and Prevention 'NCC-MERP'. (2011). About medication errors. Available from: www.nccmerp.org/aboutmederrors.htm [accessed November 2011].

References

Neubert A. (2011). Pharmacovigilance in paediatrics: current challenges. *Paediatr Drugs*, [Epub doi: 10.2165/1596590].

Neubert A, Dormann H, Weiss J, Criegee-Rieck M, Ackermann A, Levy M, Brune K, Rascher W. (2006). Are computerised monitoring systems of value to improve pharmacovigilance in paediatric patients? *Eur J Clin Pharmacol*, 62(11): 959-965.

Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, Brune K, Hinz B. (2004). The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf*, 27(13): 1059-67.

Neubert A, Rascher W. (2007). Adverse drug reactions in children. Identification and evaluation. *Monatsschr Kinderheilkd*, 155: 700-708.

Neubert A, Verhamme K, Murray ML, Picelli G, Hsia Y, Sen FE, Giaquinto C, Ceci A, Sturkenboom M, Wong ICK, TEDDY Network of Excellencel. (2010). The prescribing of analgesics and non-steroidal anti-inflammatory drugs in paediatric primary care in the UK, Italy and the Netherlands. *Pharmacol Res*, 62(3): 243-248.

NPSA. (2007). National Patient Safety Agency, Safety in doses: medication safety incidents in the NHS. The fourth report from the Patient Safety Observatory, National Patietn Safety Agency, London. [accessed February 2011].

NPSA. (2009). National Patient Safety Agency, Safety in doses: improving the use of medicines in the NHS. Learning from national reporting 2007, National Patient Safety Agency, National Reporting and Learning Service, London. Available from: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=61392 (accessed June 2011).

NPPG. (2009). ManMed Award, Neonatal & Paediatric Pharmacists Group (NPPG) in association with Mandeville Medicines. http://www.nppg.scot.nhs.uk/awards.htm.

Oshikoya KA, Njokanma OF, Chukwura HA, Ojo IO. (2007). Adverse drug reactions in Nigerian children. *Paediatr Perinat Drug Ther*, 8: 81-88.

Paediatric Regulation. (2006). 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. Available from: http://eurlex.europa.eu/LexUriServ/site/en/oj/2006/l_378/l_37820061227en00010019.pdf (accessed September 2011).

Passarelli MC, Jacob-Filho W, Figueras A. (2005). Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. *Drugs Aging*, 22(9): 767-77.

Patel P, Zed PJ. (2002). Drug-related visits to the emergency department: how big is the problem? *Pharmacotherapy*, 22(7): 915-23.

PCNE. (2006). Pharmaceutical Care Network Europe, DRP Classifications version 5.01. (accessed September 2011). Available from: http://www.pcne.org/sig/drp/documents/drp/PCNE%20classification%20V5.01.pdf

Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*, 329(7456): 15-19.

Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. (1998). Adverse drug reactions: fortnightly review. *BMJ*, 316: 1295-8.

Prince BS, Goetz CM, Rihn TL, Olsky M. (1992). Drug-related emergency department visits and hospital admissions. *Am J Hosp Pharm*, 49(7): 1696-700.

Rashed AN, Wong ICK, Cranswick N, Hefele B, Tomlin S, Jackman J, Lee K, Hon KLE, Ong J, Ghaleb M, Chua SS, Hui TM, Rascher W, Neubert A. Adverse Drug Reactions in Children - International Surveillance and Evaluation (ADVISE): a multicentre cohort study. *Drug Saf* (*In press*).

Rashed AN, Wong ICK, Cranswick N, Tomlin S, Rascher W, Neubert A. (2012). Risk factors associated with adverse drug reactions in hospitalised children: international multicentre study. *Eur J Clin Pharmacol*, 68(5):801-810, doi:10.1007/s00228-011-1183-4 [Published online first: 14 December 2011].

Rawlins MD, Thompson JW. (1991). Mechanisms of adverse drug reactions. In Davis DM (ed) Textbook of adverse drug reactions, Oxford, Oxford University Press.

Rieder MJ. (1994). Mechanisms of unpredictable adverse drug reactions. *Drug Saf*, 11(3): 196-212.

Roughead EE. (1999). The nature and extent of drug-related hospitalisations in Australia. *J Qual Clin Pract*, 19(1): 19-22.

Runciman WB, Roughead EE, Semple SJ, Adams RJ. (2003). Adverse drug events and medication errors in Australia. *Int J Qual Health Care*, 15(Suppl 1): i49-59.

Sánchez Muñoz-Torrero JF, Barquilla P, Velasco R, Fernández Capitan MD, Pacheco N, Vicente L, Chicón JL, Trejo S, Zamorano J, Lorenzo Hernandez A. (2010). Adverse drug reactions in internal medicine units and associated risk factors. *Eur J Clin Pharmacol*, 66 (12): 1257-64.

Sanghera N, Chan PY, Khaki ZF. Planner C, Lee KK, Cranswick NE, Wong IC. (2006). Interventions of hospital pharmacists in improving drug therapy in children: a systematic literature review. *Drug Saf*, 29(11): 1031-47.

Schramm A, Rashed AN, Hefele B, Rascher W, Neubert A. Adverse drug reactions in hospitalised children in Germany are decreasing: Results of a nice year cohort-based comparison. PLoS ONE (*Accepted*).

Schumock GT, Thornton JP. (1992). Focusing on the preventability of adverse drug reactions. *Hosp Pharm*, 27(6): 538.

Seger AC, Jha AK, Bates DW. (2007). Adverse drug event detection in a community hospital utilising computerised medication and laboratory data. *Drug Saf*, 30(9): 817-824.

Shalviri G, Mohammad K, Majdzadeh R, Gholami K. (2007). Applying quantitative methods for detecting new drug safety signals in pharmacovigilance national database. *Pharmacoepidemiol Drug Saf*, 16(10): 1136-1140.

Snaz EJ. (2003). Concordance and children's use of medicines. *BMJ*, 327(7419): 858-60.

Star K, Norén GN, Nordin K, Edwards IR. (2011). Suspected adverse drug reaction reported for children worldwide: an exploratory study using VigiBase. *Drug Saf*, 34: 415-28.

STATA-11. (2009). STATA Quick reference and Index, Release 11. A Stata Press Publication, StataCorp, College Station, Texas, USA.

Strand L. (1997). Pharmaceutical care: the Minnesota model. *The Pharmaceutical Journal*, 258: 899-904.

Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. (1990). Drug-related problems: their structure and function. *DICP*, 24(11): 1093-7.

Strom BL. (2006). What is Pharmacoepidemiology? in Strom BL, Kimmel SE (eds.). Textbook of Pharmacoepidemiology, 4th edition. John Wiley & Sons Ltd, USA; 3-5.

Sturkenboom MC, Verhamme KMC, Nicolosi A, Murray ML, Neubert A, Caudri D, Picelli G, Fatma E, Giaquinto C, Cantarutti L, Baiardi P, Felisi MG, Ceci A, Wong ICK. (2008). Drug use in children: cohort study in three European countries. *BMJ,* 337: a2245.

Tafreshi MJ, Melby MJ, Kaback KR, Nord TC. (1999). Medication-related visits to the emergency department: a prospective study. *Ann Pharmacother*, 33(12): 1252-7.

Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. (2008). Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. *Pediatrics*, 121(4): e927-e935.

Tavassoli N, Duchayne E, Sadaba B, Desboeuf K, Sommet A, Lapeyre-Mestre M, Muoz MJ, Sie P, Honorato J, Montastruc JL, Bagheri H. (2007). Detection and incidence of drug-induced agranulocytosis in hospital: a prospective analysis from laboratory signals. *Eur J Clin Pharmacol*, 63(3): 221-228.

Tegeder I, Levy M, Muth-Selbach U, Oelkers R, Neumann F, Dormann H, Azaz-Livshits, Criegee_Rieck M, Schneider HT, Hahn EG, Geisslinger G. (1999). Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. *Br J Clin Pharmacol*, 47(5): 557-564.

Temple ME, Robinson RF, Miller JC, Hayes JR, Nahata MC. (2004). Frequency and preventability of adverse drug reactions in paediatric patients. *Drug Saf*, 27(11): 819-829.

Thomas EJ, Brennan TA. (2000). Incidence and types of preventable adverse events in elderly patients: population based review of medical records. *BMJ*, 320(7237): 741-744.

Thuermann PA, Windecker R, Steffen J, Schaefer M, Tenter U, Reese E, Menger H, Schmitt K. (2002). Detection of adverse drug reactions in a neurological department: comparison between intensified surveillance and a computer-assisted approach. *Drug Saf,* 25(10): 713-724.

Thurmann PA. (2001). Methods and systems to detect adverse drug reactions in hospitals. *Drug Saf*, 24(13): 961-968.

Tremlett HL, Oger J. (2008). Ten years of adverse drug reaction reports for the multiple sclerosis immunomodulatory therapies: a Canadian perspective. *Mult Scler*, 14(1): 94-105.

Turner S, Nunn AJ, Fielding K, Choonara I. (1999). Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr*, 88(9): 965-968.

Turner S, Longworth A, Nunn AJ, Choonara I. (1998). Unlicensed and off label drug use in paediatric wards: a prospective study. *BMJ*, 316(7128): 343-5.

Ufer M, Kimland E, Bergman U. (2004). Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. *Pharmacoepidemiol Drug Saf*, 13(3): 147-152.

van den Bemt PM, Egberts AC, Lenderink AW, Verzijl JM, Simons KA, van der Pol WS, Leufkens HG. (1999). Adverse drug events in hospitalized patients. A comparison of doctors, nurses and patients as sources of reports. *Eur J Clin Pharmacol*, 55(2): 155-158.

van den Bemt PM, Egberts TC, de Jong-van den Berg LT, Brouwers JR. (2000a). Drug-related problems in hospitalised patients – a review. *Drug Saf*, 22(4): 321-33.

van den Bemt PM, Egberts AC, Lenderink AW, Verzijl JM, Simons KA, van der Pol WS, Leufkens HG. (2000b). Risk factors for the development of adverse drug events in hospitalized patients. *Pharm World Sci*, 22(2): 62-66.

van den Bemt PM, Egberts AC. (2007). Drug-related problems: definitions and classification. *EJHP Practice*, 2007(13): 62-64.

van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH, Sturkenboom MCl. (2008). Adverse drug reaction-related hospitalisations: a population-based cohort study. *Pharmacoepidemiol Drug Saf*, 17(4): 365-371.

van der Hooft CS, Sturkenboom MC, van Grootheest K, Kingma HJ, Stricker BH. (2006). Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. *Drug Saf*, 29(2): 161-8.

van Mil JW, Westerlund LO, Hersberger KE, Schaefer MA. (2004). Drug-related problem classification systems. *Ann Pharmacother*, 38(5): 859-67.

Van Rosse F, Maat B, Rademaker CM, van Vught AJ, Egberts AC, Bollen CW. (2009). The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systemic review. *Pediatrics*, 123(4): 1184-90.

Vazquez De La Villa A, Luna del Castillo JD, Galdó Muñoz G, Puche Cañas E. (1989). Adverse reactions caused by drugs in pediatrics. *An Esp Pediatr*, 31(1): 49-53. (Article in Spanish, only abstract in English).

References

Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. (2009). Medication use among children <12 years of age in the United States: results from the Slone Survey. *Pediatrics*, 124(2): 446-54.

Virani A, Crown N. (2003). The impact of a clinical pharmacist on patient and economic outcomes in a child and adolescent mental health unit. *Can J Hosp Pharm*, 56(3): 158-2.

Volume 9A. (2008). The rules governing medicinal products in the European Union – Guidelines on pharmacovigilance for medicinal products for human use. Available from: http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf (accessed November 2011).

Wade A. (2001). Study size. *Sex Transm Infect*, 77(5): 332-4.

Warner A. (1986). Drug use in the neonate: interrelationships of pharmacokinetics, toxicity, and biochemical maturity. *Clin Chem*, 32(5): 721-7.

Weiss J, Krebs S, Hoffmann C, Werner U, Neubert A, Brune K, Rascher W. (2002). Survey of adverse drug reactions on a pediatric ward: a strategy for early and detailed detection. *Pediatrics*, 110(2 Pt 1): 254-7.

Westerlund LT, Marklund BR, Handl WH, Thunberd ME, Allebeck P. (2001). Nonprescription drug-related problems and pharmacy interventions. *Ann Pharmacother*, 35(11): 1343-1349.

Westerlund M, Braanstad JO, Westerlund T. (2008). Medicine-taking behavior and drug-related problems in adolescents of a Swedish high school. *Pharm World Sci*, 30(3): 243-250.

Westerlund T, Marklund B. (2009). Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. *J Clin Pharm Ther*, 34(3): 319-27.

Westerlund T. (2002). Drug-related problems: identification, characteristics and pharmacy interventions (dissertation). Department of Social Medicine, Göteborg University, Göteborg, Sweden, 25-6.

Westerlund, T, Almarsdottir AB, Melander A. (1999). Drug-related problems and pharmacy interventions in community practice. *Int J Pharm Pract*, 7(1): 40-50.

WHO. (2005). World Health Organisation, AIDS treatment for children, available from: http://www.who.int/3by5/paediatric/en [accessed June 2011].

References

WHO. (1972). World Health Organisation, Technical Report series No 498. Available from: http://who-umc.org/graphics/24756.pdf [accessed in July 2011].

WHO. (2002). World Health Organisation. The importance of pharmacovigilance: safety of monitoring of medicinal products. Available from: http://whqlibdoc.who.int/hq/2002/a75646.pdf (accessed July 2011).

WHO. (2003). World Health Organisation, Adverse Reaction Terminology. Available from: http://www.umc-products.com/graphics/3036.pdf (accessed July 2011).

WHO. (2007). World Health Organisation, International Statistical Classification of Diseases and Related Health Problems. 10th Revision, version for 2007. Available from: http://apps.who.int/classifications/apps/icd/icd10online2007/ [accessed July 2011].

WHO Collaborating Centre for Drug Statistics Methodology. (2011). World Health Organisation (WHO). Available from: http://www.whocc.no/atc_ddd_index/ (accessed November 2011).

Wilson EB, *J Am Stat Assoc* 1927; 22: 209-212. Available from: http://www.hutchon.net/Wilsons.htm [accessed October 2011].

Whyte J, Greenan E. (1977). Drug usage and adverse drug reactions in paediatric patients. *Acta Paediatr Scand*, 66(6): 767-775.

Winnick S, Lucas DO, Hartman AL, Toll D. (2005). How do you improve compliance? *Pediatrics*, 115(6): e718-24.

Winterstein AG, Sauer BC, Helper CD, Poole C. (2002). Preventable drug-related hospital admissions. *Ann Pharmacother*, 36(7-8): 1238-1248.

Wong I. (2009). Ways to reduce drug dose calculation errors in children. *J Health Serv Res Policy*, 00(0): 1-3.

Wong IC, Wong LY, Cranswick NE. (2009). Minimising medication errors in children. *Arch Dis Child*, 94:161-4.

Wong IC, Ghaleb MA, Franklin BD, Barber N. (2004). Incidence and nature of dosing errors in paediatric medications: a systematic review. *Drug Saf*, 27(9): 661-70.

Yosselson-Superstine S, Weiss T. (1982). Drug-related hospitalization in paediatric patients. *J Clin Hosp Pharm*, 7(3): 195-2003.

Zargarzadeh AH, Emami MH, Hosseini F. (2007). Drug-related hospital admissions in a generic pharmaceutical system *1. Clin Exp Pharmacol Physiol*, 34(5-6): 494-8.

Zed PJ. Drug-related visits to the emergency department. (2005). *Journal of Pharmacy Practice*, 18(5): 329-335.

Zopf Y, Rabe C, Neubert A, Hahn EG, Dormann H. (2008a). Risk factors associated with adverse drug reactions following hospital admission: a prospective analysis of 907 patients in two German university hospitals. *Drug Saf*, 31(9): 789-98.

Zopf, Z, Rabe C, Neubert A, Gassmann KG, Rascher W, Hahn EG, Brune K, Dormann H. (2008b). Women encounter ADRs more often than do men. *Eur. J. Clin. Pharmacol,* 64(10): 999-1004.

Zopf Y, Rabe C, Neubert A, Janson C, Brune K, Hahn EG, Dormann H. (2009). Gender-based differences in drug prescription: relation to adverse drug reactions. *Pharmacology*, 84(6): 333-9.

APPENDICES

Appendix 1: Summary of studies reported in the two meta-analyses (Impicciatore et al. 2001; Clavenna & Bonati 2009)

Reference Country/ Year	Study title	Study duration	Setting	Methodology	Number of reports or reporting rate/ ADRs incidence rate
Turner et al UK/1999	Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study	13 Weeks	5 paediatric wards at regional children's hospital	Prospective cohort study A green card for any suspected ADRs was requested to be completed by healthcare professional on all study wards. Then a research pharmacist reviewed the completed forms and reviewed the clinical records of each reported case. Sample size: 1046 admissions, patient age range from 1 day to 18 years.	Overall ADRs incidence was 11%.
Choonara & Harris UK/1984	Adverse drug reactions in medical inpatients	6 Months	General medical ward at children's hospital	Prospective study. Method not clear. Record of drugs given in hospital. Also drug history was obtained from parents, referral letters and to questionnaire to GP. ADRs searched prospectively by medical and nursing staff daily. Sample size: 268 admitted children aged 1-12 years	15 of 268 children had definite or probable ADRs during admission
Gill et al UK/1995	Adverse drug reactions in a paediatric intensive care unit	28 Months	PICU at children's hospital	Prospective study. Green card for ADR detection was requested to be filled by medical staff (nurse, doctor, pharmacy). Then clinical research pharmacist reviewed the clinical records for each reported ADR case. Sample size: 899 patients, age range from 0-16years.	63 of 899 had an ADR (incidence 7.01%).
Whyte & Greenan UK/1977	Drug usage and adverse drug reactions in paediatric patients	10 Months	Medical paediatric unit	Admissions with responsibilities for cardiac investigation and the treatment of leukaemia were intensively monitored using a method similar to Slone et al (1966).drugs; medical and	This paper focusing on drug usage Total ADR=119 Overall ADR incidence 6% (51/844), ADR incidence of 6.5% reported for

Continued..

Reference Country/ Year	Study title	Study duration	Setting	Methodology	Number of reports or reporting rate/ ADRs incidence rate
				nursing recodes were examined daily research nurse who interviewed parents also. Sample size: 932 admission episodes related to 844 patients, age range (0-12+)	only children (595) who received medication in the hospital, 1 (39/595).
Mitchell et al. US/1979	Drug utilization and reported adverse reactions in hospitalized children	1974-1977	340-bed paediatric teaching hospital	Prospective study. Intensive monitoring using a Pediatric Drug Surveillance (PeDS) program. Trained paediatric nurses collected data for all children admitted to the study ward using data forms. Then, a nurse and physician at the drug epidemiology unit reviewed these forms. Later the data entered onto a computer file after certain validation tests. Patients exclusion: a) patients have been previously monitored by the PeDS program, b) under care of physician who works on other wards, c) patients admitted for <24hrs, d) patients transferred from unmonitored wards. Sample size: 1669 patients (aged 0-≥ 17 years).	16.8% of patients had ADRs.
Mitchell et al. US/1988	Adverse drug reactions in children leading to hospital admission	11 years	Paediatric wards at 4 teaching hospitals and three community hospitals	Prospective study. Previous PeDS program which quantify acute AED of drugs in paediatric population, Trained nurses intensively monitored medical records of admitted children to the selected study wards and collected information systematically. Neonate and patients with cancer were excluded. Sample size: 10,297 patients (age range ≤30 days and ≥ 15 years).	2.1% of admissions in the teaching hospitals were provoked by ADRs. While ADRs were the cause of 1.8% admissions in community hospitals.

Continued..

Reference Country/ Year	Study title	Study duration	Setting	Methodology	Number of reports or reporting rate/ ADRs incidence rate
Martinez-Mir et al. Spain/1996	A prospective study of adverse drug reactions as a cause of admission to a padiatric hospital	Summer (105 days). Winter (99 days)	Two medical paediatric wards at Hospital Infantil Universitario La Fe in Valencia	Prospective study. One of the authors screened the medical records for all admitted patients and collected data using structured questionnaire and interview parents/caregivers. Patients' charts were then evaluated for suspected ADRs. Sample size: 512 admissions related to 490 patients (aged 1-24 months).	4.3% of admissions were found to be due to ADRs.
McKenzie et al. US/1976	Adverse drug reactions leading to hospitalization in children	3 Years	Paediatric medical services of teaching hospital.	Prospective study. Patients' chart review and attending physician rounds were performed to collect the data for all patients admitted due to ADR. Sample size: 3556 admissions Age: not specified???	64 (2%) patients admitted because of ADRs.
Martinez-Mir et al. Spain/1999	A prospective study of adverse drug reactions in hospitalized children	Two periods: Summer (105 days). Winter (99 days)	Two medical paediatric wards at Hospital Infantil Universitario La Fe in Valencia	Same cohort study as paper 1996, but in this they look at ADRs in general not only those causing admission Sample size: 512 admissions related to 490 patients (aged 1-24 months).	Cumulative ADR incidence 16.6% from both periods.
Gonzalez-Martin et al Chile/1998	Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study	Jan-Dec 1997	Hospital of Universi-dad Catolica de Chile. (ward not specified)	Prospective study Intensive drug surveillance program where medical orders and progress notes were searched daily by clinical pharmacist. Sample size: 219 patients, age range (0-16 years)	30 (13.7%) patients suffered an ADR majority of ADRs were classified as mild (51.2%), 27.9% were severe.
McKenzie et al. US/1973	A pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients	1st Feb-30th Sep 1971 (8 months)	Pediatric medicine services at Shands teaching hospital in Gaiesville	Prospective study Physician interviews and charts review was done by pharmacist who also participated in ward rounds. Sample size: 658 patients, age range (<1y->10y)	113 (17.2%) patients suffered an ADR. ADR incidence in hospital was 10.6% (70 patients). Incidence of ADR leading to admission 3.0% (19 patients)

Continued..

Reference Country/ Year	Study title	Study duration	Setting	Methodology	Number of reports or reporting rate/ ADRs incidence rate
					Incidence of ADR on admission 8.1% (53 patients) Incidence of patients with ADRs on admissions and developed ADR during hospital stay 1.6% (10 patients).
Vazquez De La Villa et al. Spain/1989	Adverse reactions caused by drugs in paediatrics (article in Spanish, only abstract in English)	12 Months	Paediatrics' services of the University of Granada Hospital	ADR detected using screening program aimed at detecting ADRs to medications. The program based on monitoring the patients for 12 months period. Sample size: 597 patients, age range (1-8years)	4.4% of patients had an ADR. ADRs classified as confirmed in 33.3%, probable in 30%, possible in 36.6%. (Naranjo scale used)
Yosselson-Superstine & Weiss Israel/1982	Drug-related hospitalization in paediatric patients	7 Months	Paediatric ward in the Hadassah-Hebrew University Hospital in Jerusalem	Data collected by clinical pharmacist who participated in physician's rounds, interviewed patients/their guardians, and reviewed medical charts. Sample size: 906 admissions, age range (0-16years)	They were looking to three types of drug-related hospitalization: 1. Inappropriate therapy related to 11.0% of admissions 2. Non-compliance related to 3.4% of admissions 3. ADRs related to 3.2% of admissions.
Easton et al. Australia/1998	The incidence of drug-related problems as a cause of hospital admissions in children	56 days (from 24th Jun-19th Aug 1996)	University-affiliated paediatric hospital	Prospective study Data collected by ward pharmacists and researcher who reviewed case notes and interviewed parents to determine if an admission was associated with a DRP. Surgical, trauma or oncology patients were excluded. Also, patients whose parents/guardians who couldn't speak adequate English were excluded. Sample size: 1682 patients, age range (19 weeks -18years)	They were looking for incidence of DRP causing admission not ADR incidence in particular. They used the 8 categories of DRPs defined by Strand et al (1990) 3.4% of admissions were associated with DRPs. Incidence of ADR (as one of the 8 categories) leading to admission was 0.95% (10 cases).

Continued..

Reference Country/ Year	Study title	Study duration	Setting	Methodology	Number of reports or reporting rate/ ADRs incidence rate
Lamabadusuriya & Sathiadas Sri Lanka/ 2003	Adverse drug reactions in children requiring hospital admission	11 Months	Medical units of Lady Ridgeway hospital	Prospective, descriptive study Investigator visited the medical ward and collected information from patient's records. Sample size: 39,625 Children (aged 1-5 years).	0.16% of admissions were due to ADRs
Jonville-Bera et al. France/2002	Frequency of adverse drug reactions in children: A prospective study	1 Week	175-bed regional paediatric hospital. 35 private paediatricians	Prospective study Sample size: 260 children (mean age 76.1 ± 61.5 months). 1. Intensive monitoring of all admissions was performed by the nurse in charge using a specific form designed for this study. Then medical records were screened to confirm admission reasons by one of the authors. 2. 35 private paediatricians were asked to record the reason for consultation for all children seen.	1.53% of children were admitted due to ADRs, 2.64% developed ADRs during admission, 0 .93% attended A&E due to ADRs, and 0.67% consulting a private paediatrician for ADRs.
Buajordet et al. Norway/2002	Adverse drug events in children during hospitalization and after discharge in a Norwegian University Hospital	5 Months	Paediatric department at Ullevaal university hospital	Sample size: 665 patients (aged 0-16 years). Intensive monitoring of all admitted patients and data collection was done in two ways: a) Spontaneous reporting of suspected ADEs either by the physician or by the parents. b) Reviewing medical records by pharmacist.	28% of 579 children treated with drugs had ADEs; 7% at time of admission, 18% during hospitalization, and 9% after discharge.
dos Santos & Coelho Brazil/2006	Adverse drug reactions in hospitalized children in Fortaleza, Brazil	5 Months	Paediatric ward of public hospital	Prospective cohort study. Sample size: 272 children (aged 0-16 years). Data collected for all admitted patients by clinical pharmacist using questionnaire giving to children's mothers or relatives and a formulary to collect data from medical records, prescriptions and nurse notes.	47ADRs detected in 33 of 265 children treated with drugs, incidence 12.5%.
Neubert et al. Germany/2006	Are computerized monitoring systems of value to improve pharmacovigilance in	6 Months	22-bed paediatric isolation ward at the children's university hospital	Prospective Study Sample size: 396 patients (aged 0-18 years) 1. ALS generated by CMS* 2. Spontaneous reporting by physician	73 ADRs detected among 52 patients

Continued..

Reference Country/ Year	Study title	Study duration	Setting	Methodology	Number of reports or reporting rate/ ADRs incidence rate
	paediatric patients?			3. Intensive chart review	
Neubert et al Germany/2004	The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients	8 Months	10-bed paediatric isolation ward at University hospital Erlangen-Nuremberg	Prospective study Intensive patient charts reviewed by pharmacoepidemiology team. All prescriptions were evaluated retrospectively as to unlicensed or off-label uses on the bases of product information. Sample size: 178 patient, age range (0-17years)	46 ADRs detected in 31patients, incidence 17.4%
Oshikoya et al Nigeria/2007	Adverse drug reactions in Nigerian children	Two periods: Jan2004-Jun2006 6 Months	Children's ward at Lagos state university teaching hospital	Retrospective and prospective study Retrospective suspected ADRs noted in the hospital record from Jan 2004-Jun2006 were collected. Sample size: 3139 children. Prospective: pharmacovigilance by a multidisciplinary team was performed. Sample size: 682 children	From both study: 17 (0.4%) admitted due to ADRs, 27 (0.7%) had ADRs in hospital.

Appendix 2: ADVISE Data collection form

Date: Ward:

Patient Details	Pt Initials		Pt Study ID:	
	D.O.B/Age			
	Pt Gender			
	Pt weight			
	Ethinicity	Recorded:	Not Recorded ☐	
	Pt hieght	Recorded:	Not Recorded ☐	
	Pt allergies	Recorded:	Not Recorded ☐	NKDA ☐
	Admission ID			
	Admission Date			
	Type of admission	☐ Scheduled ☐ Emergency ☐ Transferred from.....		

Diagnosis Details	Diagnosis on Admission	
	Actual Diagnosis/ Medical History	
	Diagnosis Date	
	Tpye of diagnosis	
	Comments	

Continued..

Continued: Appendix 2

Discharge Details	Discharge Date	
	Type of discharge	

Pt Vitals on admission if abnormal	Temperature (°C)	
	Blood Pressure	
	Heart rate	
	Respiratory rate	
	Pulse	
	Oxygen Saturation	
	Comments	

Continued..

Continued: Appendix 2

Drugs on Admission (Drug History)

Pt Study ID	
Drug History (DH)	☐ No DH for the Pt ☐ No DH recorded
DH taken from parent(s)/ medical notes	
Comment	

Continued..

Continued: Appendix 2

Medications on the Ward (Pt Study ID:.....)

Drug name	Dose	Frequency	Route	Start Date/Time	End Date/Time	Order Type	Comments

Continued..

Continued: Appendix 2

Intravenous and Subcutaneous infusions (Pt Study ID:.....)

Date	Infusion Fluid		Addition to infusion		Route IV/SC	Start time	Rate ML/Hr)	Comment
	Type/Strength	Volume	Drug	Dose				

Continued..

Continued: Appendix 2

Pt Study ID	Medical Notes
Any other treatment	
Remarkable nurse's note	
Remarkable physician's note	
Comment	

Continued..

Continued: Appendix 2

Lab Data (Pt Study ID: .....)					
Lab Test(s)					
Order Date					
Lab Unit					
Sample Date					
Sample Time					
Result					
Standard Range	Upper Limit			Lower Limit	
Comments					

Continued..

Continued: Appendix 2

Follow up notes (Pt Study ID .....)	
Date	
Comment	
Date	
Comment	
Date	
Comment	
Date	
Comment	

Continued..

Appendix 3: ADVISE Letter of Ethics Approval_UK

NHS
National Research Ethics Service

Riverside Research Ethics Committee
Room 4W12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Telephone: 020 8846 7282
Facsimile: 020 8846 7280

Dr Antje Neubert
Research Fellow
Centre for Paediatric Pharmacy Research
The School of Pharmacy, University of London
First Floor, BMA House,
Tavistock Square, London
WC1H 9JP

08 October 2008

Dear Dr Neubert

Full title of study: **ADVerse drug reactions in children International Surveillance and Evaluation (ADVISE)**
REC reference number: **08/H0706/96**

Thank you for your letter of 22 October 2008, responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA). The favourable opinion for the study applies to all sites involved in the research. There is no requirement for other Local Research Ethics Committees to be informed or SSA to be carried out at each site.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Appendix 4: ADVISE Letter of Ethics Approval_Germany

Medizinische Fakultät
Ethik-Kommission

Friedrich-Alexander-Universität
Erlangen-Nürnberg

Ethik-Kommission • Krankenhausstr. 12• D-91054 Erlangen

Herrn
Prof. Dr. Dr. h.c. W. Rascher
Direktor der Kinder- und Jugendklinik
Loschgestr. 15
91054 Erlangen

Geschäftsstelle der Ethik-Kommission
Tel. (09131) 85-22270
Fax (09131) 85-26021
E-Mail: ethik@zuv.uni-erlangen.de
http://www.ethik.med.uni-erlangen.de

Erlangen, 15.11.2007

Antrag an die Ethik-Kommission/Re.-No. 3731
International Pharmacovigilance Study in Children.
Studienprotokoll Draft Version 2
(Eingang der vollständigen Unterlagen am 02.11.2007)

Sehr geehrter Herr Kollege Rascher,

die Ethik-Kommission der Medizinischen Fakultät hat in ihrer Sitzung vom 13.11.2007 über berufsethische und berufsrechtliche Aspekte Ihres oben bezeichneten Antrags beraten.

Die Studie wurde zustimmend bewertet.

Auch bei einer positiven Beurteilung des Vorhabens durch die Ethik-Kommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg verbleibt die ärztliche und juristische Verantwortung für die Durchführung des Projekts uneingeschränkt bei Ihnen und Ihren Mitarbeitern/innen.

Sollten sich zu diesem Projekt ethisch relevante Nachträge ergeben, bitte ich Sie, diese der Ethik-Kommission unverzüglich zusammen mit einer Bewertung der Nutzen-Risiko-Relation bekannt zu geben. Änderungen in den Dokumenten sind zum Zweck einer beschleunigten Bearbeitung deutlich zu kennzeichnen. Die Ethik-Kommission erbittet einen Kurzbericht nach Abschluss der Studie sowie im Falle einer Publikation einen Sonderdruck.

Mit freundlichen kollegialen Grüßen

(Prof. Dr. med. P. Betz)
Stellv. Vorsitzender der Ethik-Kommission

Anlage:
Teilnehmerliste

Appendix 5: ADVISE Letter of Ethics Approval_Australia

AGENDA ITEM 3.2

The Royal Children's Hospital, Melbourne

Flemington Road, Parkville
Victoria, Australia, 3052

RCH CLINICAL AUDIT AND QUALITY ASSURANCE APPROVAL FORM

Please forward:
- *completed 2 page Audit Form form, with original signatures*
- ***and a 1 page project description***

1 4 APR 2008

To the Ethics and Research Office, 1st Floor Main Building, RCH.

RCH REFERENCE NO: (Internal Use only) CA 28030
PROJECT TITLE: Audit of adverse drug reactions using the ADR detection tool
DURATION: 1 month
INVESTIGATOR(S): **A/Prof Noel Cranswick** **Dr Valerie Sung**

Principal Investigator: (print name) A/Prof Noel Cranswick

Appointment: ...Director, Department of Clinical Pharmacology

Mailing Address:... Department of Clinical Pharmacology, Royal Children's Hospital

Contact Phone Number:.....9345 6987

I undertake that I have the necessary resources to conduct this clinical audit/quality assurance activity and I have discussed the likely impact of the project with all Departments to be involved.

PRINCIPAL INVESTIGATOR:.....(signature)

(Date) 28-3-08.

Appendix 6: ADVISE Letter of Ethics Approval_HK

香港中文大學醫學院
Faculty Of Medicine
The Chinese University Of Hong Kong

醫院管理局
新界東醫院聯網
Hospital Authority
New Territories East Cluster

Joint The Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee
香港中文大學–新界東醫院聯網 臨床研究倫理 聯席委員會

Flat 3C, Block B, Staff Quarters, Prince of Wales Hospital, Shatin, HK
Tel : (852) 2632 3935 / 2144 5926 Fax : (852) 2646 6653 Website : http://www.crec.cuhk.edu.hk

To: Prof. Kenneth Kwing Chin LEE (Principal Investigator)
School of Pharmacy
The Chinese University of Hong Kong

15 OCT '09

Ethics Approval of Research Protocol

CREC Ref. No.:	**CRE-2009.474**
Date of Approval:	**06 October 2009***
Study Title:	**Adverse Drug Reactions in Children - International Surveillance and Evaluation Study Protocol (ADVISE)**
Investigator(s):	**Kenneth Kwing Chin LEE, Ellis K.L. HON and Benjamin S.C. LEE**

I write to inform you that ethics approval has been given for you to conduct the captioned study in accordance with the following document(s) submitted:

- Study Protocol, Version 3 (ADVISE_v3_20080804)

This ethics approval* will be valid for 12 months. Application for further renewal can be made by submitting the Ethics Renewal and Research Progress Report Form to the CREC (Download the electronic form template from the http://www.crec.cuhk.edu.hk or http://ntec.home/Research%20Ethics/main.asp). You are kindly requested to report to the Committee upon completion of the project.

The Joint CUHK-NTEC Clinical Research Ethics Committee is organized and operates according to ICH-GCP and the applicable laws and regulations.

Miss Winkie Lui
CREC Officer
Joint CUHK-NTEC
Clinical Research Ethics Committee

Encl.
WL/ci

Appendix 7: ADVISE Letter of Ethics Approval_Malaysia

PEJABAT TIMBALAN KETUA PENGARAH KESIHATAN
OFFICE OF THE DEPUTY DIRECTOR-GENERAL OF HEALTH
(PENYELIDIKAN & SOKONGAN TEKNIKAL)
(RESEARCH & TECHNICAL SUPPORT)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Aras 12, Blok E7, Parsel E, Presint 1
Level 12, Block E7, Parcel E, Precinct 1
Pusat Pentadbiran Kerajaan Persekutuan
Federal Government Administrative Centre
62590 PUTRAJAYA

Tel : 03 88832543
Faks : 03 88895184

WATANKUASA ETIKA & PENYELIDIKAN
RUBATAN
MENTERIAN KESIHATAN MALAYSIA
Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Ruj. Kami : (2) dlm.KKM/NIHSEC/08/0804/P08-173
Tarikh : 11 Jun 2008

Pn Tea Ming Hui
Pegawai Farmasi
Hospital Serdang

Puan,

NMRR-08-847-2002
Adverse drug reactions in paediatric patients

Lokasi projek : Hospital Serdang

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) mengambil maklum bahawa projek tersebut tidak mempunyai intervensi ke atas subjek kajian dan ianya melibatkan pengambilan maklumat dari rekod perubatan pesakit.

3. Segala rekod dan data pesakit adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah hospital di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Puan perlu akur dan mematuhi keputusan beliau.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

(DR CHANG KIAN MENG)
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

s.k. Urusetia NIH

Appendix 8: DRPs Data collection form

Drug-related problems (DRPs) in hospitalised children

Drug-related Problem Registration Form

[Modified from: DRP-Registration Form V5.01 (PCNE Classification 2006)]

Ward: ❑Medical ❑PICU ❑NICU ❑A&E

Patient Data:

MRN.....

StudyID:.....

Sex: ❑Male ❑Female **Allergy:**.....

Age of patient (days/months/years): .../.../....

❑**Weight (Kg):**

Date of admission: .../.../.....

Type of Admission: ❑Scheduled ❑Transferred ❑Emergency

Diagnosis: Principle diagnosis .....

Associated disease states .....

All Medications*

Generic name	Dosage/unite	Route	Dosage form	Frequency	Start date/time	End date/time	Comment

*Include OTC and complementary medicines

Continued..

Continued: Appendix 8

DESCRIPTION OF DRP

Name of medication: .....
Main active substance: .....

❑Rx ❑OTC
❑New ❑Refill

No. of drugs prescribed.....

❑According to caregiver
❑According to medication record

Problem discovered: ❑by physician ❑by nurse ❑by pharmacy ❑none Date: .../.../.....

Details of DRP (with related labs when needed):

Time spent on evaluation and intervention : .....min

Intervention initiated by:
❑Pharmacist ❑Other

Date evaluation of outcome:.../.../.....

❑Problem solved
❑Problem partially solved
❑Problem not solved
❑Unknown

TYPE OF PROBLEM (please tick only ONE problem)

P1. Adverse Reactions
- ❑ Side effect suffered (non allergic)
- ❑ Side effect suffered (allergic)
- ❑ Toxic effect suffered
  (please specify drug name & plasma drug level:
  .....)

P4. Drug Use Problem
- ❑ Drug not taken/administered at all
- ❑ Wrong drug taken/administered
- ❑ Admix incompatible or unstable drugs

P5. Interactions

Continued..

Continued: Appendix 8

- ❑ Potential interaction
- ❑ Manifest interaction

P2. Drug Choice Problem

- ❑ Inappropriate drug
- ❑ Inappropriate dosage form
- ❑ Inappropriate duplication of drug(-group)
- ❑ Contra-indication for drug
- ❑ No clear indication for drug
- ❑ No drug but clear indication

P3. Dosing Problem

- ❑ Drug dose too low or dosing interval too long
- ❑ Drug dose too high or dosing interval too short
- ❑ Duration of treatment too short
- ❑ Duration of treatment too long
- ❑ Inappropriate infusion rate
- ❑ Inappropriate concentration

P6. Others

- ❑ Wrong patient
- ❑ Illegible writing and inappropriate abbreviation
- ❑ Patient dissatisfied with therapy
- ❑ Insufficient awareness of health and disease
- ❑ Therapy failure (unknown reason)

CAUSE OF DRP (max. 3 boxes to be ticked)

C1. Drug or Dose Selection

- ❑ Inappropriate drug selection
- ❑ Inappropriate dosage selection
- ❑ More cost-effective drug available
- ❑ Pharmacokinetic problems
- ❑ Synergistic/preventive drug required
- ❑ Deterioration/improvement of disease state

C4. Patient/Psychological

- ❑ Caregiver forgets to use drug
- ❑ Caregiver has concerns with drugs
- ❑ Caregiver suspects side-effects
- ❑ Caregiver unwilling to carry financial costs
- ❑ Caregiver unwilling to bother physician
- ❑ Caregiver unwilling to change drugs

Continued..

Continued: Appendix 8

- ❑ New symptom/indication revealed
- ❑ Manifest side effect, no other cause

C2. Drug Use Process

- ❑ Inappropriate timing of dosing
- ❑ Drug underused/ under-administered
- ❑ Drug overused/ over-administered
- ❑ No therapeutic drug monitoring
- ❑ Drug abused
- ❑ Patient unable to use drug/form as directed

C3. Information

- ❑ Instructions for use/taking not known
- ❑ Caregiver unaware of reason for drug treatment
- ❑ Caregiver has difficulties reading/understanding drug label
- ❑ Caregiver unable to understand local language
- ❑ Lack of communication between health professionals
- ❑ Poor documentation of drug history
- ❑ Misinterpretation of computer drug record

- ❑ Caregiver unwilling to adapt life-style
- ❑ Burden of therapy
- ❑ Treatment not in line with health beliefs
- ❑ Patient takes food that interacts with drug

C5. Logistics

- ❑ Prescribed drugs not available
- ❑ Prescribing error (slip of the pen)
- ❑ Dispensing error

C6. Others

- ❑ Other cause
- ❑ No obvious cause

TYPE OF INTERVENTION (Max. 3 boxes to be ticked)

- ❑ **I0. No Intervention**

I3. Drug Level

Continued..

Continued: Appendix 8

I1. Prescriber Level

- ❑ Prescriber informed only
- ❑ Prescriber asked for information
- ❑ Intervention proposed, approved by prescriber
- ❑ Intervention proposed, not approved by prescriber
- ❑ Intervention proposed, outcome unknown within 72 hours

I2. Patient/Carer level

- ❑ Patient (medication) counseling
- ❑ Written information provided only
- ❑ Patient referred to prescriber
- ❑ Spoken to family member/caregiver

- ❑ Drug changed to .....
- ❑ Dosage changed to .....
- ❑ Formulation changed to .....
- ❑ Instructions for use changed to .....
- ❑ Route of administration changed to .....
- ❑ Duration of treatment changed to .....
- ❑ Drug Stopped
- ❑ New drug started
- ❑ Recommend monitoring of drug concentration
- ❑ Recommend monitoring of related laboratory data

I4. Others

- ❑ Other intervention .....
- ❑ Side effect reported to authorities

OUTCOME OF INTERVENTION (Tick one box only)

O0. Unknown

- ❑ Outcome of intervention unknown

O1. Solved

- ❑ Problem totally solved

O3. Problem NOT solved

- ❑ Lack of cooperation of caregiver
- ❑ Lack of cooperation of physician
- ❑ Intervention not effective
- ❑ No need or possibility to solve problem

Continued..

Continued: Appendix 8

O2. Partially solved

❑ Problem partially solved

INSTRUCTIONS FOR COMPLETING THE DRP (DRUG-RELATED PROBLEM) REGISTRATION FORM

1. Use only one form for each drug-related problem you detect.
2. You may indicate more than one cause for a particular drug-related problem (max 3).
3. You may indicate more than one intervention made per drug-related problem (max 3).
4. The drug(s) involved in the drug-related problem are entered under the 'Name of medication' section.
5. Rx relates to a prescribed drug, and OTC relates to products purchased without prescription.
6. Complete the section 'New' and 'Refill' only if the medicine involved is a prescribed medicine.
7. If the caregiver initiates the discussion of the drug problem, tick the 'by caregiver' box in the 'Problem discovered:' section. If the drug problem is discovered by a member of the Pharmacy staff, tick the 'by pharmacy' box in the 'Problem discovered:' section.
8. The 'Number of drugs prescribed' refers to the number of different prescription drugs taken by the patient, according to the patient's medication profile or according to the caregiver.
9. The 'Time spent on intervention' is the time spent actively involved in dealing with the drug problem. This includes the time from identification of the drug problem, time spent in discussion with the caregiver, with any other healthcare professional, obtaining information and final communication with the caregiver at the resolution of the drug-related problem.

Continued..

Appendix 9: Appendix 10: DRPs Ethics approval_KSA

Kingdom of Saudi Arabia
National Guard
Health Affairs
King Abdulaziz Medical City - Jeddah

المملكة العربية السعودية
رئاسة الحرس الوطني
الشئون الصحية
مدينة الملك عبدالعزيز الطبية - جدة

Research Committee, KAMC, WR
☎ : (02) 624-0000 x 21891 / ✉ : 6466

INTERNAL MEMORANDUM

To	:	Dr. Ahmed Attar — ml 20.6.10 Consultant Neurologist, Medicine Dept. Chairman, Medication Safety Committee
Date	:	19th June 2010G / 07th Rajab 1431H
Study title	:	**Evaluation of service to resolve drug-related problems in children on admission to hospital (multi center study)**
HRC ref. #	:	**RCJ0510-141**

Upon receipt of the amended protocol in response to our memo of 31st May 2010 which requires revision of your application, please be advised that the Hospital Research Committee, Jeddah hereby approve your submitted research study proposal entitled above.

Condition of approval:-

- This notice of acceptance is based on the approved application, protocol and supporting documentation. Any significant deviations or unanticipated developments within the research study should be brought to the attention of the Hospital Research Committee for subsequent approval.
- This approval is valid for "1 year" in which you have to apply for re-approval should you need further extension.

Kindly note that we may, for the purpose of audit, contact you from time to time to ascertain the status of your study and we do hope in due course to be informed of the progress and final outcome of the study once it is completed.

Best wishes for the successful completion of your study.

Kind regards

Dr. Salman A. Karsou
Chairman, Research Committee
Section Head, Nephrology Unit
King Abdulaziz Medical City, W.R.

c:\mydoc\hrorc\studies\RCJ0510-141\approval.doc

P.O.BOX 9515 **FAX : 624 7444** فاكس : ٦٢٤٧٤٤٤ ص.ب ٩٥١٥
JEDDAH 21423 **TEL.: 624 0000** تليفون : ٦٢٤٠٠٠٠ جدة ٢١٤٢٣
KINGDOM OF SAUDI ARABIA المملكة العربية السعودية

oracle 11n237

Appendix 10: DRPs Ethics amendment approval_UK

NHS
National Research Ethics Service

Riverside Research Ethics Committee
Room 4W12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Tel: 020 8846 7282
Fax: 020 8846 7280

Dr Antje Neubert
Centre for Paediatric Pharmacy Research
The School of Pharmacy, University of London
First Floor, BMA House,
Tavistock Square, London
WC1H 9JP

05 October 2009

Dear Dr Neubert

Study title:	**ADVerse drug reactions in children International Surveillance and Evaluation (ADVISE)**
REC reference:	**08/H0706/96**
Amendment number:	**1**
Amendment date:	**07 September 2009**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	4	04 September 2009
Notice of Substantial Amendment (non-CTIMPs)	1	07 September 2009
Covering Letter		04 September 2009

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H0706/96:	Please quote this number on all correspondence

Yours sincerely

Atul Patel
Committee Co-ordinator

E-mail: atul.patel@imperial.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Maureen Boylan*

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England