ADVERSE DRUG REACTIONS CAUSING ADMISSION IN CHILDREN

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by

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ABSTRACT

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Children are vulnerable to adverse drug reactions (ADRs) but have been under-represented in studies which have addressed their incidence and prevention. The aim of my thesis was to undertake a prospective study of ADR-related hospital admissions. The first step involved the development of the methodology by undertaking a prospective observational pilot study assessing all unplanned admissions over a 2 week period. There were 19 admissions to the main hospital wards related to an ADR, giving an estimated ADR incidence of 4%. Among the methodological considerations assessed in the study was the definition of what constitutes an admission (whether to include patients admitted to the Accident & Emergency observation ward), the feasibility of the data collection methods, and an assessment of the feasibility of managing the workload between three investigators.

ADR causality assessment in the pilot study was undertaken using the validated Naranjo tool. However, this was found to be lacking in sensitivity, with underestimation of the likelihood of an ADR. A causality assessment tool (CAT) that would overcome some of these issues, while at the same time making it as easy, or easier, to use than the Naranjo tool was formulated by an expert focus group. We undertook a comparison of the new Liverpool CAT with the Naranjo tool using seven assessors. This showed that the Liverpool CAT assigned the full range of causality categories and showed better inter-rater reliability than Naranjo.

ADRs causing paediatric hospital admission were subsequently studied over a one year period. There were 247 ADRs in 240/8345 patients admitted acutely to the hospital, giving an estimated ADR admission incidence of 2.9% (95% CI 2.5, 3.3). There were no deaths attributable to an ADR. 120/249 (48.2%) ADRs resulted from treatment for malignancies. The origin of prescription for causative drugs was assessed; prescriptions originating in the community accounted for 44/249 (17.7%) of ADRs with the remainder from hospital. Assessment of the avoidability of the ADR cases using the Liverpool CAT showed that 22.1% (95% CI 17%, 28%) of the reactions were either ‘definitely’ or ‘possibly’ avoidable. Few studies in the literature have reported specific avoidability outcomes, which is important to prioritise interventional strategies to reduce the burden of ADRs.

ADRs in children are an important public health problem. Most of those serious enough to require hospital admission are due to hospital-based prescribing, of which just over a fifth may be avoidable. Strategies to reduce the burden of ill-health from these ADRs are needed.

DECLARATION

This thesis is the result of my own work. The material contained in this thesis has not been presented, nor is currently being presented, either wholly or in part for any other degree or qualification.

The research was carried out at Alder Hey Children's Hospital, Liverpool, UK.

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ABBREVIATIONS

ADR	Adverse drug reaction
ADRIC	Adverse Drug Reactions In Children
AED	Accident and Emergency department
BARDI	Bayesian Adverse Reaction Diagnostic Instrument
BNF	British National Formulary
CAT	Causality assessment tool
CSM	Committee on the Safety of Medicines
FDA	Food and Drug Administration
GCSF	Granulocyte-colony stimulating factor
GP	General Practitioner
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
NSAID	Non-steroidal anti-inflammatory drug
OD	Overdose
PICU	Paediatric intensive care unit
RCT	Randomised controlled trial

SPC	Summary of Product Characteristics
UK	United Kingdom
US	United States
WHO	World Health Organisation
WHO-UMC	World Health Organisation Uppsala Monitoring Centre

Initials of researchers involved in the work in this thesis:

RG	Ruairi Gallagher
JM	Jennifer Mason
KB	Kim Bird
MT	Mark Turner
TN	Tony Nunn
MP	Munir Pirmohamed
RS	Rosalind Smyth

PUBLICATIONS AND PRESENTATIONS ARISING FROM THE WORK IN THIS THESIS

The work contained in Chapter 2 has been published in the Journal of Clinical Pharmacy and Therapeutics (Gallagher et al. 2010).

The work contained in Chapter 3 has been published in PLOS ONE (Gallagher et al. 2011).

The work contained in Chapter 4 has been published in PLOS ONE (Gallagher et al. 2012) and has been presented at the European Society for Developmental, Perinatal and Pediatric Pharmacology Annual Congress (Oslo 2011). The work was also presented, by invitation from the UK Medicines and Healthcare products Regulatory Agency, to the Commission on Human Medicines Pharmacovigilance Expert Advisory Group (July 2010) and the Paediatric Medicines Expert Advisory Group (February 2011).

A copy of the publications arising from the work in Chapters 2, 3 and 4 is included in **APPENDIX F**.

CHAPTER 1 INTRODUCTION

"Do not rashly use every new product of which the peripatetic siren sings. Consider what surprising reactions may occur in the laboratory from the careless mixing of unknown substances. Be as considerate of your patient and yourself as you are of the test tube." Sir William Osler (1849 – 1919)

1.1 BACKGROUND

Adverse drug reactions (ADRs) are a common problem and have been recognised for many years (Laughlin & Jackson 1986). More ADR literature concerns adults rather than children. However, children have been affected by ADRs, and serious occurrences of reactions, for several decades (McKenzie et al. 1976). In fact, episodes of ADRs in children have shaped the nature of drug regulation and adverse event monitoring internationally (Neubert 2012). Perhaps the most well-known of these episodes was the thalidomide disaster of the 1960s (Botting 2002). In the 1950s and early 1960s the drug thalidomide was used as a hypnotic/sedative agent. It was used widely in pregnancy to alleviate morning sickness. In 1961, a link was shown between maternal ingestion of thalidomide and the occurrence of limb defects, specifically phocomelia, in their offspring. The effect of this was seen in many countries across the world (Laughlin & Jackson 1986) and had a major, lasting, impact on governments and national legislation regarding drug regulation and safety. These events lead to the

United Kingdom (UK) government setting up the Committee on the Safety of Medicines (CSM) to regulate the use of medicines in Britain. In January 2010, 50 years after the description of the link between Thalidomide and phocomelia, the UK government issued an apology, and a new £20m compensation package, to 'thalidomiders' (a self-styled name for sufferers from the disaster in the UK).

The United States (US) Food and Drug Administration (FDA) has a longer history than the CSM. Its origins lie in the mid 1800's. However, the nature of US legislation regarding drug regulation, and the duties of the FDA, were shaped by a tragedy of different proportions, but not necessarily of less impact, than that of the thalidomide episode (Wax 1995). In 1937, a previously much used tablet and powder-based drug for the treatment of streptococcal throat infections, sulfanilamide, was re-formulated after a reported demand from the public for a new product in liquid form. The drug was dissolved in diethylene glycol by the manufacturing chemists to make an elixir. This new formulation was not tested for toxic effects since testing for safety was not a legal requirement at that time in the US. After shipments were sent all over the country, it was found that there were deaths occurring after exposure to the new medicine. In all, more than one hundred people, mostly children, died in the incident. The drug was re-called after intervention from the FDA. In the next year, the US government instituted new legislation which made it illegal to introduce new medicinal products without testing for toxicity (1938 Federal Food, Drug, and Cosmetic Act (Hamrell 1985)). It was probably this tragedy, leading to the new legislative powers of the FDA, that prevented thalidomide, a drug with little or no evidence of safety in

pregnant women, from gaining a licence in the US, thereby sparing the US public from the international disaster that occurred in many other countries around the world (Bren 2001).

Formulation of two of the world's oldest medicines regulatory bodies, the UK Medicines and Healthcare Products Regulatory Agency (MHRA, previously CSM, the UK government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe) and the US FDA, were largely brought about by paediatric medicine tragedies. These government bodies have formal processes to assess pharmaceutical manufacturers' evidence of the efficacy and safety of drugs. The regulators also decide, based on this information, whether to grant a licence for the drugs to be used in their respective countries. It would seem, at face value, that the disasters described above could not be repeated, especially in children, in these countries. However, there are other complicating factors that may mean serious ADRs can still occur in children.

The two ADR examples highlighted are very serious and both occurred before major legislative change allowed regulatory bodies to control the licensing of drugs based on evidence of their efficacy and safety. The safety profile of a medicine, when suitability for a licence is being assessed by a regulatory body, is derived primarily from adverse event data in clinical trials. This is supplemented by "pre-clinical" studies in animals. Human safety data is derived from early phase clinical studies and randomised controlled trials (RCTs). RCTs are usually designed to enable an analysis of efficacy of a drug and when compared to clinical use are often of relatively short duration and

include relatively small numbers of patients (Sammons & Choonara 2005). RCTs are useful for identifying common ADRs that will occur with exposure to a drug and they may also elucidate some serious ADRs. However, RCTs are less likely to be able to elucidate serious uncommon ADRs (Stricker & Psaty 2004). Ioannidis and Lau reported that the quantity and quality of safety reporting in RCTs is largely inadequate (Ioannidis & Lau 2001). Several types of ADR may not be identified during RCTs including:

Rare ADRs

Rare ADRs may not be picked up with the relatively small sample size of RCTs. However rare ADRs, for example Stevens-Johnson Syndrome, may be severe and difficult to relate to the drug.

Delayed ADRs that occur on prolonged use

Some ADRs, for example cough associated with Angiotensin Converting Enzyme inhibitors, may only appear after many months of use in the majority of patients. Whilst some of these ADRs may not be severe they may nonetheless cause discomfort or embarrassment to the patient.

Delayed ADRs that occur after drug cessation

Although this is likely to be rare in general medical patients, these reactions may be severe for certain subgroups of patients. For example, patients exposed to cytotoxic chemotherapy may present with neutropenia days after the drugs have been

administered once only. Alternatively, patients who have received prolonged chemotherapy or immunosuppressant therapy may be at an increased risk of malignancy later in life.

ADRs in special populations that are not routinely included in drug development

Traditionally, the young and the old were not included in clinical studies during drug development. In Europe, the situation has changed with respect to children since the introduction of the European Union Regulation about Medicines for Children in 2007. However, many medicines used in children were developed before children were routinely involved in clinical studies of new medicines. Much medicines use in children continues to be off-label (prescribing medication for an unapproved indication or in an unapproved age group, unapproved dose or unapproved form of administration). This means that routine surveillance for ADRs in children is important.

ADRs to excipients

Excipients are an important factor in medicine production, formulation and preservation. ADRs may occur due to excipients and not the active drug. These ADRs may be difficult to identify (Mori et al. 2012).

For these reasons, RCTs alone are not enough to establish the full safety profile of a drug. Evaluation of drug safety requires careful examination of data from heterogeneous sources (Singh & Loke 2012). Post-licensing safety data, which will be discussed later in this chapter, must be collected to further understand the adverse reactions associated with a drug and build up a true profile of its safety. Studies of adverse reactions associated with specific drugs, or groups of drugs, can also be helpful to negotiate the complex issue of benefit versus risk. With accumulating knowledge about a drug's adverse reaction profile over time, it may be that a drug previously thought to be safe and effective could be deemed too risky to the population exposed to it. Knowledge about the risks of a particular medication can be accumulated in several ways. Observational studies of ADRs are one important source of information.

Thus there is a need to gather information about adverse events associated with medicines, particularly medicines given to children. This thesis describes a range of studies that gather information about ADRs. The purpose of this work was to define opportunities to reduce the impact of ADRs on children. The studies explore the methodological challenges of gathering information about ADRs in children and provide novel data about this topic. This introductory chapter sets the scene by introducing the terminology and conceptual frameworks used to describe the data gained from observational studies.

1.2 PHARMACOVIGILANCE

Pharmacovigilance, as described by the World Health Organisation (WHO), is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems (WHO-UMC 2002). The practice of pharmacovigilance aims to enhance patient care and safety in relation to the use of medicines, especially with regard to the prevention of unintended harm, to improve public health and safety in relation to the use of medicines by the provision of reliable, balanced information resulting in more rational use of medicines; and to contribute to the assessment of the risk-benefit profile of medicines, thus encouraging safer and more effective use of medicines.

One important aspect of pharmacovigilance is data collection and analysis of adverse effects associated with a drug after a license has been granted. The reason for collecting this data is because of the likely limited safety data gained from RCTs, as described earlier in this chapter. There are now many countries with good pharmacovigilance practice. Many of these are individual regulatory bodies within countries and many are part of larger bodies such as the WHO monitoring centre.

In the UK, the MHRA is the government body that regulates the licensing of medicinal products. The Yellow Card scheme is the spontaneous reporting system in the UK which collects information about ADRs after a drug has been granted a license and has been authorised for use in the UK population (MHRA). The scheme works by collecting spontaneous reports of drug reactions. At first, the Yellow Card scheme

allowed only physicians to report possible ADRs. In 1997, the scheme was extended to include pharmacists. After this, other health care practitioners, including nurses, were invited to report possible ADRs. Patients/carers were finally invited to report their adverse experiences of medication in 2008. Reports can be submitted in one of three ways: by completing a 'yellow card' in writing, which can be found at the back of the British National Formulary (BNF), a medical pharmaceutical reference book commonly used in hospitals, general practice surgeries and pharmacies; by completing an electronic yellow card on the MHRA website; or by phoning the yellow card hotline number (available on the MHRA website).

The information from Yellow Card reports is entered onto a specific database. The data is analysed on a weekly basis by the MHRA and the reports can be used in the following ways:

- Requesting additional information from the reporter to understand better the suspected reaction.

- Noting the patient perspective of a suspected adverse effect, to understand better the impact of these effects on the people who use medicines.

- Requesting further information from other sources, including from the manufacturer/s of the medicine.

- Highlighting the report as a possible safety issue on the MHRA database and keeping a close watch on the safety of the medicine by monitoring similar reports.

- Conducting a specific analysis of similar Yellow Card reports to identify potential safety signals.

- Discussing the suspected adverse effect with other medicines regulatory agencies, within and outside the European Union.

Any or all of these actions can result in a number of different outcomes with regard to a medication. The regulators may make no changes or may add additional information to the product literature, alter the license (dose, indication or some other aspect) or, rarely, withdraw the product from the market.

1.3 DEFINITIONS OF ADVERSE DRUG REACTIONS

There are many definitions of what constitutes an ADR. The WHO, more than thirty years ago, defined an ADR as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function." The WHO definition would seem to comprehensively describe ADRs but it has come under scrutiny from pharmacologists. Although comprehensive, the definition, by using the word noxious, encompasses all adverse reactions no matter how minor. This definition, if used by

those reporting ADRs to regulatory bodies, may lead to the submission of large numbers of common minor ADRs. Pharmacologists would argue that this is not very helpful in signal detection of new, or more clinically relevant, ADRs.

Edwards and Aronson (Edwards & Aronson 2000) suggest a definition of an ADR as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." Edwards and Aronson argue that their definition is more specific to ADRs that cause harm and do not include adverse events/overdose (OD). This definition is more acceptable to pharmacologists who are interested in studying clinically relevant ADRs. The definition by Edwards and Aronson has been used in several studies since its publication and will be used in the studies in this thesis.

1.4 TYPES OF ADVERSE DRUG REACTION

In describing ADRs in differing contexts (studies, case reports, post-marketing surveillance reports), it can be useful to classify the type of ADR/s being described. Definitions of these types of ADRs have evolved with time. In the first instance, ADRs were classified as one of two types (Rawlins 1977).

A. *Type A* reactions (Augmented) are dose-related, and, therefore, predictable from the known pharmacology. They are more common than type B.

B. *Type B* reactions (Bizarre) are not dose related, unpredictable from the known pharmacology and are rarer than type A. Type B reactions may also be more likely to be severe.

To some extent, these classifications can be helpful when determining why an ADR occurred and whether or not it may have been avoidable. Avoidability (preventability) will be discussed later in this chapter. This early classification of the type of ADR was expanded subsequently to include four more categories. These are as follows:

Type C reactions (Chronic) occur after some time of prolonged administration and are usually dose and time-related. They usually refer to ADRs which are due to cumulative dose. The drugs that cause these types of ADRs may also need gradual decrease in dose for withdrawal.

Type D reactions (Delayed) occur some time after use of the drug. They are usually uncommon and may be dose-related.

Type E reactions (End of treatment) occur sometime after withdrawal of the drug. They are uncommon and usually occur shortly after drug cessation/withdrawal.

Type F reactions (Failure) occur as a result of unexpected failure of therapy. Unfortunately, this is common. However, it may not lead to ADRs as described by Edwards and Aronson as no appreciable event will have taken place.

The definitions of types C-F may provide more in depth description of the ADRs that have occurred. However, it is likely that all ADRs can still be described by types A/B.

The ADRs described in the studies in this thesis will be classified as either Type A or B. This will allow for comparison with other studies that have used these classifications.

1.5 CAUSALITY ASSESSMENT OF ADRS

It is not always possible to absolutely relate a reaction to a drug. In fact, this may be rarely possible and is due, in part, to the nature of illness in patients and the interaction of drugs with illness. Patients rarely take medication unless they are unwell or have chronic problems. This is especially true in children. A lot of the difficulty in assessing the causal relationship (causality) between drug and adverse effect is that disease/illness may have an unexpected course and the symptoms of illness may overlap with symptoms of ADRs. For example, children can often develop a rash during viral infections and a similar rash may be precipitated by many drugs. In reality, the viral illness may even make a patient more susceptible to developing a rash. This makes it extremely difficult to decide whether the rash is due to drug or disease. This is a common situation in clinical practice with many different symptoms imitated by drug reactions caused by many different drugs. Even something seemingly as minor as a drug eruption can provoke anxiety in the parents of a baby or young child and may make management decisions for clinicians more difficult than had the rash not been present.

Causality assessment is not a new idea in medicine. In 1965, Sir Austin Bradford Hill wrote an article describing a set of criteria that investigators should consider when assessing whether a causal link can be established between an environmental factor and the onset of a particular disease process (Hill 1965). His paper is regarded as seminal and attempted to describe the process of making the leap from a clear association between two variables to stating likely causation of one based upon exposure to the other. This thinking, underpinned by appropriately robust research methodology and studies, has aided researchers' advancement of knowledge of risk factors for disease e.g. smoking and lung cancer. The features to be assessed between the two variables in question, according to Hill, were as follows:

1) *Strength.* The effect of one variable on another must be assessed to gain an understanding of the magnitude of the association. The stronger the association, as long as other factors are assessed cautiously, the more likely the relationship will be causative.

2) *Consistency.* Has the association been observed repeatedly by different persons, in different places, circumstances and times?

3) *Specificity.* Hill states that one must be cautious in interpreting specificity. "If other causes of death are raised 10, 20 or even 50% in smokers whereas cancer of the lung is raised 900-1,000% we have specificity - a specificity in the magnitude of the association." In this example, if the magnitude of association is not specific to lung cancer one must be cautious in interpreting the results – it

may be that there is another underlying factor which could explain any or all of these increases in death rates.

4) *Temporality.* The temporal relationship of an association is important when assessing for possible causation. It might be particularly relevant to assess this carefully with diseases of slow development.

5) *Biological gradient.* If the association is one which has a biological gradient, or positive dose-response, this evidence should be assessed.

6) *Plausibility.* It is helpful to persuade others of causation if there is a biologically plausible mechanism. However, Hill states that plausibility is a feature which cannot be demanded, saying "What is biologically plausible depends upon the biological knowledge of the day.....the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd."

7) *Coherence.* The cause-and-effect interpretation of data should not seriously conflict with the generally known facts of the natural history of a disease.

8) *Experiment.* It can be important, if possible, to use experimentation. This can also be important if an intervention is undertaken. Did the intervention have any effect on the frequency of the associated events?

9) *Analogy.* In some circumstances it can be fair and appropriate to judge by analogy. Similar evidence from a similar situation can add weight to the possible causation regarding a similar new exposure-adverse event pairing.

Although Hill's criteria relate to environmental exposure and occurrence of disease, there is no doubt that applying similar logic to possible ADR cases will aid in causality assessment. When assessing a possible ADR it can be useful to describe the certainty with which the assessor relates the drug to the reaction. There are several ways of trying to achieve this including; assessor opinion/structured guidance, structured algorithms, and Bayesian statistical methods. One of the aims of using structured guidance or an algorithm to assess possible ADRs is to reduce the between rater variability of assessments. Each of these methods will be discussed in turn.

1.5.1 Assessor Opinion

The use of assessor opinion relies on expert assessor judgement of how likely a drug caused a reaction, using knowledge of the drug and their clinical experience, without using a structured causality assessment tool (CAT) or any guidance. In studies of ADRs these are usually clinicians, pharmacologists and possibly pharmacists. These assessments can be made by one clinician, or by a group of more than one who then seek to provide a consensus causality assessment about each case.

In one study, five experts assessed 30 cases of reported ADRs (15 sampled from cases spontaneously reported to the Regional Pharmacovigilance Centre of Bordeaux and 15

sampled from ADR cases collected during a nationwide incidence study conducted the same year (Pouyanne et al. 2000)) using a visual analogue scale showing poor agreement between raters (kappa 0.2) (Arimone et al. 2005). The agreement between raters was lower for intermediate levels of causality (unlikely, doubtful, unassessable/unclassifiable, and plausible) than for cases assessed at the extremes of the analogue scale (excluded, likely, and certain). This is unsurprising as it is probably easier to assess cases which are 'clear cut.' This result may also demonstrate that it is easier to agree about cases where there is more evidence of causality, or more evidence against any causality. This study showed that experts, even those involved in assessing ADRs for regulatory authorities, can struggle to reach agreement about causality in the absence of a structured assessment tool.

1.5.2 Structured Guidance

Methods of assessing causality that provide structured guidance usually make use of several headings or categories which describe the likelihood of relationship between drug and reaction (e.g. 'possible', 'probable', 'definite'). Each category is linked to a description of the criteria of the components needed to assign that level of causality. The information regarding the reaction in the case being assessed is then cross-referenced, by the assessor, with the descriptions in the guidance so that the causality category which fits best can be chosen. Each category increase in causality is accompanied by a description which requires more evidence of the likelihood of drug-ADR relationship. These structured guidelines can be viewed as being in the same

category as expert opinion, as they are generally devised by experts based on their clinical experience. However, they aim to give non-experts, and experts alike, a framework for assessing ADRs in a more systematic fashion.

The WHO, with the Uppsala Monitoring Centre (WHO-UMC) in Sweden, reviewed the limitations of causality assessment and produced their own structured guidance on assessing causality (WHO-UMC 2011). Causality is grouped into six categories with corresponding criteria to be filled to reach that level of causality. These categories are; Certain, Probable/Likely, Possible, Unlikely, Conditional/Unclassified, and Unassessable/ Unclassifiable. The last two categories allow for classification of ADR reports in which the evidence may still be under scrutiny or not available. The use of this method, using assessor opinion, is often called 'global introspection'. This structured assessment guidance has been used in many studies of ADRs.

1.5.3 Structured Algorithms

There has been criticism of the use of expert judgement in assessing ADR causality. This has led to many authors proposing structured assessment tools in the form of algorithms to aid assessment of ADR causality. An algorithm is a method for solving a problem using a finite sequence of instructions. Structured assessment systems of this type can be used to aid assessors in estimating the likely relationship between drug and reaction. They involve answering individual questions about the reaction in a stepwise order which leads to a final causality assessment being assigned.

CATs can take the form of a group of structured questions or a flowchart (algorithm). CATs which use structured questions usually have an individual score for each question/answer. The sum of the scores for each question/answer pair provides a total score. The causality categories are each represented by a range of total score and the assessor matches their score with the appropriate category.

Flowcharts, or algorithms, use a series of decision boxes which contain questions. Each decision box is linked to one or more boxes by arrows, which represent answers, which lead the user to the next appropriate box, depending on the answer selected at the previous decision box. The user starts with a question in the first decision box. He/she chooses one of the available answers that they think is the most appropriate or correct. The answer, which is represented by an arrow from the decision box, leads the user to a new decision box with a new question. This process is repeated until the flowchart eventually leads to a solution, from which there are no more arrows, answers or questions. This provides the user with the final assigned causality category.

Some of these methods, both structured questions and flowcharts, are more than 30 years old and all were published following Hill's causality paper. Irey, in 1976, was the first to publish an ADR causality algorithm (Irey 1976). This algorithm relies heavily on time-relationships, and pathological evidence, of drug and event. Karch and Lasagna, in 1977, published an algorithm using three decision-tables which lead the user to assess potential drug reactions, assess the certainty of the link between the drug and event, and evaluate the underlying causes of the identified untoward events (Karch & Lasagna 1977). The tool requires previous bibliographical evidence of the ADR and,

therefore, is not appropriate for assessing/identifying new ADRs. Kramer expanded upon the work of Karch and Lasagna by publishing a new six decision-table algorithm with a new scoring system of minus and positive scores for answers given to questions within the tables (Kramer 1979). This algorithm was tested among four practicing clinicians and four interns. It had an impressive effect on inter-observer agreements between the senior clinicians (33% without algorithm to 77% with, weighted kappa 0.27–0.67) but did not significantly affect agreement levels between interns. It is likely that a degree of experience is needed to use the tool effectively.

Another algorithmic tool, published in 1981by Naranjo et al (Naranjo, Busto & Sellers 1981), consists of ten questions regarding the details of the reaction. Each question has a corresponding answer of 'yes', 'no' or 'don't know' with each answer having a weighting ranging from -1 to +2. The values assigned to each question answered are totalled, and the final score corresponds to causality categories of 'definite', 'probable', 'possible' or 'doubtful'. The Naranjo ADR Probability Scale is easily the most widely used algorithm in the ADR literature (this literature does not include algorithms or causality methods used for ADR case reports submitted to national regulatory authorities in post-marketing surveillance). In developing this scale, two physicians and four pharmacists independently assessed 63 randomly selected alleged ADRs with agreement ranging from 38% to 63% (kappa varied from 0.21 to 0.40). Six weeks later the same observers independently reanalyzed the 63 cases using the ADR probability scale. The between-raters reliability (range: percent agreement = 83% to

92%; kappa = 0.69 to 0.86) improved on use of the scale. The between-raters reliability was maintained on retesting at 22 weeks.

Although the results are impressive, the cases used in the internal validation of the Naranjo algorithm were published case reports of ADRs. Published ADR case reports usually contain more information than other types of ADR reports and usually only get published if there is enough evidence of more than an association. It is not surprising to see that there may be a high degree of agreement between raters when using a structured tool in assessing cases with strong evidence of causality. This tool may not be as useful for assessing ADR cases in clinical practice or in other situations such as reports from clinical trials, observational studies and post-marketing surveillance.

1.5.4 Bayesian Statistical Method

Bayesian statistics can be used to calculate the odds of an adverse reaction having occurred (posterior odds) by using detailed knowledge of the details of the case and prior knowledge of the chance of the event occurring (epidemiological and clinical trial information) (Agbabiaka, Savovic & Ernst 2008). There is no limit to the amount of factors that can be incorporated into the method and it can be used to quantify the odds of more than one factor having caused the event. It is regarded as possibly the most accurate and logical method for estimating causality of an ADR as there is no limit to the information that can be used to make an assessment of causality, unlike the algorithmic methods which ask for the answer to defined questions. Also, the method

is demonstrably reproducible i.e. an investigator can show exactly how they came to their conclusions.

The Bayesian Adverse Reaction Diagnostic Instrument (BARDI) is the probabilistic instrument most often evaluated in ADR causality literature (Lane et al. 1987). The output of a Bayesian probability method ranges from 0% (not a drug-induced event) to 100% (definitely a drug-induced event). This method may be the most appropriate for assessing causality in individual cases when certainty of causality may be very important, such as the first report of a severe reaction. However, Bayesian methods are limited by complexity, the need for expertise, time to complete and the statistical information needed, which may not be available (Lanctot & Naranjo 1995).

1.5.5 Comparison of causality assessment methods

A recent systematic review of causality assessment tools, published in 2008, identified 34 different published causality assessment methods (Agbabiaka, Savovic & Ernst 2008). These tools consisted of four expert opinion/global introspection, 26 algorithms and four Bayesian methods. The use of assessor opinion for the assessment of causality of ADR reports, whilst common, has been shown to produce poor reliability among clinicians. It seems logical that a structured scoring system may lead to better reliability between raters. Many structured scoring/algorithmic systems have been formulated. In some, the authors have found good reliability between internal assessors after formulation of the assessment tool. Authors have attempted to compare the inter-

rater reliability between different causality tools in an attempt to find the 'best' assessment system. A summary of these assessments is tabulated below (**Table 1.1**).

Table 1.1 Summary of published causality method comparisons

Authors	*Comparison*	*Number of raters/reports*	*Results*
Frick, 1997	Kramer vs Karch & Lasagna	Single rater assessed 200 published ADR reports	41% agreement between methods. Kramer more likely to assign category of possible, Karch more likely to assign category of unlikely.
Busto, 1982	Naranjo against Kramer	2 raters assessed 63 possible ADR case reports	Highly correlated score between raters for each method and between methods. Naranjo took less time to complete.
Michel, 1986	Kramer, Naranjo and Jones methods compared against each other	Raters assessed 28 hospital pharmacovigilance system ADR case reports	Kramer vs Naranjo; 67% agreement, kappa 0.43 (moderate). Kramer vs Jones; 67% agreement, kappa 0.48 (moderate). Naranjo vs Jones; 64% agreement, kappa 0.28 (fair). Naranjo compared more favourably with Kramer than Jones.
Lanctot and Naranjo, 1995	Naranjo method vs BARDI (Bayesian method)	2 raters assessed 106 cases (91 clinic reports and 15 pharmaceutical company reports)	Kappa 0.48 (moderate) between the two methods. BARDI more likely to result in category of highly probable or highly improbable, Naranjo more likely to result in possible or probable causality.
Macedo, 2005	15 different algorithms rated against WHO global introspection	5 clinicians/ pharmacists rated 200 possible ADR reports from post-marketing surveillance	Agreement of between 21% and 56%, with an average of 47%. Kappa of 0.26 (fair) for average agreement between all algorithms and global introspection.
Rehan, 2007	Global introspection against Naranjo	2 raters assessed 100 possible ADR cases from spontaneous reports	69% agreement, kappa 0.21 (fair). Naranjo more likely to produce lower probability category. Naranjo took longer to complete.

Frick et al used a single rater to assess 200 published adverse drug events (132 case reports and 68 letters to editors) using the Kramer algorithm compared to the Karch and Lasagna algorithm (Frick, Cohen & Rovers 1997). The algorithms agreed in 41% of the cases. The methods did not differ in the proportion of events rated definite ($p=0.52$) or probable ($p=0.3$). There was an obvious discrepancy between the assessment methods for those cases which had less evidence of causality within the report, with Kramer more likely to lead to a classification of 'possible' and Karch to 'unlikely' ($p<0.01$).

Plenty of interest was shown in the use of less complex algorithms for assessing causality after publication of the Naranjo scale. There have been several published comparisons of Naranjo to other methods with a few of these undertaken by Naranjo himself. A high between-rater reliability was shown when using the Naranjo method compared to the more complex Kramer method (Busto, Naranjo & Sellers 1982). The authors showed that the Naranjo method took less time to complete assessments than the Kramer algorithm. They concluded that the Naranjo method was preferable, for future use in their hospital-based pharmacovigilance practice, due to its applicability and similar results obtained in comparison with the more detailed Kramer algorithm.

Lanctot and Naranjo compared a Bayesian method for assessing causality, BARDI, with the Naranjo ADR probability scale (Lanctot & Naranjo 1995). The investigators had previously used BARDI to assess the same cases between one and five years previously (the method is complex and time-consuming). The investigators then individually assessed the same cases with the Naranjo scale. The correlation between

the two raters was high for the Naranjo scale. Therefore, the mean Naranjo score for each case was compared to the probability generated by the BARDI method. The reliability between the two methods was moderate, with weighted kappa 0.48, when considering a diagnostic cut-off for cases assigned above 50% (posterior probability 0.5) probability for the BARDI method and above a score of 5 ('probable' causality) for the Naranjo scale. Despite this agreement a difference between the tools still remained. Use of BARDI was more likely to result in a causality assessment of highly probable (probability 0.76-1) or highly improbable (probability 0-0.25), whilst use of Naranjo was more likely to result in possible or probable causality. This is due to the Naranjo scale being more uncertain for idiosyncratic reactions (of which there were many in the case series analysed) than for dose-related reactions. Also, the answer weightings and causality category score ranges are arbitrary for Naranjo, whereas the BARDI method can use prior odds and other extra information to input extra variable data into the statistical equation. Therefore, for idiosyncratic reactions with prior epidemiological evidence, BARDI is more likely to be able to assign a higher causality rating.

Similar conclusions were drawn by Michel at al (Michel & Knodel 1986) when comparing the methods Kramer, Naranjo and an ADR causality assessment flowchart by Jones. The initial standard for assessing causality of ADR reports was made by using the Kramer algorithm as this seemed to be more comprehensive. The methods of Naranjo and Jones were then compared to Kramer. The results of all three methods were translated into categories of suspicion (A = definite or probable; B = probable; C

= possible; and D = unlikely, doubtful, or remote), due to the differences in outputs between the three methods. Comparisons were then made using % agreement and kappa analysis (**Table 1.1**). The simpler and less time-consuming Naranjo algorithm compared favourably with the Kramer method, both in causality categorisation and total numerical score.

In comparing 200 possible ADR reports from post-marketing surveillance, Macedo et al assessed used 15 different algorithmic assessment methods against the opinion of a panel of experts (two hospital clinicians, two pharmacists and one general practitioner (GP)) using the WHO global introspection assessment method (Macedo et al. 2005). The average level of agreement between all the algorithms and global introspection was fair, with kappa of 0.26.

Rehan et al compared the two most frequently used assessment methods, namely global introspection and the Naranjo scale, in 100 spontaneously reported adverse drug events (Rehan, Chopra & Kakkar 2007). Agreement on causality was found in 69% of cases, showing fair reliability with a kappa of 0.21. The Naranjo scale was more likely to produce a lower probability category than global introspection. Global introspection took significantly less time to complete than Naranjo. Both of these results may be due in part to more information needed from the case report to complete all questions within the Naranjo scale.

The above summary of published comparisons of causality assessment methods is not systematic but is comprehensive and characterises what many investigators think about

these methods. Namely, 1) there is evidence that assessor opinion and global introspection provide poor inter-rater reliability; 2) algorithms are of varying complexity, and are limited by the information that is required to complete assessments, but they can improve inter-rater reliability between assessors; 3) Bayesian methods are likely to produce the most realistic assessment of causality, with the most comprehensive and adaptable assessment process, but are complex, extremely time-consuming, and require expertise to complete. The most studied and widely used method is the Naranjo ADR probability scale, as it is quick to complete and has moderate reliability when compared to more comprehensive and detailed methods. The Naranjo method was chosen to assess ADR cases when commencing planning for the studies in this thesis.

1.6 SEVERITY ASSESSMENT

Assessment of severity of ADRs is important. For regulatory authorities, assessment of severity can aid decisions of how best to investigate spontaneous reports of ADRs. New reports of a severe ADR may need urgent action to elucidate the potential problem and may require intervention as described earlier in this chapter. In studies of ADRs, severity assessment can aid in the analysis of ADR importance and highlight the burden to patients, burden to the setting (e.g. hospital/primary care) and areas for potential intervention.

Severity assessment can be undertaken in one of two ways; assessor opinion or use of structured guidance in the form of descriptions. Generally, in publications, authors describe how they assessed severity for their own study without use of structured guidance (assessor opinion), use structured guidance which has been previously published or propose a new schema. Dormann et al suggested a severity scale consisting of questions and weighted answers, much like the Naranjo probability scale for causality, which they used in a study comparing a computer-based ADR monitoring system with spontaneous reporting in a hospital setting (Dormann et al. 2000). A disadvantage of this system is the user must answer each question in turn and is limited to using the information asked for in the individual questions. Also, some of the questions ask for opinion regarding future outcomes such as, "Did the adverse drug reaction lead to permanent inability to work?", which may require follow-up of the patient.

The WHO defines reactions by seriousness, in the following categories:

- requires inpatient hospitalisation
- prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is life-threatening or results in death.

The WHO state clearly that they use the term serious, or not serious, to describe ADRs as this relates to patient/event outcomes, whereas the definition of 'severe' implies a description of the intensity of an event e.g. a 'severe' headache may affect a patient but

unless it causes admission to hospital, or some other measure of poor outcome, it is not a ‘serious’ headache.

The UK MHRA defines ‘serious’ reactions as those that are:

- Fatal or life-threatening
- disabling or incapacitating
- the cause of admission to hospital
- cause of prolonged hospital stay
- cause congenital abnormalities
- are medically significant.

They state “by contrast with serious reactions, a severe reaction refers to the degree of harm, disability or effect on quality of life.” They use a similar example of severe headache as the WHO above to highlight this difference. However, the UK regulatory authority does state that they “are interested to receive reports of any suspected adverse reaction, irrespective of severity, for all black triangle drugs and vaccines.” Medicines that are being monitored particularly closely by regulatory authorities in the European Union (EU) are described as being under 'additional monitoring' and have an inverted Black Triangle displayed in their patient information leaflet and summary of product characteristics (SPC).

However, regarding children specifically, the MHRA also comment that all suspected ADRs should be reported “even if they occurred with an established drug and regardless of whether or not the medicine is licensed for use in children. This is because the nature and course of illness and ADRs may differ between adults and

children. In general, children are not exposed to medicines in clinical trials, therefore very little is known about the safe use of medicines in this group. Furthermore, many drugs which are routinely used to treat children are not actually licensed for their use, so it is particularly important to focus on their safety in children." (MHRA 2009, 2012)

Hartwig et al described the severity assessment they used in assessing ADRs reported by pharmacists in a hospital-based pharmacovigilance program (Hartwig, Siegel & Schneider 1992). This schema for severity assessment is a seven step increasing scale from level one, 'an ADR occurred but required no change in treatment with the suspected drug,' to level seven, 'the adverse reaction either directly or indirectly led to the death of the patient'; level 4 includes 'the ADR was the reason for admission.' One advantage of this scale is that it describes potential outcomes in more detail, for hospital settings, than the WHO/MHRA criteria. The Hartwig severity scale has been used, sometimes having been altered for a particular setting, in many hospital-based ADR studies.

1.7 AVOIDABILITY ASSESSMENT

Retrospective review of adverse events is undertaken in many settings, not just healthcare organisations. A review of an adverse event aims to determine the impact on the subjects/organisation involved, define the steps that led to the occurrence of the event and, usually, to look at avoidability/preventability to ensure that interventions, if necessary, can be put in place to reduce the risk of re-occurrence. A comprehensive

review is usually prompted by a spontaneous report of a potentially serious event (sometimes called a near miss) or as a result of actual harm. Davies et al showed that, in the case of ADRs occurring in hospital, similar risk assessments can be applied to ADRs as to other non-ADR events, such as prescription and administration errors (Davies et al. 2010).

There are several methods for assessing avoidability. As with other types of assessments of ADRs, many clinicians and researchers use assessor opinion to decide whether or not the event in question could have been avoided. This has the advantage that assessments can be completed in a timely manner but the disadvantage that it relies on the experience and knowledge of the investigator.

Hallas et al suggested a quick schema to aid in assessor rating of avoidability of ADRs (Hallas et al. 1990). The schema consists of three categories, with a description of each to aid the assessor in determining which category is appropriate to assign, as follows:

- *Unavoidable.*

  The ADR could not have been avoided by any reasonable means.

- *Possibly avoidable.*

  The ADR could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice.

- *Definitely avoidable.*

  The ADR was due to a drug treatment procedure inconsistent with present day knowledge of good medical practice.

The definitions for each of the three categories is quite broad and the assessor will rely on their experience and knowledge to determine which is best suited to describe the avoidability of the reaction in question. This method still encompasses assessor opinion, with the advantage that it is quick to use, but provides some simple structure for the assessor. Another disadvantage is the description used in the 'possibly avoidable' category; according to the definition, "an effort exceeding the obligatory demands of present day knowledge of good medical practice" is necessary to deem a reaction to be possibly avoidable. The difficulty with this definition is that the assessor must have obtained the knowledge of what constitutes good medical practice, which may vary in differing health care settings, populations or medical specialties. Also, the use of 'obligatory' is difficult to decipher; does this mean that all clinicians should be aware of the good medical practice necessary to avoid the ADR? If the answer to this question is yes, it is difficult to see that any ADRs could be labelled as 'possibly avoidable.' However, the assessor opinion involved in this method may allow this category to be used, as individuals will have their own opinions of what obligatory good medical practice entails.

Schumock and Thornton attempted to devise an avoidability assessment tool that was more clinically focussed (Schumock & Thornton 1992). Their tool consists of seven

questions to which the answers are either yes or no. If any of the questions are answered with ‘yes’, the reaction is deemed to be avoidable. The questions are:

1. Was the drug involved in the adverse drug reaction not considered appropriate for the patient’s clinical condition?

2. Was the dose, route, and frequency of administration not appropriate for the patient’s age, weight and disease state?

3. Was required therapeutic drug monitoring or other necessary laboratory testing 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 documented?

7. Was poor compliance involved in the reaction?

The tool, whilst attempting to structure assessment of causality more formally, was not entirely satisfactory and was modified by other investigators to include previous ADRs to classes of drugs, and not just individual drugs. Dormann et al modified the tool further to say that if there were no other form of treatment (e.g. cytotoxic therapy for cancer), or a positive benefit-risk ratio could be assigned for the causative ADR drug, then the ADR was judged to be ‘tolerable.’ This category, in essence, is not avoidable.

However, care should be taken in assessing ADRs to be in this category as they may be amenable to prevention by using prophylactic treatment.

Ferner and Aronson (Ferner & Aronson 2010b) conducted a systematic review aiming to identify and analyse the approaches used to define 'preventability' in relation to ADRs. The authors identified eight general methods for attributing avoidability of drug-related harm; analysis without explicit criteria, assessment by consensus, preventability linked to error, preventability linked to standards of care, preventability linked to medication-related factors, preventability linked to information technology, categorization of harmful treatments in explicit lists, and a combination of more than one approach. The method by Hallas is included in the methods of preventability linked to standards of care and the method of Schumock and Thornton belongs to methods of preventability linked to medication-related factors. The authors of the review importantly state that there is no compelling evidence for the use of any one tool used to assess avoidability over another.

Ferner and Aronson state that the methods identified in the review generally rely on two principles; the judgement of one or more investigators or the use of pre-defined explicit criteria. They conclude that neither method is satisfactory and suggest a novel approach based on analysis of the mechanisms of adverse reactions and their clinical features could be preferable. They propose such a method, based on previous publications of new classifications of types of ADRs (Aronson & Ferner 2010). These classifications are the EIDOS and DOTS methods. EIDOS is based on the mechanism of action of the drug and includes assessment of the **E**xtrinsic species (drug), the

Intrinsic species (subject or organ), the **D**istribution of the drug and target together, the resulting **O**utcome (adverse effect), and the **S**equelae (adverse reaction) (Ferner & Aronson 2010a). The DOTS ADR classification considers classifying ADRs by **Do**se-relationship between drug and event, **T**ime relationship between drug and reaction, and **S**usceptibility of individuals (Aronson & Ferner 2003).

This new classification system is comprehensive in comparison to the methods in the systematic review. However, it is also more complex than other methods and, although its use has not yet been investigated by other authors, it is likely to be more time consuming. The main strength of the new method is that it not only assigns whether an ADR was preventable but also gives an indication as to how the ADR could have been prevented. This could allow health care workers to assess cases and potentially implement interventions to prevent recurrence. Due to the structure of the method, and its apparent complexity, it is probably best used for assessing individual clinically important cases, or small series' of cases, of possible ADRs. In this thesis, avoidability will be assessed using the definitions derived by Hallas. This will allow timely assessment of possible ADR cases, which may be an important factor in assessing large numbers of cases from an observational study, and comparison with other observational and retrospective studies which have used this method.

1.8 OBSERVATIONAL STUDIES OF ADRS CAUSING ADMISSION IN CHILDREN

There have been previous observational studies of ADRs causing admission in children. These studies have been incorporated into four systematic reviews.

1.8.1 Impicciatore et al

The first systematic review included non-selected studies, from 1966 to May 2000, investigating ADRs in hospitalized children, in outpatient children, and ADRs causing paediatric hospital admissions (Impicciatore et al. 2001). The review aimed to explore the usefulness of data derived from observational studies in defining and preventing the risk of pharmacological interventions in children. Five studies investigating ADRs as a cause of admission of children to hospital were included. A summary of these studies is provided (**Table 1.2**). Some of the works regarding more accurate formal methods of ADR assessment were borne by some of these important early observational studies of ADRs.

Table 1.2 Summary of studies of paediatric ADR admissions included in the Impicciatore review

Author (year) Setting	No. ADR admission	Methodology	Causative drugs (most frequent)	Assessments undertaken	Assessments not undertaken
McKenzie (1976) Paediatric teaching hospital, US	72/3556 (2%)	All admitted patients using chart review and clinical rounds for three years. Review by pharmacologist.	Cytotoxics (38%), corticosteroids (15%), anti-convulsants (13&), antibiotics (13%)	96% definite causality (self-defined). 40% ADRs severe. Four deaths. Increase risk in age>6 years.	No formal method for causality (pre-dates). No avoidability assessment.
Yosselson-Superstine (1982) AED University hospital, Israel	29/906 (3.2%)	Pharmacist participating in physician rounds, interviewing patients and/or their guardians and reviewing medical charts over seven months	Cytotoxic drugs, corticosteroids, anticonvulsants, antibiotics	41% ADRs severe. One death. Causality undertaken (McKenzie/Whyte). ADRs more common in girls.	No avoidability assessment. No risk factor assessment.
Mitchell (1988) Four teaching hospitals/three community hospitals, US	288/7271 (4%)	Derived from The Pediatric Drug Surveillance Program (over 11 years). Trained nurses on selected wards collected data about a sample of patients admitted for more than 24 hours. Ward nurses and house staff (clinicians) were consulted.	Cytotoxic drugs, phenobarbital, aspirin, phenytoin, ampicillin or amoxicillin, theophylline, co-trimoxazole, diphtheria-pertussis-tetanus vaccine.	51% definite causality (self-defined) ADRs increased in age from infancy to 5 years. Two deaths.	No formal causality method. No avoidability assessment.
Martinez-Mir (1996) Children's hospital, Spain	21/517 (4.3%)	Paediatrician collected data on 512 consecutive admissions under the age of 25 months during two periods (105 days in summer, 99 days in winter)	Respiratory drugs (35%), anti-infective agents (25%), drugs active on the central nervous system (15%), drugs used in dermatology (10%).	38% severe ADRs. Causality (Meyboom 1992). No deaths. ADRs more common in girls (no statistical difference, small sample)	No avoidability.
Easton (1998) Children's hospital, Australia	10/1682 (0.6%)	Ward pharmacists assessed all admissions over a 56 day period	Anti-epileptic drugs	Nine cases possible causality (Naranjo).	No avoidability reported. No risk factor assessment.

The first study assessing ADRs as a cause of admission, included in the review, was a prospective observational study by McKenzie et al, published in 1976 (McKenzie et al. 1976). 72/3556 admissions (2%), in 64 patients, were judged to have resulted from ADRs. Cytotoxic drugs were the most frequent drug class causing admission (38%) during the study. In four admissions the ADR was thought to have contributed to death (bone marrow aplasia and pneumonia following cytotoxic chemotherapy; bone marrow depression and pseudomonas bacteraemia following cytotoxic chemotherapy; digitalis toxicity and cardiac arrhythmia; thrombocytopenia and bleeding from epistaxis following cytotoxic chemotherapy). The authors assigned only three of the ADRs as having less than probable causality. This may be due to over-attribution of causality by the authors because of lack of use of a causality assessment method or because the data collection methodology was not sensitive to picking up less well-defined ADRs. There was no reported assessment of whether or not the reactions were avoidable.

Cytotoxic drugs were also the leading cause of ADR admissions to a university hospital in Israel (Yosselson-Superstine & Weiss 1982). One admission, occurring as a result of cytotoxic therapy, was fatal. In this study, 29/906 (3.2%) admissions were attributed to ADRs. Avoidability of the reactions was not assessed.

In a large US study, trained nurses assessed admissions caused by ADRs over an 11 year period (Mitchell et al. 1988). Trained nurses were stationed on selected wards where they collected information, including a drug history of the three months prior to admission, about a sample of patients admitted for more than 24 hours. Only one admission per patient was studied over the period. The study nurses also elicited the

judgement of ward nurses and house staff (clinicians). The study assessed ADRs causing admission in three separate groups: neonates, children with cancer and 'other children'. In babies admitted to three neonatal intensive care units the study team found 6/3,026 admissions resulted from ADRs, all of which occurred in referrals from another hospital.

In the same study, in children with cancer, ADRs caused 157/725 (22%) admissions. Cytotoxic therapy accounted for the majority of admissions (94%). The study included radiotherapy as an ADR, occurring in 10% of admissions, and three admissions were prompted by other non-cytotoxic drugs. There were three deaths due to medication; two due to immunosuppression and one to cardiotoxicity (attributed to doxorubicin given two months prior to admission). In the 'other children' studied in two teaching hospitals and three community hospitals, 131/6,546 (2%) admissions were related to an ADR. There was no difference regarding gender and the occurrence of an ADR. There were two deaths due to ADR. A child with congenital myopathy, treated with erythromycin and theophylline for a respiratory illness, developed arrhythmia and cardiopulmonary arrest. Interestingly, this death was attributed to theophylline toxicity, however the case occurred before the interaction of erythromycin and theophylline had been described. A second child died after transfer to hospital from a dental facility with hypernatraemia and cardiac arrest, where she had been given halothane and nitrous oxide. The death was attributed to complications of general anaesthetic. Avoidability was not assessed formally for the ADRs in the study.

Martinez-Mir et al investigated ADRs causing admission of children, aged 2 years and under, to a hospital in Spain (Martinez-Mir et al. 1997). Of the 517 admissions, 21 (4.3%) were thought to be due to an ADR. The most common ADRs causing admission were convulsions (4), dizziness (4), vomiting (3), tremor (2), fever (2), itching (2) or apnoea (2). The drugs most commonly implicated as causative agents were respiratory drugs (35%), anti-infective agents (25%), drugs active on the central nervous system (15%) and drugs used in dermatology (10%). There was no difference in the mean number of drugs taken during the month before admission between the ADR (n=5.8) and non-ADR (n=4.6) admissions. Eight cases (38%) were judged to be severe, defined as directly life-threatening. There were no significant differences in age (<1 or >1 year) or gender (14 female, 7 male) for the ADR admissions, although ADRs were more common in girls (14/263, 5.3%) compared to boys (7/249, 2.8%). The incidence of ADR admissions reported in this study is higher than the other studies included in the systematic review but caution should be used when interpreting the results. This is a smaller study in an age-limited population and the results may be influenced by drug utilisation or the population studied.

The last study included in the systematic review by Impicciatore was published in 1998. Easton et al assessed all admissions to an Australian children's hospital, over a 56 day period, for the occurrence of drug related problems, of which ADR was one category (Easton et al. 1998). There were 58 admissions due to drug related problems. 10/1682 (0.6%) admissions, in nine patients, were due to an ADR. Anti-epileptic medication was implicated in causing 3 admissions. The Naranjo scale was used to

assess causality, with nine cases classified as ‘possible’ and one ‘probable.’ Using an adapted schema, derived from Schumock and Thornton, the authors assessed preventability of all drug related problems citing that 2/3 of cases were preventable. However, no detail of preventability was given for the ADR subgroup.

For these five studies included in the systematic review, the meta-analytic weighted average gave an incidence of 2.09% (95%CI, 1.02, 3.77) for ADRs causing paediatric admission. Of the ADRs causing admission, 39.3% (95%CI, 30.7, 47.9) were life threatening. Although the incidence for admissions caused by ADR was low in comparison to the frequency of ADRs occurring in hospital (9.53%; 95%CI 8.43, 16.17), the high proportion of severe reactions signifies that this aspect of ADRs in the paediatric population is a significant public health issue. The review found that poly-pharmacy was a potential risk factor for development of an ADR. The ADR studies included were undertaken in different countries, different healthcare settings and by different types of investigators (nurses, pharmacists, paediatricians and pharmacologists). Variables such as patient age and prescription patterns were not reported consistently. This heterogeneity between studies does not lend itself to accurately identifying risk factors for ADRs.

1.8.2 Clavenna and Bonati

A second systematic review, published in 2009 by Clavenna and Bonati, aimed to assess the incidence of ADRs in the paediatric population since 2001 (Clavenna & Bonati 2009). The review included eight studies, of which four collected data

regarding ADRs as a cause of admission to hospital. The meta-analytic weighted average for the incidence of ADRs causing hospital admission due to ADRs was 1.8% (95% CI 0.4, 3.2).

The first included study was conducted over a period of five months by Buajordet et al in the paediatric department of a university hospital in Norway, assessing children up to the age of 16 years for the occurrence of adverse drug events (Buajordet et al. 2002). Parents and staff were asked to report adverse drug events occurring before and after admission. In addition, an investigator (a pharmacist) visited clinical areas daily to enquire about possible events and screen medical records. There were 919 admissions in 665 patients in the study period with 579 patients having been exposed to medication. Although the study was designed to assess adverse drug events, the authors state that 5% of admissions were due to ADRs according the WHO definition. ADR admissions were most frequently due to cytotoxic therapy (22) and vaccinations (9). Most of the cases (81%) were identified by screening of patient records, with the remainder identified from cases reported by physicians or parents. Of all the drug events/ADR cases identified in the study, a significant proportion occurred in children undergoing treatment for cancer.

Over the course of one week, all children admitted to a regional children's hospital in France were assessed for ADRs (Jonville-Bera et al. 2002) by an investigator who collected information daily. Four admissions (4/260 admissions, 1.5%) were due to ADRs: convulsion with an antiepileptic drug, myoclonia with an analgesic, melaena

with acetyl salicylic acid, and neonatal withdrawal syndrome with methadone). No formal assessments were undertaken on these cases.

During a prospective observational study of ADRs in a Sri Lankan hospital, over an 11 month period, investigators found 63/39625 (0.16%) admissions occurred as a result of ADRs (Lamabadusuriya & Sathiadas 2003). The commonest drugs implicated in causing ADR related admissions were antibiotics (32), metoclopramide (7), nalidixic acid (6) and Japanese encephalitis vaccine (6). The most common reactions occurred in skin (52%) and central nervous system (27%). There were no deaths although 11 reactions were serious (life threatening). ADRs were more common in girls at a ratio of 1.4:1. It is likely, given the very low incidence of ADR admissions in this study, that there were issues with prospective collection of data or identification of ADRs. No assessment of avoidability was made for the ADR cases.

A study in a Nigerian hospital found 17/3821 (0.4%) children were admitted to the children's ward because of ADRs (Oshikoya et al. 2007). The study used data pooled from two studies; a retrospective medical record review of 3139 paediatric admissions, from January 2004 to June 2006, and a six month long observational study of 682 admissions, undertaken by a multi-disciplinary team, from July to December 2006. The incidence for the prospective aspect of the study was 0.6%. Antibiotics were the group of drugs most likely to be associated with an ADR. Skin reactions were the most frequent ADR. 22 children had severe ADRs and two children died as a result of ADRs (one death from hepatic failure after ingestion of a herbal medicine and one death from Steven’s Johnson syndrome after antibiotic use). 43 ADRs were judged to

be preventable, although no detail regarding these cases was reported. The incidence of ADRs reported in this study is low and is likely to be due to the mixed methodology used, with retrospective case-note review being less likely to give an accurate estimate of the frequency of ADRs.

1.8.3 Aagaard et al

Aagaard et al. published a third systematic review in 2010 which included 19 studies, six of which investigated ADRs as a cause of hospital admission. The review concentrated on the quality of the studies and compared methods and reported outcomes between them, including; type and occurrence of ADR (incidence and prevalence), type of reporter, seriousness, and patient demographics. The average incidence rate for inpatients hospitalized due to ADRs was 9% and the prevalence 4%. Five of the six ADR admission studies were included in the first systematic review by Impicciatore et al. With respect to ADR admission studies, Aagaard did not include any of the studies in the review by Clavenna et al, indicating a less than comprehensive search strategy.

The sixth study included in the Aagaard review (but not the first systematic review by Impicciatore) was published in 2005 by Haffner (Haffner et al. 2005), who investigated ADRs in two general paediatric wards and a paediatric intensive care unit (PICU). Patients on the paediatric oncology ward were excluded. Haffner et al compared intensified ADR surveillance with computerised signal detection, in

admissions and inpatients, concluding that intensified surveillance discovered a higher frequency of ADRs, and ADRs that were more severe, but required higher personnel resources. The incidence of ADR admissions, combining both intensified and computerised surveillance, over a 51 day prospective data collection period was 2.7%.

1.8.4 Smyth et al

A fourth systematic review was undertaken as part of the Adverse Drug Reactions in Children (ADRIC) research programme (Smyth et al. 2012) aiming to investigate ADRs reported in observational studies in three settings: causing admission to hospital, occurring during hospital stay and occurring in the community. The authors aimed to describe the methods used for detecting and assessing ADRs within the studies and to better understand how ADRs may be avoided. 102 studies were included in the review, of which 72 assessed causality, 34 assessed severity and only 19 studies reported avoidability assessments. Of the 19 studies reporting avoidability, only three had reported the case-specific rationale for potentially avoidable ADRs.

There were 42 studies investigating ADRs as a cause of admission. Less than half (n=20) of these studies investigated admissions solely, with the remainder investigating ADRs occurring in multiple settings. 12 studies did not report rates of ADR occurrence. A pooled estimate of 30 studies investigating ADRs causing admission showed an incidence rate of 2.9% (95% CI 2.6, 3.1). Individual studies, not included in the other reviews, are not described in more detail here. The review included both retrospective and prospective studies. Some of the study data revealed

very low incidence rates for occurrence of ADRs causing admission (mainly retrospective studies). Both prospective observational studies described in this thesis, in chapters 2 and 4, are included in the review.

1.9 PREVENTION OF ADRS

There are many ways of attempting to prevent ADRs. The majority of these methods relate to good clinical practice, such as prescribing for an appropriate indication, appropriate dosing of medication, good allergy reporting and monitoring of therapy. However, even when information from drug manufacturers advises monitoring to prevent ADRs, the evidence of when to do this, how frequently, how long for and how to interpret the monitoring findings (often investigations) may not be available (Pirmohamed & Ferner 2003).

Various attempts have been made to reduce the burden of harm from drugs by other means. Raschke et al, in an adult medical setting, used an integrated computer system to alert physicians of possible drug related problems in 37 drug-adverse event pairings (Raschke et al. 1998). The system issued 1116 alerts over a six-month period when physicians were prescribing medication to patients. 596/1116 (53%) alerts were true positives, with 265/596 (44%) alerts going unrecognised by clinicians prior to alert notification by the system. Although an integrated prescribing system can aid decision making regarding prescription of drugs, and potentially lower the rate of drug-related harm, it is time and cost-expensive and needs to be fully integrated with lab and

clinical data to have an impact on routine patient care. It may also only make cost-savings, for example in length of stay, in environments where there is a high rate of drug-related harm or a significant rate of serious harm which creates a cost-burden for the institution involved.

The advent of stratified medicine (the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a particular treatment) has been hailed as a potential step forward in aiding drug safety and assessment of likely drug efficacy (Trusheim, Berndt & Douglas 2007). Pharmacogenetics is the study of genetic variability in drug response between individuals or, more commonly, groups of individuals. The study of this variation holds promise in identifying at risk groups for ADRs from particular drugs, or classes of drugs. This could potentially swing the benefit-risk ratio positively in favour of certain subgroups of patients. An example of this is the identification of an association between human leukocyte antigen (*HLA*)-*B*1502* in Chinese patients and an increased risk of Carbamazepine induced Stevens-Johnson syndrome. This allele has not been found in a caucasian population in the UK (Alfirevic et al. 2006). This knowledge allows for genetic testing prior to commencement of treatment with Carbamazepine to reduce the risk of a potentially serious reaction within the high risk group.

1.10 COST OF ADRS

There is little doubt that ADRs increase the cost of patient care. However, the cost of ADRs is difficult to calculate accurately. There have been studies assessing the direct costs of ADRs. One such study calculated that each ADR during admission increased the cost of admission by almost 2000 Euro (Evans et al. 1994). Pirmohamed et al, in a large observational study of ADRs causing admission to two hospitals in an adult population, estimated the cost of ADR admissions to the National Health Service (NHS) to be £466m (€706m, $847m) a year (Pirmohamed et al. 2004). There are few estimates of the costs of ADRs in paediatric populations and these are usually in relation to inpatient ADRs. There is difficulty in attributing direct costs as a result of ADRs due to the heterogeneity of healthcare settings and populations studied. However, direct costs are not the whole story when considering costs. There are major methodological problems when assessing total costs of the burden of ADRs due to the indirect costs such as absence from work (Gautier et al. 2003).

1.11 CONCLUSIONS

ADRs are likely to be an important source of avoidable harm to children. A systematic approach to reducing this harm is required. The ADRIC project was funded by the NIHR to provide this systematic approach. The project set out to describe risk factors for ADRs with a view to modifying practice to address those risk factors.

Thus the studies described in this thesis aim to address elements of a systematic approach to minimising the harms of ADRs in children. The focus of this thesis is ADRs that result in hospital admission (the ADRIC1 study). A companion study (ADRIC 2) examined ADRs among children who were hospital inpatients.

The first element covered in this thesis is a description of the problem. There have been several studies aiming to assess the impact of ADRs that cause children to be admitted to hospital. A recent comprehensive systematic review of these studies estimated the incidence of ADRs causing admission to be 2.9% (95% CI 2.6%, 3.1%) and showed that severe ADRs are likely to be common (Smyth et al. 2012). The majority of studies have been undertaken prospectively in an aim to maximise the accuracy of the estimate of frequency of ADR admissions. However, some of the studies were small and undertaken over a short period of time. These studies are unlikely to provide information that can be generalised to other healthcare settings or countries. There were several larger studies, which are described earlier in this chapter, which give more reliable data on the burden of ADRs causing admission of children to hospital. Some of these studies were undertaken some time ago and patterns of drug usage are likely to have changed since their publication. Mitchel et al reported, in 1988, that the top three drugs causing ADRs were Phenobarbital, Aspirin and Phenytoin. These three drugs are used less in children now, for varying reasons, than they were in 1988. It is likely that the frequency and characteristics of ADRs causing admission will have changed as a result. None of the studies undertaken addresses the problem of ADRs causing admission of children to UK hospitals and none of them

examine the risk factors for ADRs. The first step in addressing these issues is to undertake a prospective study to assess the frequency of the problem, the types of ADRs occurring and the drugs/drug classes implicated.

Moreover, very few of the studies describe the case-specific rationale for assessment of avoidability of the reactions identified; that is, the investigators give no indication as to how the ADRs might have been prevented. Although assessments of avoidability can be subjective, and difficult to undertake, they may identify patterns of drug use, or areas of clinical practice, where interventions might be fruitful in decreasing the frequency, or severity, of ADRs. Thus, the second step is to examine the extent to which the problems are avoidable.

There is a paucity of information regarding costs of ADRs in the paediatric population. The lack of direct cost estimates for ADRs causing paediatric admissions reduces the stimulus for change or intervention. The third step is to estimate the direct costs that can be attributed to ADR admissions in children. These steps require some work to develop appropriate methods.

1.12 AIMS OF THIS THESIS

The aims of this thesis are to describe ADRs causing admission of children to a UK hospital with respect to epidemiology and avoidability. In particular:

1. To undertake a pilot study to determine the methodology to be used for a larger study of ADRs causing admission to a UK paediatric hospital

2. To develop a causality tool (since existing tools were found to be inadequate during the pilot study)

3. To undertake a one year prospective observational study of acute admissions to a UK paediatric hospital, and assess the following:

    a. The incidence of ADRs causing admission.

    b. The type of ADRs causing admission.

    c. The drugs and drug classes most frequently causing ADR admissions.

    d. The severity and causality of ADRs.

    e. The avoidability of the ADR admissions as well as the types of interventions that could reduce the burden of avoidable ADRs.

    f. Potential risk factors for occurrence of an ADR causing admission.

    g. The cost of ADRs to the study hospital.

CHAPTER 2 ADVERSE DRUG REACTIONS CAUSING ADMISSION TO A PAEDIATRIC HOSPITAL: A PILOT STUDY

2.1 INTRODUCTION

Children are vulnerable to adverse drug reactions. A systematic review of ADRs in children, published in 2001, included 5 prospective studies (Easton et al. 1998; Martinez-Mir et al. 1997; McKenzie et al. 1976; Mitchell et al. 1988; Yosselson-Superstine & Weiss 1982) and estimated the incidence of ADRs causing hospital admission in children to be 2.09% (95%CI 1.02, 3.77) (Impicciatore et al. 2001). A second systematic review of studies (Clavenna & Bonati 2009) published in 2009 included a further four prospective studies (Buajordet et al. 2002; Jonville-Bera et al. 2002; Lamabadusuriya & Sathiadas 2003; Oshikoya et al. 2007), published between 2001 and 2007, researching ADRs causing admission to hospital in children. The calculated incidence of ADRs in children causing admission to hospital was 1.8% (95% CI 0.4, 3.2) using a meta-analytic estimated average, adjusted and weighted by sample size of the included studies. These studies were conducted in a wide range of healthcare settings and in different countries. Few of the prospective studies included analysis of risk factors for developing an ADR or detail about avoidability of the reactions.

Spontaneous reporting systems, such as the UK Yellow Card Scheme (MHRA), under report ADRs (Hazell & Shakir 2006). To obtain reliable information about the incidence of ADRs prospective studies are needed. A large prospective study in an adult population showed as many as 6.5% of admissions were caused by ADRs (Pirmohamed et al. 2004). There are no recent large studies of the incidence and nature of ADRs causing admission of children to hospital in the UK.

The National Institute for Health Research (NIHR) Programme Grants for Applied Research were established in 2006 to produce independent research findings that will have practical application for the benefit of patients and the UK NHS. In 2007, the NIHR funded the ADRIC research programme. The aim of the programme was to develop clinical tools to identify, prevent and manage ADRs in children. There was little study data regarding the extent of ADRs in a UK paediatric population. Therefore, the first step in this process was to investigate the epidemiology of ADRs in children which may contribute to acute hospital admissions in the UK. A one-year observational study of ADRs causing acute admissions to a UK children's hospital was planned. The aim of this first study of the ADRIC programme is the prospective identification of ADRs in children causing admission to hospital to quantify the burden and identify key features.

The setting for the study was Alder Hey Children's Hospital NHS Foundation Trust, a large specialist children's hospital in the north of England which accepts referrals from primary and secondary care. The hospital serves a catchment area of 7.6 million and treats approximately 200,000 children and young people, with 30,000 inpatients

annually. Approximately 60,000 children attend the Accident and Emergency department (AED) each year.

A similar approach to Pirmohamed et al (Pirmohamed et al. 2004) was planned for our study: 2 research pharmacists, as part of a multi-disciplinary investigating team, studied 18,820 acute admissions across 2 hospital sites demonstrating an ADR incidence of 6.5% (95% CI, 6.2, 6.9) (Pirmohamed et al. 2004). Our study would likely have significant differences from an adult study due to the study population age, and differences between adult and paediatric medical practice, among other factors. We aimed to conduct a pilot study, in the first instance, to develop the methodology to enable successful completion of a larger observational study.

The definition of a pilot study varies depending on the source. Use of the terms 'pilot study' and 'feasibility study' inter-changeably is widespread. The NIHR Evaluation, Trials and Studies Coordinating Centre define a pilot study as "a version of the main study that is run in miniature to test whether the components of the main study can all work together" and a feasibility study as "a piece of research done before a main study in order to answer the question "Can this study be done?" but which does not evaluate the outcome of interest (that is left to the main study)." Thabane et al., in 2010, reviewed several sources of definitions in their commentary and stated that "a pilot study is synonymous with a feasibility study intended to guide the planning of a large-scale investigation."(Thabane et al. 2010)

Lancaster et al., in a review published in 2004, state that "a well-conducted pilot study, giving a clear list of aims and objectives within a formal framework, will encourage methodological rigour, ensure that the work is scientifically valid and publishable, and will lead to higher quality RCTs." (Lancaster, Dodd & Williamson 2004) The authors provided recommendations for the methodology and reporting of pilot studies for RCTs some of which are relevant to undertaking pilots of observational studies, such as:

- Pilot studies should have a well-defined set of aims and objectives.
- Participants should not later be included in the main study.
- The analysis of a pilot study should be mainly descriptive.

The aim of this pilot study was to address questions such as what constitutes an admission (which would allow comparison with other UK hospitals providing paediatric healthcare), whether to include patients admitted to the AED observation ward, and to assess feasibility of improving medication histories by use of a specific proforma. This pilot study aims to provide an evaluation of the feasibility of the methods required to conduct a larger definitive study and a preliminary assessment of the proportion of acute admissions that were associated with ADRs.

2.2 METHODS

2.2.1 Preparation

Before the pilot study began, a comprehensive educational program was undertaken to raise awareness about ADRs within the hospital amongst clinicians of all grades. The study team held meetings with clinical teams, and attended educational meetings of clinical trainees, to highlight the study, ADRs in children and the importance of taking detailed medication histories in relation to patient symptoms. Prior to the study, hospital admission documentation was altered with the introduction of a separate medication history proforma to highlight the elucidation of recently taken medication (in the preceding 2 weeks) as being an important part of general history-taking (**APPENDIX A**). The medication history proforma was presented at a weekly hospital grand round presentation, as well as to the clinical teams in the meetings mentioned, to ensure as comprehensive co-operation as possible be obtained. The documentation was developed by the study team and one of the lead investigators, with a 2-week medication history being chosen as the time in which most important reactions causing admission were likely to have occurred after exposure to a drug. The proforma was double-sided to provide ample room for more extensive medication histories.

2.2.2 Categories Of Admissions

There are many types of admission to the study hospital. Many admissions are planned including those for: elective surgical procedures; elective medical admissions for investigation or management; day case admissions for treatment or investigations; some inter-hospital transfers for investigation or management. These were not included in the study. There are many children who return regularly to wards for ongoing treatment such as intravenous immunoglobulin infusions or dialysis. These were classed as planned admissions and also not included. Other exclusions were patients admitted because of accidental or intentional OD.

All unplanned admissions to the main hospital and the AED observation ward were included. These included emergency attendances to AED, primary care referrals, inter-hospital transfers and self-referrals (defined as patients with chronic conditions with clinician-agreed direct access to a hospital ward) who were then admitted to a main hospital ward or the observation ward. The intention was to include unplanned admissions to main hospital wards in the larger study. However, we were initially uncertain whether to include in the larger study patients admitted to the observation ward who were discharged without admission to the main hospital. The observation ward is an area within the AED department where patients can have treatment, investigation, or active observation, within a four hour time limit and are either admitted to a main hospital ward or discharged home. These patients mainly include those with acute illness who either attend voluntarily or are referred by a GP.

2.2.3 Assessment of Admissions

The study was deemed to be audit after written communication with the National Research Ethics Service. All unplanned admissions to a large tertiary paediatric hospital were prospectively screened daily for ADRs over a 2 week period including weekend days and a bank holiday. The definition of ADR used was that of Edwards and Aronson (Edwards & Aronson 2000) which is "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." This definition does not include accidental or intentional OD and, therefore, these patients were not included. All unplanned admissions in the previous 24 hours were identified on a daily basis from hospital computer systems. Members of the study team then collected information from the case notes on each patient identified as having an unplanned admission including age, sex, presenting complaint, summary of clinical history, diagnosis (if available at the time of admission), and medications taken in the 2 weeks prior to admission. If information on medication history for the preceding 2 weeks was not available from the case notes, or if clinical information needed to be clarified, the study team members interviewed the child/parents/carers as appropriate to confirm the history i.e. medication history, symptoms, and timing of events. To identify possible ADRs, one investigator screened the main hospital ward admissions, and a second investigator screened the case notes of patients admitted to the observation ward but subsequently discharged without admission to a main hospital

ward. The AED case notes are routinely electronically scanned from paper notes and stored on a password protected database. Therefore, there were very few problems with retrieval of these notes on a daily basis.

Presenting symptoms/signs were cross-referenced against the medication history for each patient using the ADR profile for relevant drugs from the SPC (Datapharm 1999) or, if not available, the British National Formulary (BNF) (*British National Formulary* 2008). The study team members identified possible ADRs using this information combined with the clinical history and temporal relationships of the medication(s) taken. All possible ADRs were reported to the responsible clinicians. Assessment of causality was performed for all cases using the method of Naranjo et al. (Naranjo, Busto & Sellers 1981). In addition, we determined the ADR type (according to the classification of Rawlins and Thompson) (Rawlins 1977), severity using the Hartwig scale (Hartwig, Siegel & Schneider 1992) and avoidability using the definitions developed by Hallas et al (Hallas et al. 1990). One of the lead investigators, a pharmacologist, had the final decision regarding assessments of ADR cases. These final decisions regarding assessments of ADRs took place at a meeting between investigators at the end of the study period.

2.2.4 Assessment Of Methodological Issues

The following were assessed during the pilot study:

- Whether to include patients admitted to the AED observation ward.

The organization of acute paediatric services varies considerably in different UK hospitals. One feature of our service is the AED observation ward. Patients can stay on the observation ward for up to 4 hours for observation and treatment and are then either discharged or admitted to a main hospital ward. We therefore needed to define what constitutes an admission, so that it would be applicable in a variety of settings. During this pilot study, our intention was to identify ADRs occurring during emergency admissions to both the main hospital wards and in the AED observation ward in patients who were not subsequently admitted to a main hospital ward. This would enable us to make a decision about whether it was worthwhile and feasible to include children admitted to the observation ward without subsequent admission to a main hospital ward in our definitive study.

- The feasibility of asking clinicians to complete a medication proforma detailing the medicines taken by each patient in the 2 weeks prior to their admission and assess the adequacy of clinical information recorded on observation ward given the relatively short stay of some cases.

- The workload, shared between 3 investigators, was assessed to identify whether it was achievable to screen prospectively both main ward and observation ward patients on a daily basis including weekends. The feasibility of collecting data from main wards and the AED observation ward at weekends and during holiday periods was assessed over a public holiday weekend during the pilot study.

2.2.5 Analysis

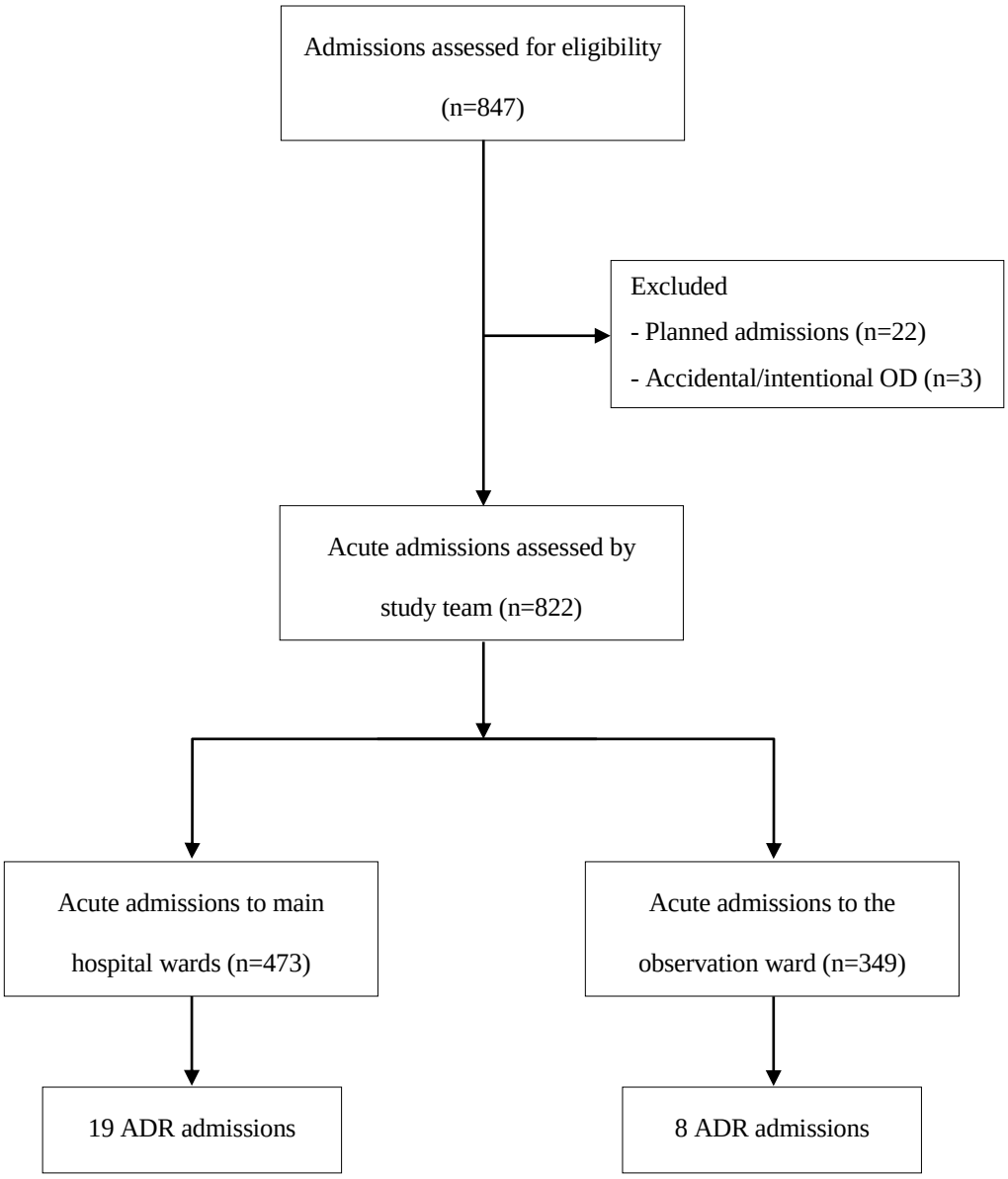
Analyses of the rates of ADRs were expressed as Number per 100 admissions with 95% confidence intervals. Other results were stated as raw numbers or tabulated.

2.3 RESULTS

2.3.1 Preliminary Estimates of Incidence of ADRs

Over the 2 week pilot, 28th April to 12th May 2008, 847 records were identified by the hospital computer system for assessment (**Figure 2.1**). 22 of these were elective admissions wrongly coded and three were due to adverse drug events (one accidental OD, two accidental poisoning). Therefore, there were 822 acute admissions, in 794 patients, to the main hospital and observation wards. Twenty-six patients had two admissions and one had three admissions during the study period. 462/794 patients (58.2%) were boys and 332/794 (41.8%) were girls. There were 473 admissions (57.5%), in 462 patients, to the main hospital wards; 274 (59.3%) boys and 188 (40.7%) girls. Nine patients had two admissions, and one had three, to the main wards. There were 349 (42.5%) admissions, in 344 patients, to the observation ward subsequently discharged home; 197 (57.3%) boys and 147 (42.7%) girls. One patient had two admissions to the observation ward in the study period. The discrepancy between the numbers of patients in each admission group occurs because 16 patients with two admissions in the study period had one each to the observation ward and main wards.

Figure 2.1 Flowchart of admissions during the pilot study



There were 27 admissions identified as being complicated by an ADR. The 27 admissions occurred in 25 patients, with two patients (one boy and one girl) in the main hospital ward group admitted twice with an ADR during the study period. 13/25 (52%) patients with an ADR were boys and 12/25 (48%) were girls. There were 19 admissions in 17 main hospital ward patients and eight admissions in 8 AED observation ward patients. This gives an incidence of 4 ADRs / 100 admissions (95% CI 2.2–5.8) in the main hospital wards and 2.3 ADRs / 100 admissions (95% CI 0.7–3.9) in the observation ward. Twenty of the 27 (74%) admissions were deemed to have been directly caused by ADRs. In six cases (22%), an ADR was deemed to be a co-factor for the admission. In one case (4%), the ADR was deemed to be incidental. Twenty-two (81%) of the ADR admissions were classified as being due to type A reactions (predictable from the known pharmacology) with five (19%) being type B reactions (not predictable). The five reactions judged to be Type B were: a maculopapular rash to the trunk, one day after starting a course of amoxicillin; a delayed onset of erythema multiforme, 1 day after finishing a course of cefaclor; a child with an oncological problem, who was admitted overnight, developed an altered conscious level after receiving PEG-asparaginase earlier in the day as an outpatient day-case; a child treated with cefaclor for an upper respiratory tract infection developed vomiting 2 days after starting therapy; and an infant who developed tongue and facial swelling, needing treatment with intramuscular adrenaline, five minutes after taking a first dose of mefloquine for prophylaxis against malaria.

The main cause of ADR-related admissions (n=10; 37%) were anti-neoplastic drugs. All of the affected children were admitted to the oncology ward. Immunosuppressants, antibiotics and analgesics were the next most commonly implicated drug groups in causing ADR-related hospital admissions to the main wards. 428/822 (52.1%) admissions had been exposed to a medication two weeks prior to admission to either the observation ward or main wards. In the 27 admissions associated with an ADR, children had been exposed to a total of 169 courses of medication (mean of 6.3 medicines per admission). The median number of medicines taken by patients in the ADR admissions group was four with an inter-quartile range 2-10 (4; 2, 10). There were 401 admissions of children, exposed to medication, who did not experience an ADR. The total number of courses of medicines in the non-ADR admissions, for children who had been exposed to a medicinal product, was 1065 (mean of 2.7 medicines per admission). The median number of medicines of patients in the non-ADR group was two (2; 1, 3). There were 25 ADRs identified in the 19 ADR cases (**Table 2.1**).

Table 2.1 ADRs and drugs taken for main ward admissions

ADR	Occurrences	Drugs identified
Neutropenia	6	etoposide, carboplatin, vincristine, cytarabine, daunorubicin
Vomiting	5	tacrolimus, prednisolone, etoposide, carboplatin, vincristine,
Diarrhoea	4	cefaclor, mycophenylate mofetil
Immunosuppression	2	tacrolimus
Thrombocytopenia	2	etoposide
Constipation	2	buscopan, ondansetron, tramadol
Altered conscious level	1	peg-asparaginase
Anaemia	1	cyclophosphamide, doxorubicin
Rash	1	amoxicillin
Haematemesis	1	diclofenac
Impaired renal function	1	cyclosporin

Assessment of causality using the Naranjo algorithm showed the majority of cases to be in the 'possible' classification (17/27, 63%). Some were classified probable (10/27, 37%) but none definite. All investigators reported that the Naranjo scale was difficult to use accurately in this population due to the nature of some of the questions and their relevance to current paediatric practice.

All of the ADRs were classified as grade 3 ('required treatment, or drug administration discontinued') according to an adapted Hartwig severity scale. We defined anyone requiring admission to hospital as 'needing treatment.' No ADRs contributed to a death. Investigators reported that the severity tool was easy to use. However, it may need modifying for a paediatric population as not all children admitted with an ADR needed active treatment or drug withdrawal. In two instances, active observation was undertaken until symptoms abated. There were no children admitted to PICU (or any other higher level of care) and there were no deaths during the two week period.

We determined avoidability of admissions related to an ADR by the method of Hallas et al. Eighteen (67%) of the ADRs were assessed as unavoidable, while 9 (33%) were classified as "possibly avoidable." None were classified as definitely avoidable. Investigators reported that the Hallas system was easy to use but is likely to be user-dependent given its broad classification terms. The possibly avoidable ADR admissions are detailed in **Table 2.2** .

Table 2.2 Possibly avoidable ADRs

ADR	Drugs	Description of reaction
Nausea	codeine phosphate	Infected pin site. Took codeine for headache and developed nausea.
Haematemesis	diclofenac	Coffee ground vomit after three days taking diclofenac post-operatively for bilateral hip surgery.
Infection (cellulitis)	hydrocortisone cream 0.5%	Secondarily infected eczema. Regular use of hydrocortisone.
Impaired renal function	ciclosporin	On ciclosporin for one month for graft versus host disease. Admitted with diarrhoea and renal failure. Had adenovirus in stool. Ciclosporin dose reduced and renal function improved.
Vomiting	carboplatin, etoposide	Re-admitted after cytotoxic chemotherapy with vomiting.
Rash	paracetamol	Rash after strawberry flavoured paracetamol. Previous similar rash after strawberry flavoured yoghurt.
Nausea/vomiting	vincristine, carboplatin, etoposide	Admitted with nausea and vomiting, post-cytotoxic therapy, due to reduced oral intake.
Constipation	buscopan, tramadol, ondansetron	Admitted with possible pseudo-obstruction. Previous admissions with pseudo-obstruction/constipation.
Diarrhoea	mycophenolate	Persistent diarrhoea after liver transplant. Admitted with fever, possible infection and dehydration.

2.3.2 Methodological Issues

We found that the majority of main hospital ward admissions (n=473) came from AED (n=363, 77%). This included clinical areas within AED and all GP acute referrals (all of whom are seen in AED before admission). Hospital transfers and acute self-referrals of children with known chronic disease accounted for the remainder of main hospital admissions (n=110, 23%). Observation ward admissions (n=349; 42.5%), i.e. where there was no admission to the main hospital wards, included self-referrals and acute GP referrals. The proportion of admissions to the observation ward that yielded an ADR was 2.3%. There were 9 ADRs identified in 8 observation ward cases (**Table 2.3**).

Table 2.3 ADRs and drugs taken for AED observation ward admissions

ADR	Occurrences	Drugs identified
Rash	3	paracetamol, cefaclor, MMR vaccine, pneumococcal vaccine
Irritability	2	DTaP/IPV/HIB vaccine, pneumococcal vaccine
Anaphylaxis	1	mefloquine
Fever	1	MMR vaccine, pneumococcal vaccine
Vomiting	1	cefaclor
Infection (cellulitis)	1	hydrocortisone (cream)

Of the 473 admissions to the main hospital wards, the separate medication history proforma was only used in 57 (12%). The use of the proforma was slightly higher in the observation ward (60/349; 17%). All of the proformas were completed in AED as this is the main route of admission, with none used during the study period when clinicians admitted children from other sources. Feedback from clinicians revealed that the separate proforma was difficult to use. Clinicians commented that a medication history proforma would be more usable if embedded into existing documentation, e.g. care pathways.

The study team encountered difficulties in obtaining a completely accurate two week medication history from the time prior to admission in many cases. Many parents could not recollect accurately the timings or doses of medication given, especially for anti-pyretic/analgesic over-the-counter medications. This was to be expected and is a common finding in routine clinical practice. The study team pragmatically captured as much information from the recorded history and parental history, as was feasible, to allow for assessment of whether an ADR had occurred. Also, many patients had been in hospital within the preceding two weeks and had been exposed to medications of which parents could not possibly have known the details including cytotoxic drugs and general anaesthetic agents. This necessitated comprehensive detailed medical record review.

There was an average of 34 unplanned admissions to main wards to review daily during the two week pilot study. The morning was used to collect data and the afternoon was used to input the data onto a password protected database on a secure

hospital server. The investigator would also have to return to patients whose notes were missing or who had left the ward temporarily for investigations elsewhere. Follow-up of patients was necessary to look at investigations and follow the progression of their clinical history and treatment to complete the assessment of a possible ADR. In some cases, several days to weeks were required for follow up.

The patients from the observation ward, because of short duration of admission, were not available for interview. Their case notes were the only source of information about symptoms, signs and medication history. There were 349 admissions, of 344 patients, to the observation ward during the two weeks with 5 patients being admitted twice. Therefore, there were approximately 25 reviews of electronic notes each day. Whilst the number of patients in this group was less than on the main ward, the process of recording information from one scanned electronic record to our database was time consuming, often taking half of the working day.

2.4 DISCUSSION

This pilot study demonstrated that the incidence of ADRs causing admission to the main hospital wards was 4% (95% CI 2.2, 5.8). This figure is higher than that seen in other studies including two meta-analyses of ADRs causing admission in children. McKenzie et al (McKenzie et al. 1976), in 1976, studying 3556 children over a 3 year period in the US, found that 2% of admissions were caused by ADRs, with anti-neoplastic drugs being the most frequently occurring. Easton et al (Easton et al. 1998), in Australia, investigated 2933 paediatric admissions over 22 weeks showing that 4.3% (95% CI 3.6,5.0) of admissions were due to a drug related problem, with less than a quarter of these being ADRs (29/2933, 1%). A study by Martinez-Mir et al in 512 consecutive admissions over 204 days in Spain found the incidence (4.3%) to be similar to our study, but was different in that only children under 2 years old were studied.

The analysis of data from this pilot study was rudimentary and did not include risk factor analysis due to sample size. Due to the time-frame studied, there were only a small number of patients admitted on multiple occasions. This is likely to be a more prominent feature of the admission data in the larger planned study as there will likely be some patients with multiple admissions, including multiple ADR admissions (in particular, oncology patients). These multiple admissions occurring in the same patients may not be independent from each other. The larger study will, therefore, include more detailed analysis at first-admission level.

Clearly, ours is a pilot study, with limited study duration and sample, designed to assess the feasibility of the methodology used, and as such the reported estimate of incidence of ADRs should be interpreted with caution. Caution should be exercised in assessing the generalizability of the findings of this pilot study both to the larger study and to other settings due to the study sample size, methodology and characteristics of the settings which may be different from other tertiary children's hospitals. The methodology to be used in the larger study was informed by the pilot study and was altered to take account of local hospital difficulties which may not be shared with other settings.

Amongst the methodological questions we wanted to address was the definition of an admission. We found that there were possible ADRs that occurred in patients admitted solely to the AED observation ward who were then discharged home without admission to a main hospital ward. The adequacy of clinical information in some cases, the lack of information about progression of clinical history and the short duration of stay made it difficult to assess for the occurrence of an ADR in these patients. The methodology used to retrieve information, with retrospective note review only, in this group of patients was very different to the main hospital group where prospective note review and, if needed, interview of parent/carer/child was used to assess the possibility of an ADR. The workload for the 3 investigators was also significantly increased with inclusion of the observation ward patients. This was particularly evident at weekends when only one investigator could be available. Therefore, for the above reasons, taken together with the fact that (a) the incidence of ADRs was lower in observation ward patients than those admitted to the main ward;

(b) an ADR causing admission to a main ward is intuitively more severe than one that leads to discharge within 4 hours; and (c) many paediatric departments may not have observation wards which would make generalizability of our findings difficult, we have elected not to include observation ward admissions in our main admissions study.

Amongst the unexpected methodological problems encountered was the definition of an acute admission. Hospital information systems were used to identify unplanned admissions which were coded as such by nursing staff on hospital wards routinely when each patient was admitted. However, it became apparent during the pilot study that not all the admissions were truly emergency or unplanned and did not meet the inclusion criteria for investigation (**Figure 2.1**). The study team collecting this data checked each case excluded, with the other members, in the first instance and with a senior investigator at the end of the pilot study. All the cases (planned admissions/transfers and poisoning/OD) were agreed to be correctly excluded. It was, therefore, decided to capture this information in the larger study, and exclude cases as per inclusion criteria, rather than address the problem with hospital staff coding the admissions data, as this would have been a significant undertaking with an unknown chance of improvement.

Capturing information about the drug history is crucial in studies such as this. We therefore designed a medication proforma for clinicians, with education about its use, to record the medication history over a 2 week period before admission. This was a separate sheet to be collated with existing case note pathways and clinical history recording. We however found that the use of this proforma was inadequate during the

pilot study leading to many parent/carer interviews for the investigators. We therefore plan to embed a more user friendly proforma within existing admission documentation with collaboration from clinicians and the hospital Care Pathways Co-ordinator (**APPENDIX B**, **APPENDIX C**).

Identification of ADRs posed an interesting problem for the study team. If in trying to identify ADRs a literal approach is taken, and children with signs or symptoms which correspond to the known adverse reaction profile of medication they were exposed to are identified (and this is the only information used), then the number fo cases needing further assessment would be significantly increased. This would be a common occurrence because children often present to healthcare settings with generic symptoms and signs such as diarrhoea, rash, and vomiting. Therefore, a pragmatic approach, as is the case when assessing children clinically for cause of symptoms, must be taken.

The elucidation of possible ADR occurrence encompassed use of clinical knowledge and experience of disease processes and drug reactions. To strengthen this approach, the study team was made up of multi-disciplinary professionals. To improve ADR identification by study team members, during the pilot study, cases were often discussed between the investigators. Some cases were relatively straight-forward (as is the case for oncology ADRs, for example) whereas others needed multi-disciplinary input, with study team members holding discussions with senior investigators including paediatricians, a senior pharmacist and a clinical pharmacologist. It was decided to have regular meetings, during the larger study, between study team

members and a senior investigator to discuss challenging cases. It was helpful that the clinical pharmacologist had undertaken very large observational studies of ADRs in adults.

The majority of the ADRs that were seen during our pilot study were oncology related. These were mainly children admitted with a febrile illness who were neutropenic 1-2 weeks after intravenous chemotherapy. This group of patients are often exposed to medications which cause ADRs, for example nausea, vomiting, diarrhoea, infection with neutropenia, anaemia and bleeding from thrombocytopenia, all of which may require admission for treatment. These ADRs can be expected and, for the most part, may be unavoidable given the nature of the underlying illness and the treatment required. However there may be more unusual or serious ADRs which occur and which may be important to capture. We found that although these patients are often exposed to many medications in the preceding two weeks, making their data collection more time consuming than other groups, it was possible to capture accurately their medications and clinical problems and identify ADRs that had occurred.

Data collection from the main hospital ward patients was challenging. Ideally, if data could be collected by electronic means it would undoubtedly make a study like this less complex. However, this could not be achieved as a laptop (even with encryption) was not deemed safe enough to carry between wards, ward computers were for clinical use and there were not enough of them on each ward to allow study team members to use them as and when required, and there was little WiFi cover on hospital wards to

allow for a secure wireless approach to data collection. Therefore, data collection was done on paper and transferred to a secure electronic database (Microsoft Access).

Assessment of causality using the Naranjo algorithm showed the majority of cases to be in the 'possible' classification. All investigators reported that the Naranjo scale was difficult to use accurately in this population due to the nature of some of the questions. Causality assessments were easier to apply to the oncology ADRs because of the hospital-intensive nature of their treatment, for example with continuous re-challenge to chemotherapy, and detailed clinical records of their recent drug history and clinical problems. Causality assessment using the Naranjo tool, and the reported difficulties in using Naranjo in our studies, will be discussed in more detail in Chapter 3.

Risk factor analysis was not undertaken due to the limitations in size of the study population. This is something that is planned for the larger study. One aspect of the data from this pilot study is that drug exposure was difficult to assess. Information such as start date, stop date, dose and frequency of administration of drugs was sought but was not always available or felt to be wholly accurate. This was especially true of over-the-counter drugs given when required, such as anti-pyretics. Parents could not always remember the dose given or timings of administration accurately. These are common findings in clinical practice. The definition of ADR used by the investigators incorporates drugs being used at a therapeutic dose and, wherever possible, the study team made every effort to elucidate that this was the case for patients exposed to medication. An assumption was made that, in general, parents and carers would likely follow dosage instructions prescribed by clinicians or stated on medicines information.

Therefore, data was included even if parents could not remember a specific dose, using the assumption above.

In summary, this pilot study was used to inform a much larger study to research ADRs that cause admission to hospital in the paediatric population. We anticipated that the larger study will have ~12000 admissions which will allow a more precise estimate of the incidence of ADRs among paediatric admissions and allow more detailed description of the ADRs themselves. Given the problems encountered of capturing ADRs in children in the observation area, i.e. those that stayed within hospital premises for less than 4 hours, this area will not be included in our larger study. However, this should not be taken to mean that we feel that this aspect of hospital attendance is unimportant with respect to ADRs. On the contrary, further investigation of ADRs is required in those attending AED and being discharged within 4 hours, but the methodology would have to be altered to achieve this.

CHAPTER 3 CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS

3.1 INTRODUCTION

Causality assessment of ADRs is a method used for estimating the strength of relationship between drug(s) exposure and occurrence of adverse reaction(s). Causality assessment of ADRs may be undertaken by clinicians, academics, pharmaceutical industry and regulators and in different settings, including clinical trials (Agbabiaka, Savovic & Ernst 2008; Arimone et al. 2010; Laine et al. 2009; Turner 1984). At an individual level, health care providers assess causality informally when dealing with ADRs in patients to make decisions regarding future therapy. This is often undertaken without using a formal assessment method, with many clinicians not having had teaching or experience of assessing causality. Many regulatory authorities assess spontaneous ADR reports (Arimone et al. 2010; Turner 1984) where causality assessment can help in signal detection and aid in risk-benefit decisions regarding medicines (Kling 2004; Macedo et al. 2005). Many regulatory authorities use formal assessment tools to aid in this process.

An early paper by Sir Austin Bradford Hill (Hill 1965), describing minimum criteria for establishing causality of adverse events, pre-dates the earliest attempts to formulate ADR causality assessment tools. Bradford Hill set out criteria for establishing causality which included assessment of; strength of the association, consistency of the

association, specificity, temporal relationship, biological gradient (dose response), biological plausibility, coherence, experimental evidence, and reasoning by analogy. These criteria are described in more detail in the introduction to this thesis. These elements of assessing strength of relationship between exposure (drugs) and outcome (adverse reaction) are used widely in ADR causality tools. Attempts to formalise causality assessment of ADRs into structured assessment tools have been ongoing for more than 30 years (Irey 1976; Naranjo, Busto & Sellers 1981). It is known that assessing ADR likelihood without a structure can lead to wide disagreements between assessors (Arimone et al. 2005). Disagreements may mean that opportunities to avoid or ameliorate harm are missed during clinical care or that cases are misclassified in epidemiological studies. These disagreements may be the result of differing clinical backgrounds, specialties and experience between assessors. A large number of causality tools have been developed ranging from the simple to the complex. These tools aim to limit disagreement between assessors of ADR cases as to the likelihood that a reaction is related to a particular medication taken by the patient. None has gained universal acceptance (Jones 2005).

One of the most widely used CATs is the Naranjo ADR probability scale (Naranjo, Busto & Sellers 1981). This is a simple 10-item questionnaire that classifies the likelihood that a reaction is related to a drug using concepts such as timing, plausibility/evidence, de-challenge and re-challenge/previous exposure. Each element of the questionnaire is weighted and the total score used to categorise the event into unlikely, possible, probable and definite. The tool was developed 30 years ago by adult

pharmacologists/physicians and psychiatrists. Published case reports were used to validate the reliability of the tool in assessing causality. It has been widely used, including recently by investigators in two large prospective observational studies of ADRs causing hospital admission and occurring in hospital inpatients (Davies et al. 2009; Pirmohamed et al. 2004). However, the reliability and validity of the Naranjo scale has been questioned by a number of investigators (Agbabiaka, Savovic & Ernst 2008; Avner et al. 2007; Garcia-Cortes et al. 2008; Kane-Gill 2005; Macedo et al. 2005).

While undertaking a prospective observational pilot study of ADRs in children, described in Chapter 2 of this thesis, we found several difficulties with using the Naranjo scale. The study detailed in this chapter aims to address these difficulties. Our original aim was to use the Naranjo ADR Probability Scale for the larger observational study described in Chapter 4. In the observational study we planned to assess the causality of the ADRs prospectively rather than at the end of the study period. When beginning to assess this heterogeneous mix of potential ADR cases during the pilot study (Chapter 2) with the Naranjo scale, the investigators found some questions were not appropriate in this clinical context. This led to many elements of the Naranjo scale being categorised as "unknown". In particular, question six ("Did the reaction reappear when a placebo was given?") and question seven ("Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?") were very often answered as 'unknown'. Administration of a placebo and assessment of drug concentrations are not part of practice when assessing potential causality of ADRs in this clinical setting. An answer assigned as "unknown" gives a zero score for that element in the Naranjo scale.

This will lower the total achievable score on an individual case basis. This meant that the thresholds for recognizing ADRs were not achieved, which in turn underestimated the likelihood of an ADR. This led to a lack of sensitivity for many of the early cases assessed in our study, as the overall score obtained for each causality assessment was artificially lowered. The investigators encountered several cases which were unanimously thought to be definite ADRs (e.g. repeated episodes of febrile neutropenia during oncological chemotherapy) but which did not reach the threshold for 'definite' causality using the published Naranjo scale. Accordingly, the Naranjo score did not have face validity when applied to our patient population. Moreover, the weighting for each question and the ADR classification scoring boundaries used in the Naranjo scale were not justified in the original publication or subsequently. Therefore, we developed a CAT that would overcome some of these issues, while at the same time (a) making it as easy, or easier, to use than the Naranjo scale (a feature which holds a distinct advantage for large observational studies of ADRs among other situations); and (b) ensuring that the basic principles of assessing causality, as described above, were maintained.

The specific aim of this study was to develop a CAT with good face validity and acceptable inter-rater reproducibility.

3.2 METHODS

The pilot study team (RG, JM, KB) noted concerns with using the Naranjo scale. This triggered a process in which each of seven investigators (RG, JM, KB, MP, TN, RS, MT) independently assessed the first 40 consecutive case reports from an observational study of suspected ADRs causing hospital admission (ADRIC Study 1 – described in Chapter 4 - available at http://www.ADRIC.org.uk/) using the Naranjo scale. The results of these assessments are detailed in the results section of this chapter. In summary, there were eight cases where problems with assessments were found. There was one case where major discrepancies occurred between at least two of seven raters, that is, where the range of causality probability differed by more than one category (e.g. possible and definite), and seven cases where close to half of the raters differed from the others by one causality category. The questions within the Naranjo scale which caused the discrepancies in these cases were identified and reviewed. This exercise led to the recognition that a new assessment tool was required.

The team made several choices at the start of the development of the new assessment tool. In order to relate to the existing literature it was agreed that the output of the new tool would take the same form as the Naranjo scale. That is, categorical scores from both the Naranjo scale and the new tool would take the same four point ordinal scale (unlikely, possible, probable and definite). In order to fit with clinicians' experiences the format of the new tool was an algorithm, or flowchart, with dichotomous responses to each decision followed by routing to further, specific questions, rather than the

weighted responses used in the Naranjo scale. The study team decided to develop the new tool in two stages. Firstly, use the extensive clinical and pharmacovigilance expertise in the group to develop a tool that had face validity to the team. Secondly, iteratively assess the tool to optimise inter-observer agreement within the study team.

In the first step of the process, each question in the Naranjo scale was reviewed by the investigators at a consensus meeting to assess whether it was appropriate to incorporate, discard or integrate with other questions into a new, more appropriate, causality tool (**Table 3.1**).

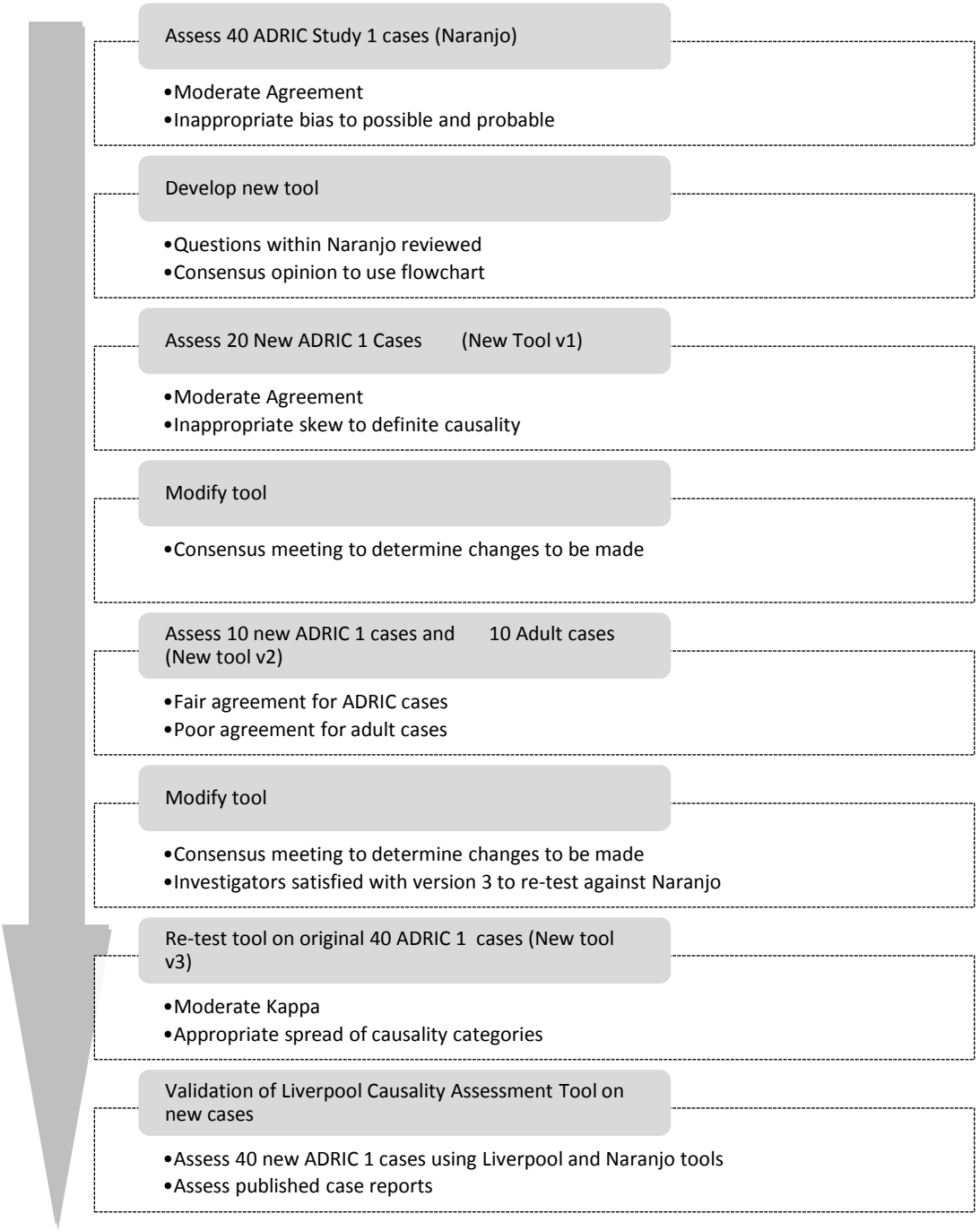
Table 3.1 Decisions made about questions within the Naranjo scale

No.	Naranjo scale questions	Yes	No	Don't know	Outcome for Liverpool Tool
Q1	Are there previous *conclusive* reports on this reaction?	+1	0	0	**Retained** – knowledge of previous reports can be important when assessing if an adverse event is due to drug or disease.
Q2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	**Modified** – timing of event in relation to drug exposure is important when determining causality.
Q3	Did the adverse reaction improve when the drug was discontinued or *a specific* antagonist was administered?	+1	0	0	**Modified** – Knowledge of de-challenge, if available, may provide further evidence as to causality of an event. However, an event may have long-lasting sequelae. A new question was added to the Liverpool tool to cover this possibility.
Q4	Did the adverse reaction reappear after the drug was readministered?	+2	-1	0	**Combined** – Knowledge of re-challenge, if available, may add to the level of certainty regarding causality assessment. This question is combined with Naranjo Q8 regarding dose-response relationship to increasing dose. This can also provide evidence to support or refute causality.
Q5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	**Modified** – This question is replaced within the Liverpool tool by a question involving likelihood of alternative cause, with an option to answer 'unsure' (which prompts the user to seek further evidence of the reaction). Naranjo Q5 is worded such that it is difficult to answer No.

Q6	Did the reaction reappear when a placebo was given?	-1	+1	0	**Rejected** – With the exception of clinical trials, placebo use is not common practice and this question is no longer relevant.
Q7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**Modified** – Objective evidence of the ADR occurrence will already be taken in to account when the user is deciding whether the event is likely to be drug or disease related. A question in the Liverpool tool asks for objective evidence of likely ADR mechanism. If apparent, this may provide evidence of causality to an assessor.
Q8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	**Combined** – This question is combined with one addressing de-challenge in the Liverpool tool. The answer to this question may be important in establishing if there is a dose-response relationship between drug and adverse event.
Q9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	**Modified** – this is included in the Liverpool algorithm, in relation to the same drug(s) only, and given the same weighting as a positive re-challenge. This may provide evidence of susceptibility, and likelihood, of the event being related to a drug.
Q10	Was the adverse event confirmed by any objective evidence?	+1	0	0	**Modified** – see Q7

The new Liverpool ADR causality tool was then used to assess 20 new suspected ADR case reports from our observational study. The collated causality categories for all seven assessors showed 1 (0.7%) unlikely, 18 (12.9%) possible, 2 (1.4%) probable and 119 (85%) definite. The assessors achieved moderate agreement with a kappa of 0.51 (95% CI 0.19, 0.82). The assessing team considered that there was an inappropriate bias towards the category of definite upon reviewing the cases and causality results. Accordingly, the assessment tool was reviewed. Major discrepancies between scorers were identified and each question within the algorithm was reviewed to assess face validity and likelihood of inter-rater disagreement. Questions that caused the bias toward 'definite,' and those that caused major discrepancies between scorers, were then modified. The new assessment tool was then tested on a further 20 case reports; ten from the ADRIC study and ten from an observational study of inpatient ADRs in an adult hospital. Collated causality categories for the ten ADRIC 1 cases showed 0 (0%) unlikely, 24 (34%) possible, 39 (56%) probable and 7 (10%) definite with a kappa of 0.27 (95% CI 0.11, 0.44). Collated causality categories for the ten adult cases showed 0 (0%) unlikely, 13 (19%) possible, 48 (69%) probable and 9 (13%) definite with a kappa of 0.13 (95% CI -0.14, 0.38). The results of these assessments prompted another review of the appropriateness of the tool and questions. A third iteration was used so that the development and evaluation of tool prototypes was based on discussions in which 80 cases were used (**Figure 3.1**).

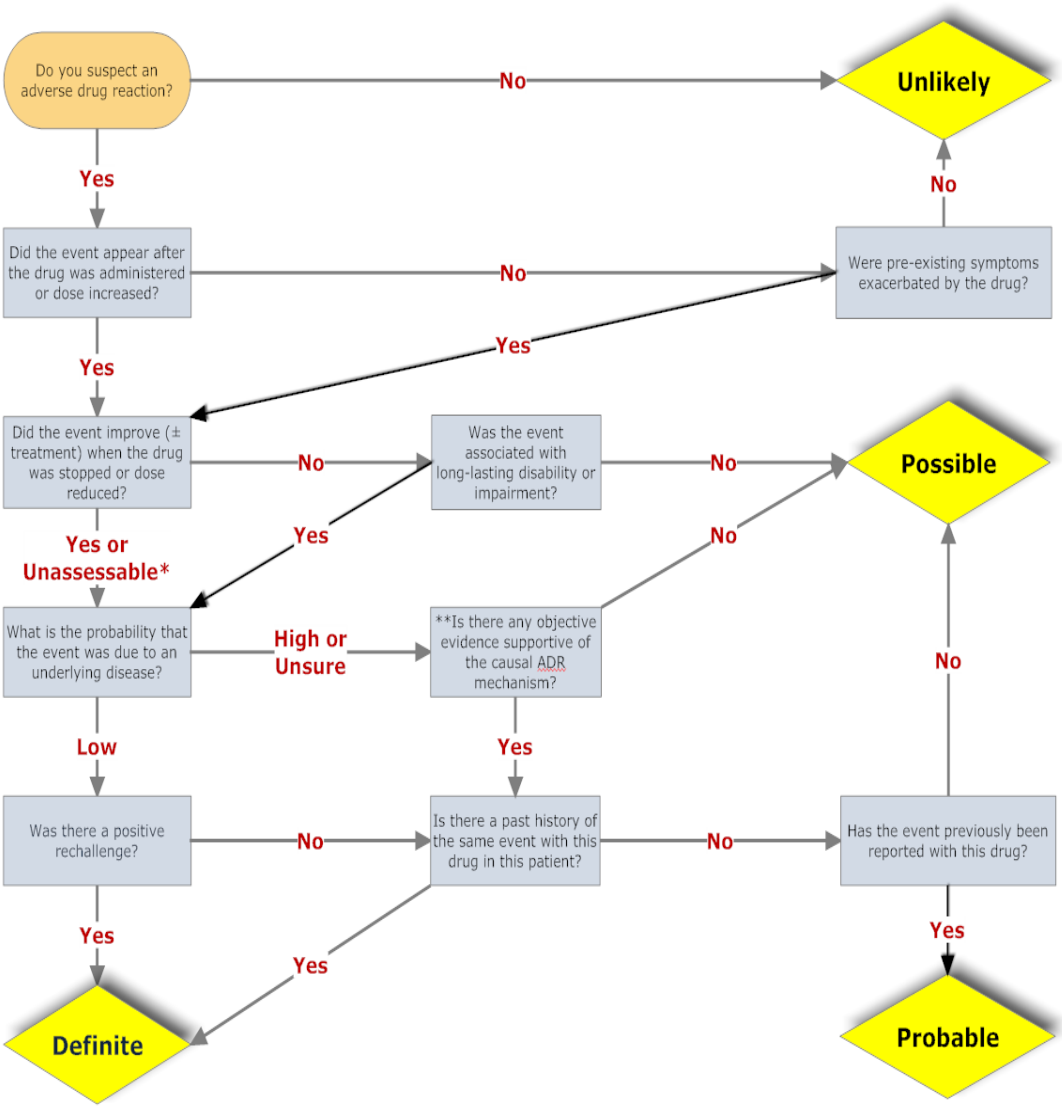
Figure 3.1 Flowchart of the development of the Liverpool ADR Causality Assessment Tool



After the third iteration the investigators were satisfied with the final version of the new tool, **Figure 3.2**, in terms of ease of use, lack of ambiguity, and appropriateness of the causality assignment. This was judged by expert opinion and consensus within the group. The assessment of inter-rater reliability within the study team for the Liverpool ADR CAT followed a step-wise procedure. All cases were presented in paper format using a modified 'yellow card' template to display the information necessary for assessment. All cases were completed by the investigators at the same time (for each stage below) and without collaboration. This was achieved by mutual agreement and commitment to the process.

- The original 40 case reports (case reports of raw clinical data from an observational study) initially assessed with Naranjo were assessed by each of the seven investigators using the new assessment tool to compare the outcomes of the methods and to compare the inter-rater reliability between the two tools.
- In order to examine the tool using cases other than those collected in our observational study, 37 cases of ADRs were randomly selected from the Annals of Pharmacotherapy (**APPENDIX E**) and independently evaluated by the seven assessors using only the new tool.
- Since the original 40 cases from our observational study had been used in the design of the new tool, a further new set of 40 ADR case reports from our study were then used to assess inter-rater reliability using both the Naranjo and the Liverpool tools.

Figure 3.2 Liverpool ADR CAT



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

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

An independent panel with extensive expertise in pharmacovigilance and statistics (the ADRIC Steering Group) were asked to review the tool upon completion of the internal evaluation.

3.3 ANALYSES

The inter-rater agreements at each stage of the assessment process were assessed using a linear weighted kappa with 95% confidence intervals for ordered categories. Exact agreement percentages (%EA) were computed to measure the absolute concordances between assessor scores. Percentage of extreme disagreement (%ED), where the causality scores between two raters of the same case are wider than one causality interval apart (e.g. definite for 1 rater and possible for the other), were also computed to measure extreme disagreements between pair-wise rater assessments. To supplement the pair-wise kappa, a global kappa score measuring nominal scale agreement across multiple assessors was calculated with 95% confidence intervals (Fleiss 1971). The global kappa score provides a single statistic to quantify assessor agreement for each set of cases. Kappa values were interpreted according to the guidance from Altman (Altman 1991): poor <0.2; fair 0.21-0.40; moderate 0.41-0.60; good 0.61-0.80; and very good 0.81-1.00 agreement.

3.4 RESULTS

Assessment of the original 40 consecutive ADR cases by the seven investigators using the Naranjo scale showed collated categorisation of causality scores for all assessors (n= 280 assessments) of 0 (0%) unlikely, 100 (36%) possible, 172 (61%) probable and 8 (3%) definite (**Table 3.2**). Exact agreement percentages for the pair-wise comparisons between raters ranged from 43% – 93%. Percentage of extreme disagreement (%ED) was 2.5% for four of the twenty-one pair-wise comparisons. There were no extreme disagreements in 17/21 pair-wise comparisons. Pair-wise kappas ranged from 0.27 to 0.86 and the assessors achieved moderate inter-rater reliability with a global kappa of 0.45 (95% CI 0.35-0.54) (**Table 3.3**). The same cases assessed using the new Liverpool tool showed collated causality categories of 1 (0.4%) unlikely, 62 (22%) possible, 92 (33%) probable and 125 (45%) definite. Exact agreement percentages ranged from 43-93%. All 21 pair-wise comparisons displayed extreme disagreement with percentages ranging from 5-20%. Pair-wise kappas ranged from 0.27 to 0.84 and the assessors achieved moderate inter-rater reliability with a global kappa score of 0.48 (95% CI 0.42-0.54) (**Table 3.3**).

Table 3.2 Causality category assignments of investigators for the original 40 cases assessed using Naranjo and the Liverpool CAT

	ADRIC Original (N=40)				
		Unlikely	Possible	Probable	Definite
		n (%)	n (%)	n (%)	n (%)
Assessor	**Tool**				
RG	Naranjo	0 (0.0)	18 (45.0)	22 (55.0)	0 (0.0)
	Liverpool	0 (0.0)	7 (17.5)	23 (57.5)	10 (25.0)
JM	Naranjo	0 (0.0)	17 (42.5)	22 (55.0)	1 (2.5)
	Liverpool	0 (0.0)	15 (37.5)	8 (20.0)	17 (42.5)
KB	Naranjo	0 (0.0)	18 (45.0)	21 (52.5)	1 (2.5)
	Liverpool	0 (0.0)	18 (45.0)	4 (10.0)	18 (45.0)
MT	Naranjo	0 (0.0)	14 (35.0)	24 (60.0)	2 (5.0)
	Liverpool	1 (2.5)	5 (12.5)	17 (42.5)	17 (42.5)
TN	Naranjo	0 (0.0)	10 (25.0)	29 (72.5)	1 (2.5)
	Liverpool	0 (0.0)	3 (7.5)	15 (37.5)	22 (55.0)
MP	Naranjo	0 (0.0)	12 (30.0)	27 (67.5)	1 (2.5)
	Liverpool	0 (0.0)	7 (17.5)	12 (30.0)	21 (52.5)
RS	Naranjo	0 (0.0)	11 (27.5)	27 (67.5)	2 (5.0)
	Liverpool	0 (0.0)	7 (17.5)	13 (32.5)	20 (50.0)
Totals	Naranjo	0 (0.0)	100(35.7)	172 (61.4)	8 (2.9)
	Liverpool	1 (0.36)	62 (22.1)	92 (32.9)	125(44.6)

Table 3.3 Naranjo and Liverpool tool assessment of 40 original ADR cases from an observational study

			Assessor 2						
			RG	**JM**	**KB**	**MT**	**TN**	**MP**	**RS**
Assessor 1	**RG**	%EA/ED		57.5/0%	42.5/0%	55.0/0%	52.5/0%	62.5/0%	55.5/0%
		Kappa (95%CI)		0.52 (0.27,0.77)	0.47 (0.21,0.73)	0.44 (0.19,0.69)	0.45 (0.21,0.69)	0.36 (0.09,0.62)	0.29 (0.04,0.54)
	JM	%EA/ED	57.5/5%		**92.5/0%**	70.0/0%	77.5/0%	72.5/0%	70.0/2.5%
		Kappa (95%CI)	0.46 (0.26,0.67)		**0.86 (0.71,1.00)**	0.46 (0.22,0.69)	0.56 (0.34,0.78)	0.47 (0.19,0.75)	0.40 (0.15,0.65)
	KB	%EA/ED	42.5/10%	**75.0/5%**		**77.5/0%**	70.0/0%	70.0/0%	77.5/2.5%
		Kappa (95%CI)	0.28 (0.08,0.49)	**0.69 (0.52,0.87)**		**0.60 (0.39,0.81)**	0.43 (0.19,0.66)	0.43 (0.15,0.71)	0.55 (0.32,0.77)
	MT	%EA/ED	55.0/7.5%	**70.0/5%**	57.5/7.5%		72.5/0%	62.5/0%	70.0/2.5%
		Kappa (95%CI)	0.31 (0.06,0.56)	**0.62 (0.45,0.80)**	0.49 (0.31,0.67)		0.45 (0.20,0.70)	0.37 (0.11,0.62)	0.48 (0.23,0.73)
	TN	%EA/ED	52.5/7.5%	62.5/15%	52.5/20%	70.0/7.5%		70.0/0%	72.5/2.5%
		Kappa (95%CI)	0.27 (0.07,0.46)	0.42 (0.21,0.62)	0.30 (0.10,0.50)	0.49 (0.26,0.72)		0.33 (0.05,0.62)	0.35 (0.06,0.63)
	MP	%EA/ED	62.5/5%	**77.5/7.5%**	67.5/12.5%	**80.0/5%**	**80.0/7.5%**		70.0/0%
		Kappa (95%CI)	0.47 (0.25,0.69)	**0.68 (0.49,0.86)**	0.54 (0.33,0.74)	**0.69 (0.49,0.89)**	**0.62 (0.39,0.84)**		0.38 (0.11,0.65)
	RS	%EA/ED	55.5/10%	70.0/12.5%	62.5/15%	**80.0/7.5%**	75.0/10%	**92.5/5%**	
		Kappa (95%CI)	0.30 (0.05,0.55)	0.54 (0.32,0.76)	0.46 (0.24,0.67)	**0.66 (0.44,0.87)**	0.52 (0.27,0.76)	**0.84 (0.66,1.00)**	

%EA/ED and kappa scores in white boxes represent Naranjo scale analyses.

%EA/ED and kappa scores in grey boxes represent Liverpool ADR causality tool analyses.

Kappa scores outlined in bold demarcate either a good or very good level of agreement.

The 37 randomly selected ADR case reports from the Annals of Pharmacotherapy assessed by the seven investigators using the Liverpool tool showed collated categorisation of causality scores (n= 259 assessments) of 1 (0.4%) unlikely, 67 (26%) possible, 136 (53%) probable and 55 (21%) definite (**Table 3.4**). Exact agreement percentages ranged from 57% – 97%. 18/21 pair-wise comparisons between raters showed some extreme disagreement, with the percentage ranging from 5-11%, while three showed no extreme disagreements. Pair-wise kappas ranged from 0.31 to 0.96 and the assessors achieved moderate inter-rater reliability with a global kappa of 0.43 (95% CI 0.34-0.51) (**Table 3.5**).

These case reports were not assessed by the investigators using the Naranjo scale. The Annals of Pharmacotherapy requires authors to apply a Naranjo assessment prior to publication of each case report in the journal. The collated categorization of the case report author assessments for the 37 cases showed 0 unlikely, 5 (14%) possible, 29 (78%) probable and 3 (8%) definite (**Table 3.4**).

Table 3.4 Causality category assignments of investigators for the 37 Annals of Pharmacotherapy published case reports

(*Authors of case reports in Annals of Pharmacotherapy completed a Naranjo causality assessment)

		Annals of Pharmacotherapy (N=37)			
		Unlikely	Possible	Probable	Definite
		n (%)	n (%)	n (%)	n (%)
Assessor	**Tool**				
RG	Naranjo	NA	NA	NA	NA
	Liverpool	0 (0.0)	11 (29.7)	18 (48.7)	8 (21.6)
JM	Naranjo	NA	NA	NA	NA
	Liverpool	0 (0.0)	11 (29.7)	20 (54.1)	6 (16.2)
KB	Naranjo	NA	NA	NA	NA
	Liverpool	0 (0.0)	12 (32.4)	19 (51.4)	6 (16.2)
MT	Naranjo	NA	NA	NA	NA
	Liverpool	0 (0.0)	10 (27.0)	18 (48.7)	9 (24.3)
TN	Naranjo	NA	NA	NA	NA
	Liverpool	1 (2.7)	10 (27.0)	20 (54.1)	6 (16.2)
MP	Naranjo	NA	NA	NA	NA
	Liverpool	0 (0.0)	10 (27.0)	17 (46.0)	10 (27.0)
RS	Naranjo	NA	NA	NA	NA
	Liverpool	0 (0.0)	3 (8.1)	24 (64.9)	10 (27.0)
Totals	Naranjo	0* (0)	5* (13.5)	29* (78.4)	3* (8.1)
	Liverpool	1 (0.39)	67 (25.9)	136 (52.5)	55 (21.2)

Table 3.5 Liverpool ADR Causality tool assessment of 37 randomly selected published ADR case reports

			Assessor 2						
			RG	**JM**	**KB**	**MT**	**TN**	**MP**	**RS**
Assessor 1	**RG**	%EA/ED		62.2/10.8%	64.9/10.8%	**73.0/0%**	56.8/8.1%	59.5/5.4%	67.6/5.4%
		Kappa (95% CI)		0.307 (0.03,0.58)	0.38 (0.10,0.65)	**0.65 (0.44,0.85)**	0.32 (0.05,0.59)	0.41 (0.16,0.66)	0.46 (0.22,0.69)
	JM	%EA/ED			**97.3/0%**	62.2/10.8%	64.9/8.1%	56.8/8.1%	64.9/8.1%
		Kappa (95% CI)			**0.93 (0.82,1.00)**	0.31 (0.04,0.59)	0.34 (0.06,0.61)	0.29 (0.02,0.57)	0.33 (0.09,0.57)
	KB	%EA/ED				59.5/10.8%	67.6/8.1%	59.5/8.1%	62.2/8.1%
		Kappa (95% CI)				0.31 (0.03,0.59)	0.41 (0.13,0.68)	0.36 (0.10,0.63)	0.34 (0.10,0.58)
	MT	%EA/ED					64.9/8.1%	64.9/5.4%	**78.4/5.4%**
		Kappa (95% CI)					0.40 (0.13,0.66)	0.48 (0.23,0.72)	**0.61 (0.38,0.84)**
	TN	%EA/ED						62.2/8.1%	67.6/5.4%
		Kappa (95% CI)						0.38 (0.11,0.64)	0.42 (0.19,0.65)
	MP	%EA/ED							70.3/0%
		Kappa (95% CI)							0.58 (0.38,0.77)
	RS								

%EA/ED and kappa scores in grey boxes represent Liverpool ADR causality tool analyses.

Kappa scores outlined in bold demarcate either a good or very good level of agreement.

The 40 newly selected ADR cases assessed by the seven investigators using the Naranjo scale showed collated categorisation of causality scores (n= 280 assessments) of 1 (0.4%) unlikely, 90 (32%) possible, 185 (66%) probable and 4 (1%) definite (**Table 3.6**). Exact agreement percentages ranged from 63% – 90%. Percentage of extreme disagreement was 2.5% for four pair-wise comparisons. There were no extreme disagreements in 17/21 comparisons. The pair-wise kappas ranged from 0.19 to 0.81 with moderate inter-rater reliability and global kappa of 0.44 (95% CI 0.33-0.55) (**Table 3.7**). The same cases assessed using the Liverpool tool showed collated causality categories of 0 (0%) unlikely, 66 (24%) possible, 81 (29%) probable and 133 (48%) definite. Exact agreement percentages ranged from 65% – 88%. Percentage of extreme disagreement ranged from 2.5-7.5% for 14 pair-wise comparisons. There were no extreme disagreements in 7/21 comparisons. Pair-wise kappas ranged from 0.51 to 0.85 and the assessors achieved good inter-rater reliability with a global kappa of 0.60 (95% CI 0.54-0.67) (**Table 3.7**).

Table 3.6 Causality category assignments of investigators for the 40 new ADR cases assessed using Naranjo and the Liverpool CAT

		ADRIC New (N=40)			
		Unlikely	Possible	Probable	Definite
		n (%)	n (%)	n (%)	n (%)
Assessor	**Tool**				
RG	Naranjo	0 (0.0)	18 (45.0)	21 (52.5)	1 (2.5)
	Liverpool	0 (0.0)	11 (27.5)	12 (30.0)	17 (42.5)
JM	Naranjo	0 (0.0)	19 (47.5)	21 (52.5)	0 (0.0)
	Liverpool	0 (0.0)	14 (35.0)	8 (20.0)	18 (45.0)
KB	Naranjo	0 (0.0)	15 (37.5)	25 (62.5)	0 (0.0)
	Liverpool	0 (0.0)	13 (32.5)	10 (25.0)	17 (42.5)
MT	Naranjo	1 (2.5)	9 (22.5)	27 (67.5)	3 (7.5)
	Liverpool	0 (0.0)	8 (20.0)	9 (22.5)	23 (57.5)
TN	Naranjo	0 (0.0)	13 (32.5)	27 (67.5)	0 (0.0)
	Liverpool	0 (0.0)	8 (20.0)	12 (30.0)	20 (50.0)
MP	Naranjo	0 (0.0)	12 (30.0)	28 (70.0)	0 (0.0)
	Liverpool	0 (0.0)	9 (22.5)	13 (32.5)	18 (45.0)
RS	Naranjo	0 (0.0)	4 (10.0)	36 (90.0)	0 (0.0)
	Liverpool	0 (0.0)	3 (7.5)	17 (42.5)	20 (50.0)
Totals	Naranjo	1 (0.36)	90 (32.1)	185 (66.1)	4 (1.4)
	Liverpool	0 (0.0)	66 (23.6)	81 (28.9)	133 (47.5)

Table 3.7 Naranjo and Liverpool tool assessment of 40 new ADR cases from an observational study

			Assessor 2						
			RG	**JM**	**KB**	**MT**	**TN**	**MP**	**RS**
Assessor 1	RG	%EA/ED		**90.0/0%**	**80.0/0%**	70.0/2.5%	75.0/0%	72.5/0%	62.5/0%
		Kappa (95%CI)		**0.81 (0.64,0.98)**	**0.61 (0.38,0.84)**	0.46 (0.25,0.66)	0.51 (0.26,0.75)	0.46 (0.20,0.71)	0.23 (0.03,0.42)
	JM	%EA/ED	**70.0/5%**		75.0/0%	67.5/0%	80.0/0%	77.5/0%	62.5/0%
		Kappa (95%CI)	**0.62 (0.43,0.81)**		0.49 (0.23,0.76)	0.45 (0.25,0.64)	0.59 (0.35,0.83)	0.54 (0.29,0.79)	0.22 (0.02,0.41)
	KB	%EA/ED	**65.0/0%**	**77.5/2.5%**		70.0/2.5%	80.0/0%	77.5/0%	67.5/0%
		Kappa (95%CI)	**0.62 (0.44,0.79)**	**0.73 (0.57,0.90)**		0.40 (0.16,0.63)	0.56 (0.29,0.83)	0.50 (0.22,0.78)	0.19 (-0.06,0.44)
	MT	%EA/ED	**70.0/2.5%**	**75.0/5%**	**75.0/7.5%**		70.0/2.5%	70.0/2.5%	72.5/0%
		Kappa (95%CI)	**0.63 (0.45,0.81)**	**0.70 (0.52,0.88)**	**0.64 (0.45,0.84)**		0.367 (0.12,0.62)	0.40 (0.15,0.65)	0.25 (0.003,0.50)
	TN	%EA/ED	**82.5/2.5%**	**77.5/2.5%**	**70.0/2.5%**	**82.5/0%**		77.5/0%	77.5/0%
		Kappa (95%CI)	**0.77 (0.61,0.93)**	**0.73 (0.57,0.88)**	**0.61 (0.43,0.79)**	**0.79 (0.64,0.93)**		0.48 (0.18,0.77)	0.38 (0.09,0.66)
	MP	%EA/ED	**70.0/2.5%**	**80.0/2.5%**	**72.5/2.5%**	**80.0/0%**	**87.5/0%**		80.0/0%
		Kappa (95%CI)	**0.63 (0.44,0.81)**	**0.75 (0.59,0.91)**	**0.64 (0.46,0.82)**	**0.76 (0.61,0.91)**	**0.85 (0.73,0.97)**		0.41 (0.12,0.71)
	RS	%EA/ED	**70.0/2.5%**	70.0/5%	65.0/5%	**80.0/0%**	**82.5/0%**	**75.0/0%**	
		Kappa (95%CI)	**0.60 (0.42,0.78)**	0.57 (0.40,0.74)	0.50 (0.31,0.69)	**0.73 (0.58,0.88)**	**0.77 (0.62,0.91)**	**0.67 (0.51,0.84)**	

%EA/ED and kappa scores in white boxes represent Naranjo scale analyses.

%EA/ED and kappa scores in grey boxes represent Liverpool ADR causality tool analyses.

Kappa scores outlined in bold demarcate either a good or very good level of agreement.

3.5 DISCUSSION

A recent systematic review of studies assessing the reliability of causality assessments concluded that "no causality assessment method has shown consistent and reproducible measure of causality."(Agbabiaka, Savovic & Ernst 2008) As part of a comprehensive assessment of ADRs in children, including the study described in Chapter 4 of this thesis, we had initially decided to use the Naranjo scale to assess causality in our patients admitted with ADRs. In order to do this, we planned to have assessments conducted independently by seven assessors. Initial assessments revealed some significant issues with the Naranjo scale which led us to develop the Liverpool ADR CAT.

In assessing the original 40 possible ADR cases with the Naranjo tool, several difficulties were found with some of the questions in the Naranjo tool. Some of the questions were frequently, or always, answered as 'unknown'. There were two questions which caused discrepancies between raters in eight cases, when scoring with Naranjo. The first question that caused difficulty was question five (**Table 3.1**) ("Are there alternative causes (other than the drug) that could on their own have caused the reaction?"). Individual raters interpreted this question in two different ways: some raters took a literal approach and interpreted the question to mean any 'alternative cause', almost always answering with a 'yes'; other raters took a more practical approach and interpreted the question as 'was there an alternative plausible cause', and in doing so these raters gave variable answers to the question. Question ten ("Was the

adverse event confirmed by any objective evidence?") was the second that caused discrepancies in Naranjo scoring. This caused problems for assessors in two very different ways: firstly, assessors had difficulty in deciding, on an individual case basis, what constitutes objective evidence; and secondly, assessors had difficulty defining whether the objective evidence related to evidence that the ADR had occurred or evidence of the mechanism. For example, a patient taking an opioid for analgesia might develop abdominal pain secondary to constipation and need admission to hospital for treatment and symptom control. In this case, raters may differ in their interpretation regarding question five and whether there may be alternative causes to explain the constipation (some of this may have to with the level of detail in the case report). Raters may also have difficulty in answering question ten. Some raters may suggest that a physical exam of a palpable faecal mass constitutes objective evidence whereas others may suggest that it is not objective and might argue that an abdominal radiograph showing faecal loading is more objective. Others might use either of these two findings to aid in their assessment of 'alternative causes.' If so, these raters might score question 5 in a positive manner because of the available evidence and then score question ten positively because of the evidence, in effect scoring positively for the same information twice. It seems counter-intuitive to take account of positive evidence and score it twice when assessing a possible ADR report. Even so, there were still very little discrepancies between the scores overall with most assessments resulting in a 'possible' or 'probable' causality being assigned.

We designed a new method, the Liverpool ADR causality tool, using an algorithm in the form of a flowchart (**APPENDIX D**). This new tool was assessed to have face validity by a multi-disciplinary investigating group. Seven assessors used both the Liverpool tool and Naranjo to initially assess 40 possible ADR cases from the large observational study. The Liverpool tool performed just as well as Naranjo in terms of inter-rater reliability but gave a broader range of causality outcomes, which was deemed more appropriate by the investigating group. When the seven investigators assessed a second different set of 40 cases the Liverpool tool outperformed Naranjo, showing a 'good' inter-rater reliability.

We believe that the Liverpool Causality tool has several advantages over the Naranjo scale. First, it performed as well as the Naranjo scale with the first set of cases that were assessed. More importantly, the inter-rater reliability improved over time with the new tool, whereas the inter-rater reliability when using Naranjo remained similar, despite the fact that there was as much exposure to this tool within the assessing group. The improved inter-rater reliability with the new tool may be explained by increasing experience of its use. The proportion of exact agreements between assessors was comparable between the two tools for both sets of cases despite the improvement in the global kappa for the new tool. This is because it is difficult to achieve a 'definite' category using the Naranjo scale and assessors mainly scored cases as 'possible' or 'probable.' Therefore, the chances of exact agreement between two assessors of the same case using the Naranjo scale are likely to be falsely elevated compared to the kappa scores which adjust for chance agreement. This paradox has been discussed

previously in the literature (Cicchetti & Feinstein 1990; Feinstein & Cicchetti 1990; Lantz & Nebenzahl 1996). The percentage of extreme disagreement between raters was higher for the Liverpool tool, when compared to Naranjo. Due to the difficulty in achieving a 'definite' score with Naranjo the chances of finding extreme disagreement, when comparing pair-wise assessments, is likely to be falsely low. The observed percentage of extreme disagreements decreased when using the Liverpool tool from the first set of 40 cases to the last set. This may also be explained by increasing experience of its use. The implication of this explanation would be that there is a learning curve associated with using the Liverpool Causality Tool. A learning package is under evaluation.

Second, the inter-rater reliability on assessing published case reports with the new tool was similar to that when we assessed our observational study cases with the Naranjo scale. Five of the seven assessors work in paediatric practice and the published case reports were adult cases. This perhaps provides an indication, albeit indirectly, of the robustness of the tool, even when used for cases from unfamiliar clinical settings.

Third, in the Naranjo scale, almost all cases were categorised as possible or probable. With the new tool, the range of categorisations was broader with some cases judged as being definite. A novel aspect of the tool which makes this possible is that prior exposure that led to the same ADR, for example during a previous course of chemotherapy, was judged as being equivalent to a prospective re-challenge. It is also important to note that the cases were extracted from an observational study of

suspected ADRs in children, and thus some case selection had occurred making it improbable to record a score of 'unlikely' when assessing with either tool.

Fourth, a flowchart rather than scoring system was used in the new tool for causality assessment and was felt by assessors to be easy to follow and quick to complete. We used a classification approach based on binary decisions (taking account of "don't know" responses). In this case we need to ensure that the binary decisions are robust. Once this has been done then the instrument should be relatively context-independent. A weighted scoring system, such as the Naranjo scale, will give more influence to some variables than others. A weighting scheme involves the validation of the items in the tool and the weightings. Ideally, the weightings need to be developed and validated in a context that is similar to the context in which it is applied. Thus a weighting scheme is more likely to be sensitive and specific within a defined context (as long as you have a gold standard) but is more likely to be context-dependent. We feel it is more important to develop a tool that is context-independent since we need to compare different settings when assessing causality of ADRs.

Nevertheless, we were unable to achieve complete agreement about causality assessment for a minority of suspected ADRs. We speculate that this reflects underlying uncertainty arising from issues such as the perceived likelihood of alternative explanations. These perceptions will vary between raters depending on their experience.

This study used a multi-disciplinary team of seven assessors, with varying clinical experience and levels of prior exposure to formal causality assessment, to formulate and test a new causality tool. This has the strength that the proposed tool may be more likely to show reproducible results in the wider context of other healthcare settings but may have less sensitivity/specificity when compared to more specific causality methods designed for use in more specific patient groups (e.g. methods to assess causality specifically for hepatotoxic drugs). The size of the investigating group caused some difficulty in co-ordinating assessments so they were completed at approximately the same time and without collaboration.

The development of the Liverpool CAT involved an iterative process conducted by a multidisciplinary team using raw case data and published case reports. The clinical team included nurses, pharmacists and physicians, including those working with adults and children. Previous experience with formal ADR assessment ranged from minimal to advanced. The assessment team comprised medical statisticians who focused discussion on how to classify cases and monitored progress using standard tools for inter-rater agreement. This approach has the strength of timeliness but the potential weaknesses of "group-think", in which independent thinking and expression of differences may be lost in the pursuit of group cohesiveness. An independent panel with extensive expertise in pharmacovigilance and statistics (the ADRIC Steering Group) reviewed the final iteration of the tool and had input into the design of the internal validation. The group commented that the Liverpool CAT showed face validity, in their experienced opinions, and that the validation plan was comprehensive.

In summary, we present a new CAT, developed by a multi-disciplinary team, which we believe to be at least equivalent, if not better, than the Naranjo scale. We believe the new tool to be practicable and likely to be acceptable for use by healthcare staff in assessing ADRs. We have undertaken an extensive validation of the tool, with a total of 819 causality assessments by seven investigators, using investigators within the ADRIC research programme. Although this validation is equivalent, if not better, than that undertaken for many other tools (Danan & Benichou 1993; Koh & Li 2005; Naranjo, Busto & Sellers 1981), one limitation is that the increase in inter-rater reliability for the second set of 40 case reports using the new tool remains unexplained. A second limitation is that the study has been undertaken internally and not yet assessed independently by other investigators. This study has been published in a peer-reviewed journal and it is hoped that the publication of the algorithm will allow other investigators to undertake independent assessments of the usefulness of this tool in other populations (e.g. using data from adult or elderly care settings), not only for spontaneous reports but also for adverse events occurring within trials.

The new Liverpool CAT was used in our larger observational study of ADRs causing admission of children to hospital detailed in Chapter 4 of this thesis.

CHAPTER 4 ADVERSE DRUG REACTIONS CAUSING ACUTE ADMISSION TO A PAEDIATRIC HOSPITAL

4.1 INTRODUCTION

Children are vulnerable to ADRs (Clavenna & Bonati 2009; Impicciatore et al. 2001; Jonville-Bera et al. 2002; Le et al. 2006; McKenzie et al. 1976; Mitchell et al. 1988). A recent retrospective study by Hawcutt et al. identified 31,726 of 222,755 (14.2%) ADR reports received by the UK MHRA through the Yellow Card Scheme, from 2000-2009, concerned children <17 years of age (Hawcutt et al. 2012). However, it is well recognised that spontaneous reporting systems, such as the Yellow Card scheme in the UK (MHRA), are subject to under reporting of ADRs, even those which are severe (Hazell & Shakir 2006). Thus, it is likely that the number of paediatric ADR reports received each year by the MHRA is a considerable underestimate of the magnitude of the clinical problem in the UK.

Hospital-based ADRs can be identified by retrospective studies using case note review. Studies of this nature may have advantages in identifying delayed ADRs that occur a relatively long time after a drug was started or stopped. Retrospective studies, however, are likely to be less reliable than prospective studies in estimating the frequency with which ADRs occur due to the inadequacy of recorded information. For

the same reason, it may also be more difficult for investigators to establish causality in the potential ADR cases identified. To obtain reliable information about the incidence of ADRs, prospective studies are needed. Previous prospective studies of ADRs causing hospital admission in children are described in the introduction to this thesis.

An aim of pharmacovigilance is to not only identify ADRs through surveillance, but also to prevent harm to patients. It seems logical to detail how the reactions identified through pharmacovigilance studies might have been avoided. This could allow clinicians and regulatory bodies to address these clinical problems with potential strategies to aid reduction in harm to patients from ADRs.

The aim of the study detailed in this thesis chapter was to prospectively identify ADRs in children causing admission to hospital during a one year period in order to quantify and characterise the burden of ADRs. One important aspect of the study was to determine the avoidability of the ADRs identified and detail the reasons for categorising the reactions as ‘possibly’ or ‘definitely’ avoidable. This aspect of ADRs causing admission in children has not been fully addressed in previous studies.

4.2 METHODS

The study hospital had an induction programme which was delivered to new members of staff to educate them about the hospital and some aspects of specific practice within the setting. This programme provided training to clinicians regarding medication prescribing and drug safety for children but did not specifically address ADRs, their diagnosis or how to report them. Therefore, before the start of this observational study, a comprehensive educational program was undertaken within the hospital amongst clinicians of all grades. The study team attended hospital induction for new clinicians (and continued to do so through the entirety of the study period) to give formal presentations about the study and ADRs in children. The study team gave a formal presentation to an audience at the main weekly educational hospital meeting (for clinicians and staff from all specialties) as well as presenting at individual specialty team meetings occurring within the hospital.

The goal of this educational programme was to raise awareness about the aims of the study and to increase clinicians' understanding of their role in information recording. Firstly, clinicians were made aware of the primary aim of the study, which was to identify prospectively ADRs causing admission to the hospital. Clinicians were reminded of the importance of good record-keeping with regard to descriptions of symptoms and signs to allow for more accurate assessment of causality by the study team. Secondly, the study team aimed to raise awareness of taking detailed medication histories in relation to identifying ADRs accurately and assigning causality. A

structured medication history was added to acute general paediatric medical admission documentation with the aim of ensuring all families were asked for details about medication taken in the preceding two weeks. A two-week medication history was chosen as the time when reactions causing admission were most likely to have occurred following exposure to a drug.

A two week pilot study (described in Chapter 2 of this thesis) to develop and refine the methodology for this larger study was conducted prior to the commencement of this study (Gallagher et al. 2010). The pilot study had a sizeable impact on the methodology for this larger study and was useful in refining the study team's approach to data collection, defining an acute admission, identifying possible ADR cases and in assessment of those cases. These are discussed in more detail in chapter 2.

The study team prospectively screened all unplanned admissions to a large tertiary paediatric hospital for ADRs over a 1 year period, including weekends and public holidays, from 1st July 2008 to 30th June 2009. Due to the nature of paediatric illness, there are seasonal variations in numbers of paediatric admissions and with certain patterns of illness and presentation. The study duration of one year was chosen so as to allow data capture from a large number of patients over a time frame that would capture these variations. This would also allow for increased generalizability of the results. Weekends were included in routine daily data collection to eliminate any bias that may occur in trends of possible ADR admissions.

Admissions were excluded if they were planned, or occurred as a result of accidental or intentional OD. The definition of ADR used was that of Edwards and Aronson (Edwards & Aronson 2000) which is "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."

Hospital information systems at the study hospital routinely recorded demographic data about admitted patients. These data, with assistance from the hospital information technology department, were automatically downloaded each morning at 06:00 hours, for the patients coded as having an emergency admission, from the hospital computer system to a password-protected Microsoft Access database, stored on a secure hospital hard-drive. Only the study team had access to the database and the patient information recorded within. As described in chapter 2, the study team had to undertake further case exclusions based on assessment of the admissions and whether they were truly unplanned.

Members of the study team, consisting of a paediatric registrar, a research pharmacist and a research nurse, collected the following information from the case notes of each patient: presenting complaint, summary of clinical history, diagnosis (if available at the time of admission), and medications taken in the two weeks prior to admission. If any information was unclear, study team members interviewed the family, patient or carers as appropriate to clarify the history, i.e. medication history, symptoms, and timing of events.

The study team cross-referenced the presenting symptoms/signs against medication history for each patient using the ADR profile for relevant drugs from the SPC (Datapharm 1999) in the Medicines Compendium or, if not available, the British National Formulary (BNF) (*British National Formulary* 2008). Possible ADRs were identified using this information combined with the clinical history and temporal relationships of the medication(s) taken. All possible ADRs were reported by the study team to the responsible clinicians during the study. All possible ADRs were reported to the MHRA using the electronic Yellow Card reporting scheme at the end of the study period. Reporting to the MHRA occurred after internal causality assessment of the possible ADR cases. The origin of prescription, for drugs thought to be associated with ADRs, was classified using the following criteria:

Community – drugs where prescriptions originated in community settings, for example general practice, or where administration took place prior to hospital admission (e.g. paramedic administered).

Hospital – drugs where the prescription originated, or administration took place, in hospital and then may or may not have been continued, for example by repeat prescription, in community or outpatient settings.

Oncology – all drugs administered, or prescribed, from the oncology ward. These drugs may or may not be cytotoxic in nature.

Initially, the causality assessment algorithm of Naranjo et al was used to assess causality of the ADR cases. It was the most widely used method in the literature, was

quick to complete and would potentially allow for comparison of case assessments with other studies. However, after assessing the first 40 cases using the Naranjo algorithm, the investigators found it contained some questions that caused major discrepancy between scorers and some questions that were rarely answerable within paediatric ADR cases. There were cases that assessors thought were 'definite' ADRs (using assessor opinion) that consisted of well-described ADRs with previous ADR occurrence to the same drug in the same patient. The majority of these cases were rated with a score of 'probable' ADR when using the Naranjo algorithm due to unanswerable questions. This led to development of the Liverpool ADR CAT, which is described in Chapter 3.

We performed assessment of causality for all cases using the Liverpool ADR CAT (Gallagher et al. 2011). Three investigators independently assessed causality for all possible ADR cases. Agreement on causality category between all three investigators was taken as accepted consensus. In cases where the three investigators did not achieve consensus, a fourth investigator assessed cases to decide on causality.

Avoidability of the ADR cases was assessed by consensus meeting between the investigators, using the definitions developed by Hallas et al (Hallas et al. 1990). Cases were assessed as definitely avoidable, possibly avoidable or unavoidable. In addition, the type of ADR for each case identified was determined according to the classification of Rawlins and Thompson (Rawlins 1977) as either Type A (predictable from the known pharmacology) or Type B (not predictable). Severity was determined using an adapted Hartwig scale (Hartwig, Siegel & Schneider 1992).

This adapted scale is shown below (**Table 4.1**). Grades 3 and 4 from the original schema are collated, as not all ADR admissions necessitate cessation of the causative drug(s).

Table 4.1 Adapted Hartwig severity scale

Severity score	Description
6	Directly or indirectly resulted in patient death
5	Caused permanent harm or significant haemodynamic instability
4	Resulted in patient transfer to higher level of care
3	Required treatment (admission), or drug discontinued
2	Drug dosing or frequency changed, without treatment
1	No change in treatment with suspected drug

We chose these assessment tools to describe the nature of the ADRs in our study as they have been used previously in ADR studies by other investigators and can be completed quickly. Three investigators independently assessed 217/4514 (4.8%) reports of admissions exposed to medication, but deemed not to have had an ADR, to assess for occurrence of possible ADR cases wrongly classified by the study team. The

study was deemed to be audit after written communication with the National Research Ethics Service. Therefore, individual consent from patients admitted to the hospital was not sought.

4.3 STATISTICAL ANALYSIS

Analyses of the rates of ADRs were based on the number of admissions with the rate expressed as ADR per 100 admissions, together with 95% confidence intervals. Other results are presented either as medians and interquartile ranges or percentage frequencies and 95 percent confidence intervals, as appropriate.

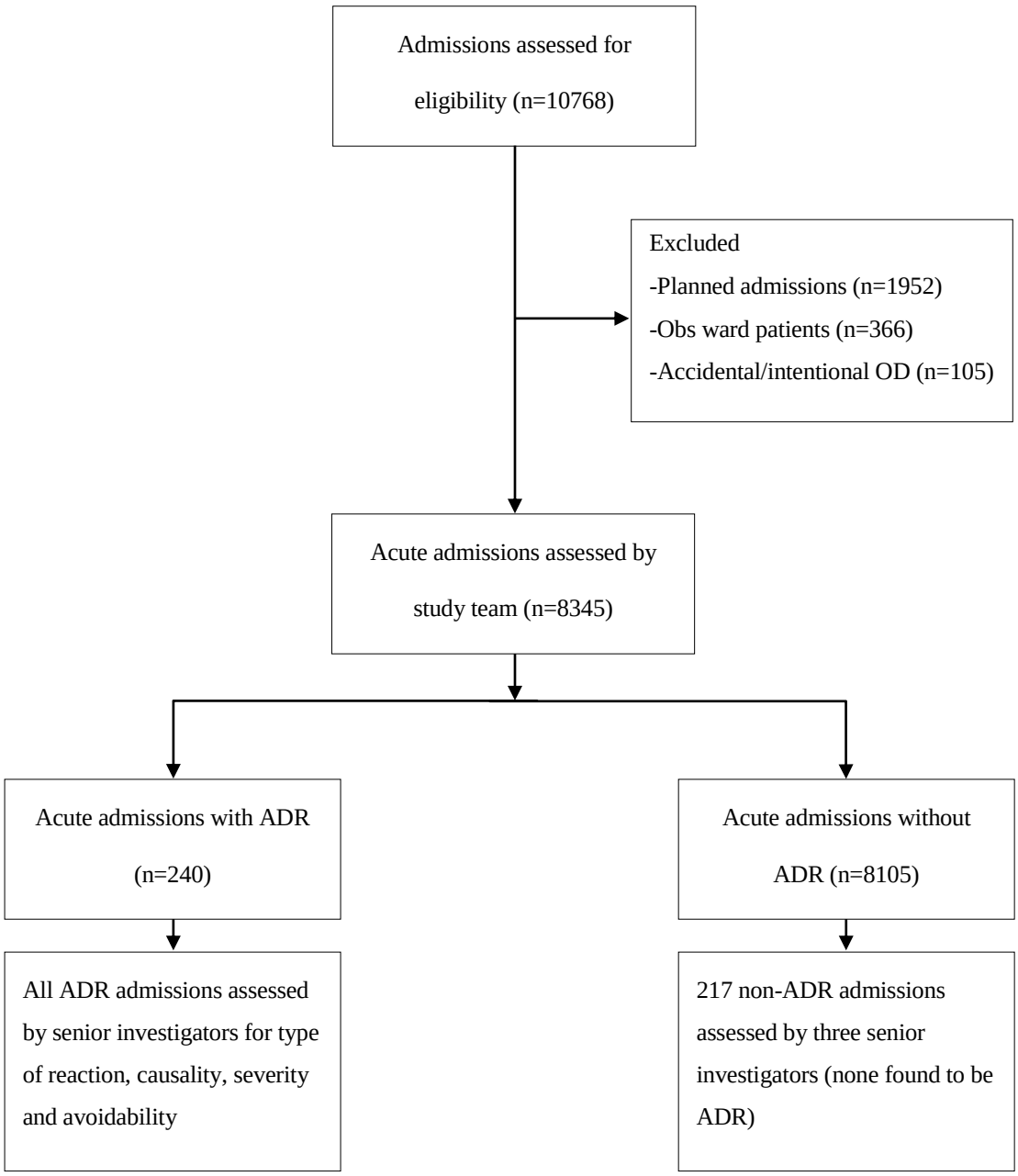
The formal statistical analysis was based on the data obtained at the first admission for patients exposed to a medication (to preserve independence for this variable, as one patient can have multiple ADR admissions which may not be independent from each other). Univariate statistical analyses were performed using the Mann-Whitney U test except for frequency data, which were analysed using a chi-square test. Multivariate logistic regression analysis was undertaken to calculate odds ratios for possible risk factors for ADR. A P-value <0.05 was regarded as being significant.

4.4 RESULTS

Over the study period, there were 10768 patient admissions coded as 'unplanned' on hospital information systems. Upon review, 2423 of these admissions were excluded from further study (**Figure 4.1**); 1952 planned admissions, 366 admissions to OBS ward (and discharged without main hospital ward admission) and 105 admissions due to accidental or intentional OD. Of 1952 planned admissions (incorrectly coded) 917 were from the patient's home, 542 were transfers from another hospital and 493 were for planned review (subsequently admitted). The study periods for the pilot study and this study did not overlap. There were, therefore, no admissions included in both studies.

6821 patients were admitted acutely to the study hospital, accounting for 8345 unplanned admissions. Boys accounted for 3961/6821 (58.1%) patients and 4793/8345 (57.4%) admissions. The median number of admissions per patient was one, with 932 patients having more than one acute admission, up to a maximum of fifteen. 178 patients experienced 240 admissions with an ADR. This gives an incidence of 2.9 ADRs per 100 admissions (95% CI 2.5, 3.3). 233 of the 240 (97.1%) admissions were deemed to have been directly caused, or contributed to, by at least one ADR. There were 249 ADRs in 240 admissions, with nine admissions having two separate ADRs. 35/178 (19.7%) patients had more than one admission with an ADR, up to a maximum of seven.

Figure 4.1 Flowchart of patient admissions and assessments during the study



There were 4656 patients exposed to a medication in the two weeks prior to their first acute admission to the hospital during the study period. Of these patients, 142 (3%)

had a suspected ADR on their first hospital admission. There was no significant difference between the proportion of boys (76/2677, 2.8%) and girls (66/1979, 3.3%) experiencing an ADR on their first admission, for the group as a whole or oncology patients studied separately (**Table 1.1**). For non-oncology patients, there was a slightly higher proportion of girls admitted with an ADR (boys 48/2627 (1.8%), girls 53/1955 (2.7%), P=0.044), although overall more boys than girls were admitted to the hospital.

Table 4.2 Univariate analyses of ADRs by gender (first admission)

Gender	**All**	**No ADR**	**ADR**	**Chi-Squared**	**P-value**
All Boys	2677	2601 (97.2%)	76 (2.8%)	0.947	0.331
All Girls	1979	1913 (96.7%)	66 (3.3%)		
Oncology Boys	50	22 (44.0%)	28 (56.0%)	0.022	0.882
Oncology Girls	24	11 (45.8%)	13 (54.2%)		
Non-Oncology Boys	2627	2579 (98.2%)	48 (1.8%)	4.062	0.044
Non-Oncology Girls	1955	1902 (97.3%)	53 (2.7%)		

The median age of the 4656 patients who had been exposed to a drug on their first admission was 3 years 1 month (IQR 9m, 9y). Patients with an ADR (6y; IQR 2y 4m, 11y) were significantly older (P<0.01) than those without (3y; IQR 9m, 9y) (**Table 4.3**). There was no age difference between the 41 oncology patients admitted with an ADR (6y; IQR 3y, 10y) and the 33 oncology patients admitted without an ADR (6y; IQR 3y 6m, 13y). There was a significant age difference (P<0.01) between 101 non-oncology patients admitted with ADR (6y; IQR 1y 7m, 11y) and 4481 admitted without ADR (2y 11m; IQR 9m, 9y).

Patients admitted with an ADR had taken a greater number of drugs than those admitted for other reasons (**Table 4.4**). For patients admitted with an ADR (n=142), the number of medicines taken was higher (6; IQR 3, 9, P<0.001) than those for other reasons (n=4514) (2; IQR 1, 3). The number of medicines taken by oncology patients admitted with an ADR (8; IQR 5, 10) was higher than those admitted without an ADR (4; IQR 3, 7) and this difference was also found for non-oncology patients (with ADR 5; IQR 3, 9: without ADR 2; IQR 1, 3).

Table 4.3 Univariate analyses of ADRs by patient age (first admission)

Age (years, months) **[Median; Q1, Q3]**	**All**	**No ADR**	**ADR**	**Mann-Whitney U**	**P-value**
All	[3y 1m; 9m, 9y] (n=4656)	[3y 0m; 9m, 9y] (n=4514)	[6y 0m; 2y 4m, 11y] (n=142)	244161	<0.001
Oncology	[6y; 3y 6m, 12y] (n=74)	[6y; 3y 6m, 13y] (n=33)	[6y; 3y 0m, 10y] (n=41)	580.5	0.296
Non-Oncology	[3y; 9m, 9y] (n=4582)	[2y 11m; 9m, 9y] (n=4481)	[6y; 1y 7m, 11y] (n=101)	178319.5	<0.001

Table 4.4 Univariate analyses of ADRs by number of medicines taken (first admission)

Drug Count	All [Median; IQR]	No ADR	ADR	Mann-Whitney U	P-value
All	[2; 1, 3] (n=4656)	[2; 1, 3] (n=4514)	[6; 3, 9] (n=142)	115391.5	<0.001
Oncology	[6; 4, 9] (n=74)	[4; 3, 7] (n=33)	[8; 5, 10] (n=41)	380.5	0.001
Non-Oncology	[2; 1, 3] (n=4582)	[2; 1, 3] (n=4481)	[5; 3, 9] (n=101)	100371.5	<0.001

Logistic regression analysis showed a trend towards boys being less likely to experience an ADR than girls, with an odds ratio (OR) of 0.77 (95% CI 0.52, 1.12, P=0.17) (**Table 4.5**). There was an increased likelihood of ADRs with increasing age (OR 1.04, 95% CI 1.003, 1.08, P=0.03). No children were admitted with an ADR in the first month of life. Oncology patients were much more likely to have an ADR causing admission (OR 29.71, 95% CI 17.35, 50.88, P<0.001). The likelihood

of a child being admitted with an ADR increased with the number of medicines taken (OR 1.24, 95% CI 1.19, 1.29, P<0.001). Therefore, for each additional medicine taken by a patient the risk of an ADR occurring increases by almost 25%.

Table 4.5 Multivariate logistic regression analysis (first admission)

Parameter	Odds Ratio (OR)	95% CI for OR	P-value
Gender (male)	0.77	0.52, 1.12	0.17
Age	1.04	1, 1.08	0.03
Oncology	29.71	17.35, 50.88	<0.01
Number of medicines	1.24	1.19, 1.29	<0.01

a. Variable(s) entered on step 1: Gender (Male), Age, Oncology, Number of medicines

4.4.1 Drug Classes and Drugs

The main class of drugs contributing to ADR-related admissions (n=110; 44.2%) was cytotoxic drugs (**Table 4.6**). Corticosteroids (n=102, 41%), non-steroidal anti-inflammatory drugs (NSAIDs) (n=31, 12.4%), vaccines (n=22, 8.8%) and immunosuppressants (n=18, 7.2%) were the next most commonly implicated drug classes causing ADR-related hospital admissions.

A total of 551 courses of medicines contributed to the 249 ADRs causing 240 admissions. The median number of drugs causing an ADR admission was two (n=79), with a maximum of six (three admissions). Seven admissions were caused by five drugs, 25 by four drugs and 57 by three drugs. 69 admissions were caused by one drug only. None of the ADRs, caused by more than one drug, occurred as a result of a pharmacokinetic drug-drug interaction. All of the ADRs caused by more than one drug were a result of pharmacodynamic interactions.

Table 4.6 Classification of drugs associated with ADR admissions

Drug class (No. of cases)	No. drugs	Drugs	ADRs
Cytotoxics (110)	275	vincristine 51, doxorubicin 38, methotrexate 35, etoposide 30, mercaptopurine 27, cytarabine 24, ifosfamide 18, cyclophosphamide 15, carboplatin 7, vinblastine 5, peg-asparaginase 5, dactinomycin 5, daunorubicin 4, cisplatin 3, irinotecan 3, temozolomide 2, fludarabine 1, amsacrine 1, imatinib 1	Neutropenia 89, Thrombocytopenia 55, Anaemia 38, Vomiting 8, Mucositis 8, Deranged LFTs 7, Immunosuppression 7, Diarrhoea 5, Nausea 4, Constipation 3, Headache 2, Abdominal pain 1, Back pain 1, Haematuria 1, Leukencephalopathy 1, Deranged renal function 1
Corticosteroids (102)	107	dexamethasone 68, prednisolone 33, hydrocortisone 2, betamethasone 1, mometasone 1, methylprednisolone 1, fluticasone 1	Immunosuppression 71, Post-op bleeding 23, Hyperglycaemia 3, Hypertension 1, Gastritis 1, Increased appetite 1, Impaired healing 1, Adrenal suppression 1
NSAIDs (31)	43	ibuprofen 28, diclofenac 15	Post-op bleeding 27, Haematemesis 2, Constipation 1, Abdominal pain 1
Vaccines (22)	37	DTP IPV HIB 11, pneumococcal conjugate 9, meningitis C 8, measles mumps rubella 7, haemophilus influenza B 1, influenza 1	Fever 8, Rash 5, Irritability 4, Seizure 4, Vomiting 3, Pallor 1, Apnoea 1, Limb swelling 1, Lethargy 1, Thrombocytopenia 1, Diarrhoea 1, Abdominal pain 1, Respiratory distress 1, Kawasaki disease 1

Drugs affecting the immune response (18)	26	tacrolimus 15, mycophenolate 7, azathioprine 2, methotrexate 1, infliximab 1	Immunosuppression 18
Anti-bacterial (16)	17	co-amoxiclav 4, penicillin v 3, amoxicillin 3, flucloxacillin 2, cefaclor 1, cefalexin 1, cefotaxime 1, teicoplanin 1, erythromycin 1	Diarrhoea 7, Rash 4, Vomiting 4, Lip swelling 1, Deranged LFTs 1, Thrush 1
Drugs used in diabetes (9)	13	insulin detemir 4, insulin aspart 3, isophane insulin 2, biphasic isophane 2, human insulin 2	Hypoglycaemia 9
Drugs used in status epilepticus (8)	12	lorazepam 5, diazepam 5, midazolam 2	Respiratory depression 8
Opioid analgesia (6)	7	dihydrocodeine 3, codeine phosphate 3, fentanyl 1	Constipation 4, Ileus 1, Decreased conscious level 1
Drugs used in nausea (4)	4	ondansetron 4	Constipation 4
Anti-epileptic drugs (2)	2	carbamazepine 1, nitrazepam 1	Constipation 1, Respiratory depression 1

Drugs that suppress rheumatic disease (2)	2	methotrexate 1, anakinra 1	Immunosuppression 2
Other (16)	4	calcium carbonate 1, amlodipine 1 oxybutynin 1, baclofen 1	Constipation 3
	2	dimeticone 1, carbocysteine 1	Rash 2
	2	desmopressin acetate 1, alimemazine 1	Seizure 2
	10	glucose and dextrose 1, propanolol 1, acetazolomide 1, spironolactone 1, loperamide 1, macrogols 1, captopril 1, alfacalcidol 1, ethinylestradiol 1	Hyperglycaemia 1, Wheeze/DIB 1, Headache 1, Hyperkalaemia 1, Intestinal obstruction 1, Diarrhoea 1, Renal dysfunction 1, Hypercalcaemia 1, Inter-menstrual bleed 1

4.4.2 Nature of the adverse drug reactions

The most common ADRs were oncology related including neutropenia (89), thrombocytopenia (55) and anaemia (38). The next most common ADR was immunosuppression (74), occurring in both oncology and non-oncology patients. Post-operative bleeding, linked to peri-operative corticosteroid administration and/or NSAIDs, caused 28 admissions (26 post-tonsillectomy). Vomiting (15), diarrhoea (14), rash (11) and constipation (9) were all common ADRs causing admission. Hypoglycaemia in insulin-dependent diabetic patients caused nine admissions. Respiratory depression following treatment for status epilepticus caused eight admissions to the hospital's PICU.

Previously unrecognised ADRs included post-operative bleeding in children exposed to corticosteroids and one case of Kawasaki disease, commencing three days after measles/mumps/rubella vaccination of a one year old child, which was deemed to have 'possible' causality by the investigators.

4.4.3 Study team identification of adverse drug reactions

The ADRs in this study were identified in a prospective manner by each member of the study team which consisted of a paediatric registrar, a pharmacist and a paediatric nurse. All three had taken part in a two week pilot study to refine the methodology for this study (Chapter 2) and had attended ADR reporting training at a MHRA regional Yellow Card pharmacovigilance centre. The patient data for all acute admissions were

collected each day by one study member. This allowed for follow-up on the other days. Working patterns altered throughout the year but each investigator completed approximately equal numbers of data collection days. There were 240 admissions associated with an ADR. The pharmacist identified the highest number of ADR admissions (n=96, 40%) in the study period. The paediatrician identified 85 (35.4%) admissions and the nurse identified 59 (24.6%).

Of the 8345 acute admissions in the study period, the pharmacist assessed 2969 (35.6%), the paediatrician assessed 2634 (31.6%) and the nurse assessed 2742 (32.9%). Therefore, the pharmacist judged 96/2969 (3.2%) admissions to be due to ADR. The paediatrician assessed 85/ 2634 (3.2%) to be due to ADR and the nurse 59/2742 (2.2%). There was no difference between the proportion of admissions judged to be due to ADR between the paediatrician and the pharmacist. However, there was a difference between the proportions of ADR cases identified by the nurse compared to both the pharmacist (p=0.01) and the paediatrician (p=0.02), with the nurse having identified ADRs less frequently than the other two investigators. Of the ADRs identified by the pharmacist, 46/96 (47.9%) were oncology patient admissions. The paediatrician identified 29/85 (34.1%), and the nurse 39/59 (66.1%) oncology patient admissions.

Independent assessment of a sample of non-ADR cases (n=217) was undertaken by three senior investigators. Each investigator assessed 75 cases independently (eight cases were duplicated in the randomisation process; six of these were distributed to two different investigators and one investigator received two copies of two reports).

The investigators highlighted five cases that required further information from the case notes. At a consensus meeting with the investigators, four of the reports, with the extra case information, were deemed not to be ADRs. This was mainly due to investigations/information confirming a disease process, such as a culture-positive stool confirming infectious gastroenteritis. One case was deemed to have insufficient information to assess the symptoms in relation to the drug history, but overall was thought unlikely to be due to an ADR. The analysis of these cases confirmed that none of these admissions were due to ADRs.

4.4.4 Origin of ADR Drug Prescriptions

Prescriptions originating from community settings accounted for 44/249 (17.7%) of the ADRs. 85/249 (34.1%) ADRs arose from prescriptions originating in hospital for the treatment of conditions other than oncology. Prescriptions originating from oncology accounted for 120/249 (48.2%) of ADRs. Of the patients with one ADR (n=140) in the study period, 39 (27.9%) occurred with community originated prescriptions, 71 (50.7%) with hospital originated prescriptions and 30 (21.4%) with oncology originated prescriptions. Of patients with two ADRs (n=22) in the study period, two (9.1%) occurred with community prescriptions, six (27.3%) with hospital prescriptions and 14 (63.6%) with oncology prescriptions. Prescriptions originating from oncology accounted for 15/16 patients with three or more ADRs. One patient, with three ADRs in the study period, had two ADRs to hospital originated prescriptions and one ADR to a community prescription.

4.4.5 ADR Assessments (Reaction Type, Causality, Severity, Avoidability)

238/249 (95.6%) ADRs were classified as type A (predictable from the known pharmacology) with 11/249 (4.4%) being type B (not predictable). Assessment of causality using the Liverpool ADR CAT showed the highest proportion of cases (94/249, 37.8%) to be in the 'definite' category. Oncology cases accounted for 80 of these 94 definite causality cases (Table 4). 41/55 (74.5%) of possibly or definitely avoidable cases were classified as 'definite' or 'probable'. 92/238 (39.1%) type A reactions were assessed to be of definite causality. 8/11 (72.7%) type B reactions were assessed to be 'possible.' The majority (16/17, 94.1%) of the more severe reactions (≥ Grade 4 adapted Hartwig severity score) were assessed to have definite or probable causality (**Table 4.7**). ADR assessments by age groupings (not standardised) are reported in **Table 4.8**.

Table 4.7 Origin of prescription of ADR drugs by type of reaction, severity score, avoidability and causality assessment

		Oncology (n=120)	*Hospital (n=85)*	*Community (n=44)*
Type of reaction	*A*	119 (99%)	85 (100%)	34 (77%)
	B	1 (1%)	0 (0%)	10 (23%)
Severity Score	*1*	5 (4%)	1 (1%)	1 (2%)
	2	0 (0%)	2 (2%)	0 (0%)
	3	111 (92%)	74 (87%)	38 (86%)
	4	2 (2%)	8 (9%)	4 (9%)
	5	2 (2%)	0 (0%)	1 (2%)
Avoidability	*Unavoidable*	112 (93%)	57 (67%)	25 (57%)
	Possibly	6 (5%)	25 (29%)	14 (32%)
	Definitely	2 (2%)	3 (4%)	5 (11%)
Causality	*Possible*	9 (7%)	51 (60%)	23 (52%)
	Probable	31 (26%)	24 (28%)	17 (39%)
	Definite	80 (67%)	10 (12%)	4 (9%)

Table 4.8 ADR assessments (type, causality, severity and avoidability) by age

		Age				
		0-11 mths *(n=27)*	***1-3 yrs*** *(n=51)*	***4-6 yrs*** *(n=51)*	***7-11 yrs*** *(n=50)*	***12-16 yrs*** *(n=70)*
Gender	*Male*	14	25	29	32	35
	Female	13	26	22	18	35
Type of reaction	*Type A*	27	45	50	48	68
	Type B	0	6	1	2	2
Causality	*Possible*	13	17	12	22	19
	Probable	12	12	16	12	20
	Definite	2	22	23	16	31
Origin of Prescription	*Hospital (Oncology)*	11 (5)	35 (26)	49 (31)	45 (21)	65 (37)
	Community	16	16	2	5	5
Severity scale	*< 3*	2	2	1	2	2
	3	24	45	46	45	63
	>3	1	4	4	3	5
Avoidability	*Unavoidable*	20	40	38	41	55
	Possibly	5	9	10	8	13
	Definitely	2	2	3	1	2

223/249 (89.6%) of the ADRs were classified as grade 3 ('required treatment or drug administration discontinued') according to the Hartwig severity scale, as we defined anyone requiring admission to hospital as 'needing treatment.' 14 (5.6%) were classified as grade 4 ('resulted in patient transfer to higher level of care') including respiratory depression (8), immunosuppression (4), neutropenia (1), fever/seizure (1) and leukencephalopathy (1). Three ADRs were classified as grade 5 ('caused permanent harm or significant haemodynamic instability'). Two of these most severe ADRs occurred in oncology patients with febrile neutropenia and septicaemia and the remaining case was a child who required bowel resection for ileus, with impacted faecal matter, following treatment with loperamide. No ADRs contributed to death. Two ADRs were classified as grade 2 ('drug dosing or frequency changed, without treatment') and seven were classified as grade 1 with ('no change in treatment with the suspected drug').

We determined the avoidability of ADRs by the method of Hallas et al. 194/249 (78%) of the ADRs were assessed as 'unavoidable,' while 45 (18%) were classified as 'possibly avoidable,' and 10 (4%) as 'definitely avoidable.' Five of the cases deemed to be definitely avoidable were associated with hospital prescribed drugs and five with community prescribed (**Table 4.9**). 31 possibly avoidable cases were associated with hospital prescribed drugs and 14 with community prescribed. 114 (47.5%) of the ADR admissions occurred in oncology patients accounting for 120 ADRs. Of the ADRs due to oncology drugs, 112/120 (93.3%) were unavoidable, with a further six being possibly avoidable and two definitely avoidable. These

'definitely avoidable' cases were oncology patients with constipation following treatment with vincristine and ondansetron (with one also having dihydrocodeine) without laxative prophylaxis.

Table 4.9 Assessments of potentially avoidable ADRs

		Possibly avoidable	*Definitely avoidable*
Type of reaction	*A*	45	8
	B	0	2
Severity Score	*1*	0	1
	2	1	0
	3	35	8
	4	9	0
	5	0	1
Causality	*Possible*	13	1
	Probable	20	7
	Definite	12	2
Origin of prescription	*Hospital*	31	5
	Community	14	5

Of the ADR admissions not associated with oncology patients (n=126 admissions and 129 ADRs), 82/129 ADRs (63.6%) were classified as unavoidable, 39 (30.2%) as possibly avoidable and eight (7.6%) as definitely avoidable. The eight 'definitely avoidable' cases comprised four patients prescribed antibiotics where the antibiotic choice or indication was deemed to be inconsistent with good practice, one patient with intestinal obstruction being treated with loperamide who had not passed stool for two days prior to admission, one patient who had a seizure after alimemazine having had two previous occurrences of seizure following the anti-histamine, one patient with deranged renal function which improved after cessation of captopril where improved renal function monitoring may have avoided the ADR, and one patient who presented with adrenal suppression following two years of continuous treatment with intranasal corticosteroids. The possibly and definitely avoidable cases and the reasons for their allocation are summarised in **Table 4.10**.

Table 4.10 Possibly and definitely avoidable cases and explanation of assessment result

?Avoidable	Frequency	ADR(s)	Drug Classes	Reason for potential avoidability
Definitely	3	Diarrhoea and/or vomiting	Anti-bacterial	Inappropriate indication, signs/symptoms of viral illness
Definitely	2	Constipation	Cytotoxics, Drugs used in nausea, Opioid analgesia	Appropriate Prophylaxis not used
Definitely	1	Lip swelling, rash	Anti-bacterial	Same ADR previously to same medication
Definitely	1	Seizure	Antihistamine	Same ADR previously to similar medication
Definitely	1	Adrenal suppression	Corticosteroids	Avoidable with more rational prescribing (prolonged use of drugs) and improved monitoring
Definitely	1	Intestinal obstruction	Anti-motility drugs	Could be prevented by improved parent/patient education
Definitely	1	Deranged renal function	Drugs affecting the renin-angiotensin system	Avoidable with improved monitoring
Possibly	9	Hypoglycaemia	Drugs used in diabetes	Avoidable with improved patient education (e.g. appropriate insulin use when unwell) and more rational prescribing
Possibly	8	Respiratory depression	Drugs used in status epilepticus, Hypnotics	Alternative medicine available, Multiple doses given - avoidable with more rational prescribing

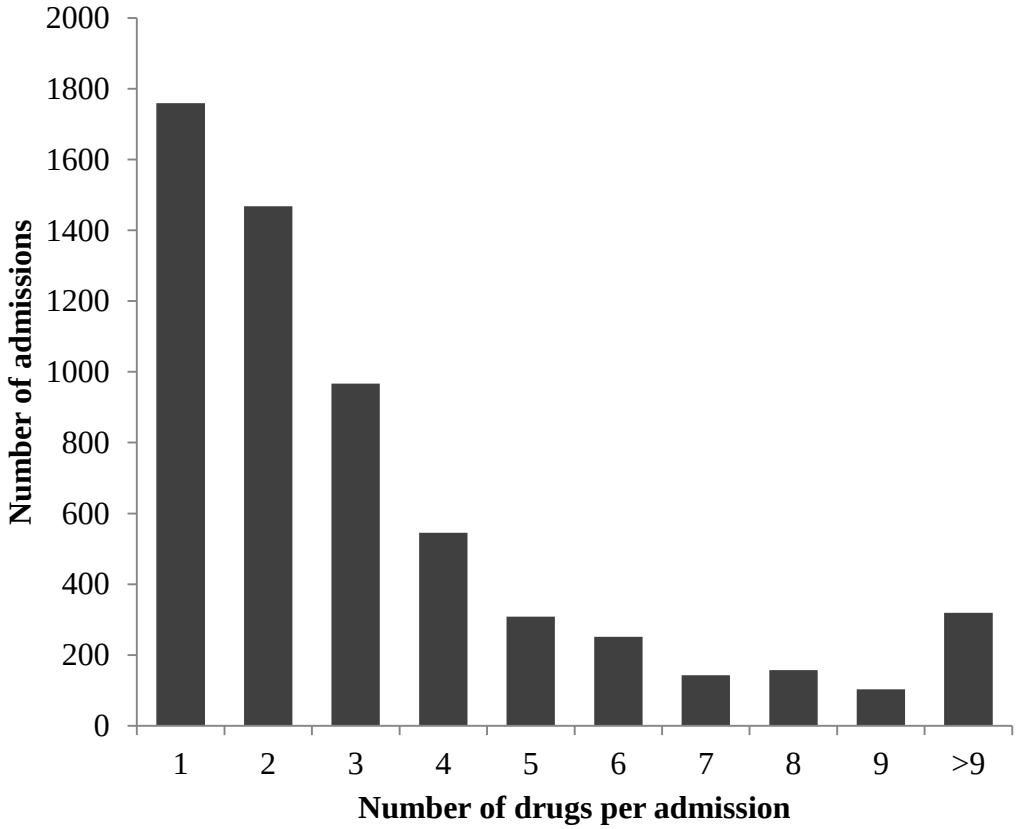
Possibly	6	Diarrhoea/vomiting	Anti-bacterial	Inappropriate indication, symptoms suggested viral infection
Possibly	5	Constipation	Antiepileptic drugs, Opioid analgesia, Drugs used in nausea, NSAIDs, Cytotoxics, Calcium-channel blockers, Calcium supplements	Prophylaxis not used
Possibly	4	Immunosuppression	Drugs affecting the immune response, Corticosteroids	Possibly Avoidable with improved monitoring of drug levels, Avoidable with more rational prescribing
Possibly	2	Haematemesis	NSAIDs	Avoidable with more rational prescribing (less NSAID use)/improved patient education
Possibly	1	Neutropenia	Cytotoxics	Same ADR previously at same dose of medication
Possibly	1	Neutropenia, thrombocytopenia, anaemia	Cytotoxics	Superficial infection after recent admission with febrile neutropenia. Possibly avoidable by prolonging antibiotic use or commencing GCSF
Possibly	1	Hyperglycaemia	Corticosteroids	Avoidable with more rational prescribing (prolonged course steroids used)
Possibly	1	Hyperglycaemia	Parenteral preparations	Avoidable with more rational prescribing (more judicial use) or improved monitoring
Possibly	1	Seizure	Posterior pituitary hormones	Possibly inappropriate medication used for a patient with seizures

Possibly	1	Diarrhoea	Laxatives	Avoidable with improved patient education
Possibly	1	Ileus	Opioid analgesia	Avoidable with more rational prescribing (possibly use alternative analgesia)
Possibly	1	CNS depression	Opioid analgesia	Avoidable with improved patient education
Possibly	1	Vomiting	Cytotoxics	Possibly avoidable with more appropriate anti-emetic prophylaxis
Possibly	1	Gastritis	Corticosteroids	Previous gastritis. Possibly avoidable with improved prophylaxis
Possibly	1	Hypercalcaemia	Vitamins	Avoidable with improved monitoring

4.4.6 Drug exposure prior to acute admission

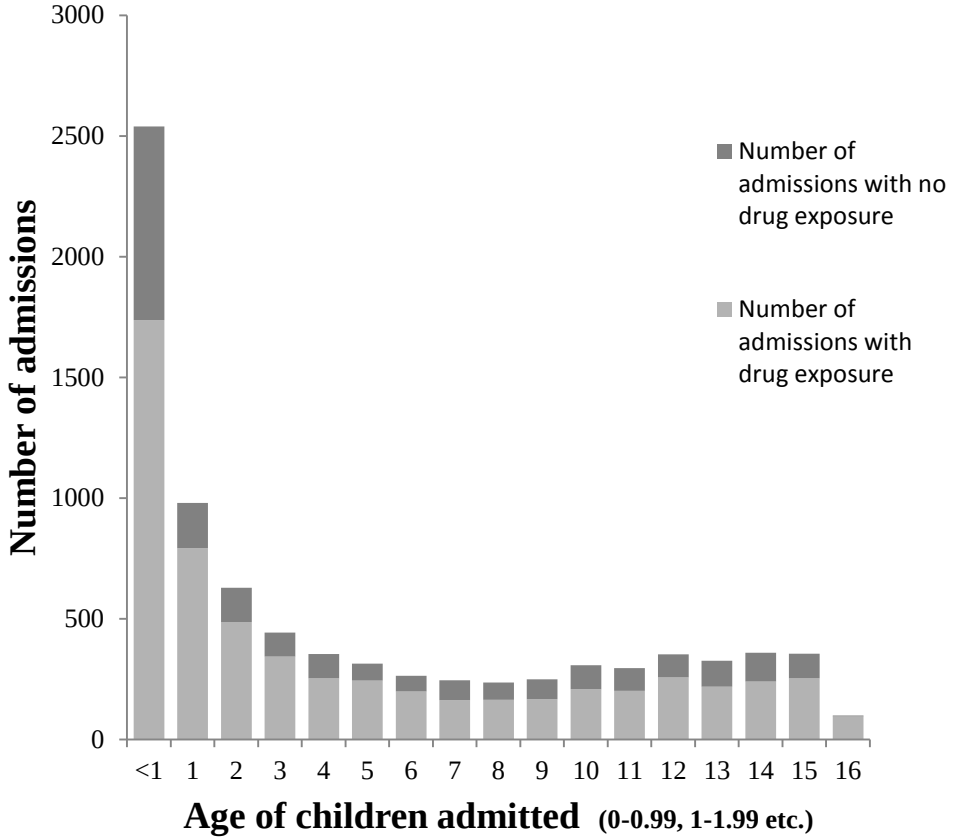
Of 8345 admissions, 6020 (72.1%) were exposed to medication in the two weeks prior to admission. 3417 (56.8%) of these were male and 2603 were female (43.2%). The median number of drugs taken was 2 (IQR 1, 4), with one child exposed to 34 courses of medication, due to an admission for cardiothoracic surgery, in the two weeks prior to re-admission. **Figure 4.2** shows the distribution of drugs per admission.

Figure 4.2 Number of drugs per admission



Children under 1 year of age accounted for the most number of admissions. 1737/2539 (68.4%) of under one year olds had been exposed to medication prior to admission (**Figure 4.3**). Of the other children admitted, the age group most frequently exposed to medication was the 16 year old group (95/99 admissions, 96%). Children aged seven were the least exposed to medication (163/245, 66.5%) prior to admission.

Figure 4.3 Age (one year intervals) and number of children exposed to medication prior to admission



Of 6020 children exposed to at least one medicine prior to admission, those aged 16 years were exposed to the most number of drugs per admission with a mean of 5.93 (95%CI 4.92, 6.93) drugs. Children aged less than one were the least exposed to medication with a mean of 2.82 (95%CI 2.71, 2.93) drugs per admission (**Figure 4.4** and **Figure 4.5**).

Figure 4.4 Mean number of drugs taken by age (one year intervals)

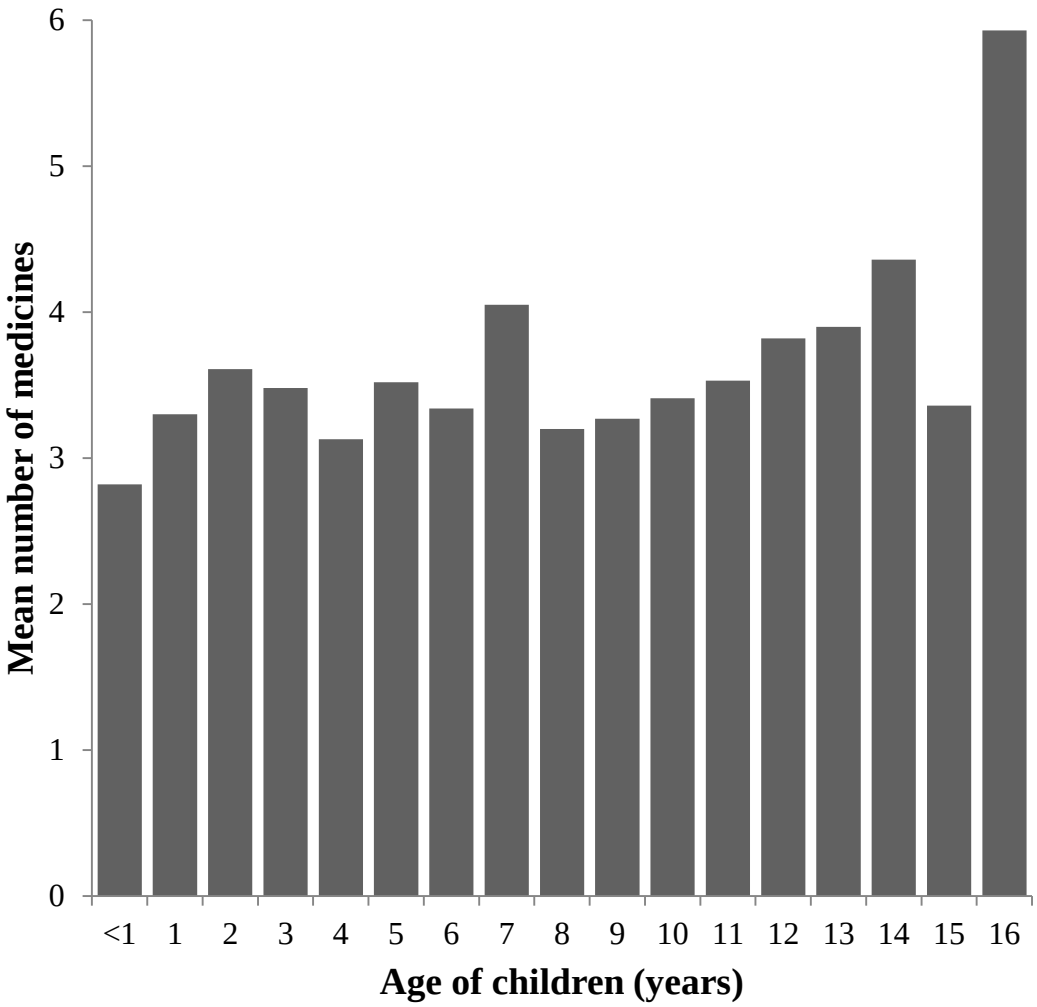
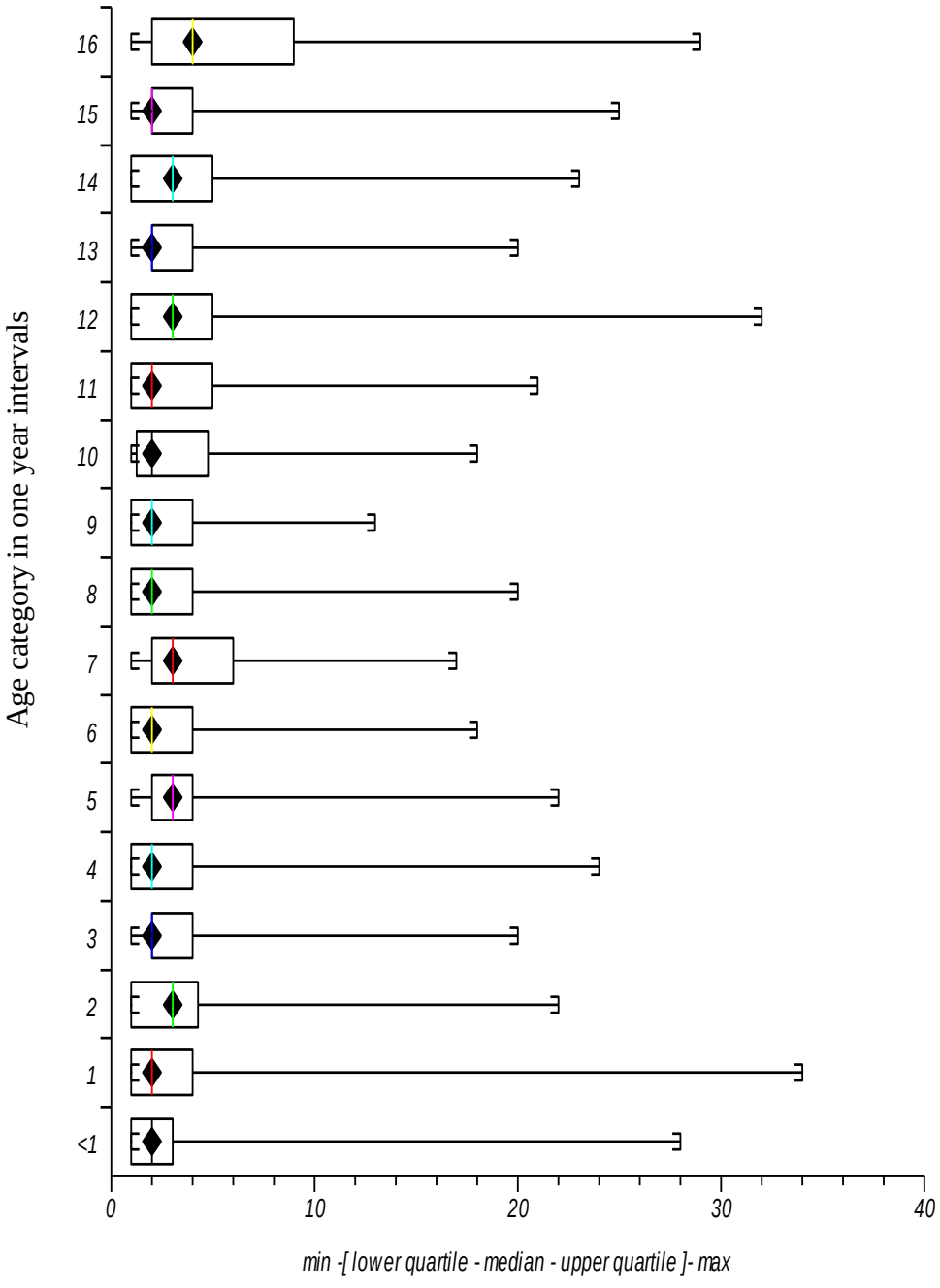


Figure 4.5 Box and whisker plot of number of medicines taken by age group



4.4.7 Cost of ADRs and Length of Stay

The mean cost of 238/240 ADR admissions to the study hospital, using information provided by the finance department, was calculated to be £4753 per admission (95% CI £3439, £6066). Cost data were missing for two ADR admissions: one oncology and one non-oncology patient admission. The mean cost of 113 oncology ADR admissions to the study hospital was £5428.91 (95%CI 4041.24, 6816.58). The mean cost of 125 non-oncology admissions was £4141.4 (95%CI 1963.84, 6318.95). The mean length of stay of all 240 ADR admissions was 5.67 (95%CI 3.28, 8.06) days. The mean length of stay for the oncology admissions was 5.45 (95%CI 4.35, 6.55) days, and 5.87 (95%CI 1.4, 10.34) days for the non-oncology admissions.

Data from the Health and Social Care Information Centre (NHS) (HospitalEpisodeStatistics) showed, in one year between 2009/2010, the total number of paediatric emergency admissions in England was approximately 597,800 (includes paediatrics and paediatric surgery, cardiology and neurology). We estimate the annual mean cost of paediatric ADR admissions to the NHS in England to be £82.4M using the mean cost of all ADR admissions to the study hospital. Using the upper and lower confidence intervals for both our estimate of ADR incidence, and study hospital costs, we estimate the cost to the NHS in England of paediatric ADR admissions to be between £51.4-119.7M.

4.5 DISCUSSION

This prospective observational study is the largest of its kind in children and the only one to comprehensively assess causality, type of reaction (predictable or not), severity, origin of drug prescription and avoidability. This is the first large study in children to investigate risk factors for the occurrence of an ADR-related admission. The majority of admissions associated with ADRs in children occurred as a result of prescriptions originating in hospital. Potential preventative strategies for ADRs causing admission in children should therefore be targeted at hospital prescribing. Analysis of the 'definitely avoidable' ADRs in this study suggests that more careful attention to practical aspects of care, such as improved monitoring, following prescribing guidelines, improved patient education, and heightened suspicion about potential adverse reactions could lead to a reduction in the frequency of ADRs causing admission. The avoidability assessment method used in this study was not subject to validation in other studies. A more accurate and validated avoidability assessment method might allow for more accurate estimates of avoidable ADRs and allow for a more targeted approach to consideration of prevention.

The incidence of ADRs causing admission in this study (2.9% (95% CI 2.5, 3.3)) was similar to the incidence in two systematic reviews, 2.09% (95%CI, 1.02, 3.77) and 1.8% (95% CI 0.4, 3.2), but was significantly less than that of a large US study published in 1988 (Mitchell et al. 1988). In that study, the top three drugs causing ADRs were phenobarbital, aspirin and phenytoin, all of which are used in children much less now than in 1988. Since these medicines were hardly used in our

population, it is possible that the discrepancy in incidence rates relates in part to the reduction in use of these medicines.

This study of ADRs causing admission of children to hospital was included in a more recent systematic review of studies of ADRs in children by Smyth et al published in 2012 (Smyth et al. 2012). Of 102 studies included in the review, 72 had assessed causality, 34 had assessed severity and only 19 studies reported avoidability assessments. A pooled estimate of 42 studies investigating ADRs causing admission showed an incidence rate of 2.9% (95% CI 2.6, 3.1). Of 19 studies reporting avoidability, only three had reported the case-specific rationale for potentially avoidable ADRs. The study detailed in this chapter provides the rationale for assessing 55 ADR admissions as 'possibly' or 'definitely' avoidable, out of the 62 avoidable ADR cases detailed in the systematic review by Smyth et al. This study should therefore encourage health professionals to aim for prevention, rather than treatment, of ADRs causing admission in children.

This prospective observational study is the first to attempt the identification of possible risk factors for ADRs causing hospital admission in children. Older children, those exposed to more medicines in the two weeks prior to admission and oncology patients were shown to have an increased risk of ADR in this study. Girls showed a trend towards being more likely to experience an ADR than boys but this result was not statistically significant. An increased risk of ADRs occurring in female gender has been described in studies in adult populations (Davies et al. 2009; Zopf et al. 2008).

The data used for the risk factor analysis was extracted from patients exposed to medication prior to their first admission, due to the occurrence of some patients having multiple admissions (some with multiple ADR admissions). Therefore, the univariate and multivariate analyses were of this data. This sample was representative of the larger sample of all admissions. All other data described in this study included all admissions to enable a more complete description of the frequency and nature of the burden of ADRs to paediatric patients. This allows for readers to compare the data more readily to their own settings.

The only measure of drug exposure used to assess risk factors for ADR occurrence in admissions was the count of drugs patients were exposed to. This was because of limitations in the dataset, as discussed in Chapter 2. There have been studies, including two studies from the ADRIC research program, assessing off-label and unlicensed drug use in children (a well-known theoretical problem and risk in terms of paediatric drug safety) in relation to the risk of ADR occurrence, without consensus as to the overall effect. The limitation of the dataset in this study was mainly from parental history of drug exposure. In part, this may be overcome with linked electronic patient records between community and hospital settings with electronic prescribing which would remove some of the reliance on clinical history. However, there would still be problems with reliance about adherence to both prescribed and over-the-counter medications. Electronic counters for medication dispensers and drug-levels are among some suggested solutions to these problems but are likely too impractical and costly for a study of this size.

Causality was determined, of the ADR cases, using a novel causality tool, the Liverpool ADR CAT, which was developed during the process of undertaking our study (Chapter 3). The majority of ADRs were classified as 'definite,' and most of these occurred in oncology patients. In order for a case report to achieve a score of 'definite' it would have to include a positive re-challenge or a previous history of the ADR to the same medication, a condition which these oncology-related ADRs satisfied. Type A reactions were more likely to be assigned a definite or possible causality and type B reactions were more likely to be deemed possible. This may be due assessors being less confident with type B ADRs, which are unpredictable and less frequent. The more severe reactions in our study were more often assessed to have definite or probable causality. This may reflect a confidence in assessing severe ADRs, which are more likely to be described in the drug safety literature.

The majority of the ADRs seen during the study were oncology related. These were mainly children with a febrile illness who developed neutropenia 1-2 weeks after intravenous chemotherapy. Clearly, patients with malignancy are often exposed to medications that cause ADRs (Lau, Stewart & Dooley 2004), such as neutropenia (with fever), nausea, vomiting, diarrhoea, anaemia and bleeding secondary to thrombocytopenia, all of which may require hospital admission. ADRs to cytotoxic chemotherapy drugs are expected and, for the most part, may be unavoidable given the nature of the underlying illness and the treatment options currently available. Although several studies have evaluated a potential preventative strategy for neutropenia (Sung et al. 2004), no definitive evidence exists regarding the routine prophylactic use of

granulocyte-colony stimulating factor (GCSF) to prevent ADRs due to myelosuppression (Sasse et al.).

Steroids, along with other immunosuppressants, increase the risk of infection (Kelly et al. 2010). Immunosuppressants featured frequently in our study as causative agents for ADRs. The nature of ADRs associated with immunosuppressive therapy included proven bacterial infections and viral infections (e.g. shingles). Although we recognise that infections may also occur in healthy children, the role of immunosuppressive therapy in predisposing patients to infections is well recognised (Glück et al. 2005; Shepherd et al. 2008; Toruner et al. 2008).

Another frequently recorded ADR in our study was post-operative bleeding, in particular secondary haemorrhage following elective tonsillectomy. The majority (23/28 admissions) of these occurred in patients exposed to intravenous Dexamethasone as prophylaxis for post-operative nausea and vomiting (PONV), and NSAIDs, with Ibuprofen being used commonly in the post-operative period. A few patients received either Dexamethasone or NSAIDs. Dexamethasone has been linked to post-tonsillectomy bleeding (Czarnetzki et al. 2008) but its role, and the role of NSAIDs, in causing secondary haemorrhage in these children needs further study (Cardwell, Siviter & Smith 2005; Steward, Welge & Myer 2003). However, intra-operative steroid has played a major role in improving outcomes for PONV in children undergoing operations (Goldman, Govindaraj & Rosenfeld 2000; Steward, Welge & Myer 2003) and has enabled daycase surgery for many conditions, thereby reducing the length of stay in hospital.

Respiratory depression following treatment of seizures with benzodiazepines, a well-recognised and potentially serious event (Stewart, Harrison & Dooley 2002), was the cause of eight admissions to PICU for ventilation until recovery. Some of these cases were transfers from other regional district general hospitals to the study hospital tertiary PICU. Some, in fact, occurred as a result of rectal diazepam being used by paramedics in out-of-hospital care of seizures. Drugs used to treat status epilepticus have been widely studied and their efficacy and adverse reactions compared (McIntyre et al. 2005; McMullan et al. 2010). There may be drugs other than diazepam which have an improved benefit-risk ratio when used to treat seizures in paediatric patients (Appleton, Macleod & Martland). Further research is therefore warranted to optimize strategies for treating seizures, for both in and out-of-hospital care.

Data collection was undertaken by a multi-disciplinary team consisting of a paediatric registrar, a pharmacist and a nurse. In this study, the nurse identified ADR cases less frequently than either the pharmacist or paediatric registrar, who identified possible ADRs at the same frequency. Despite the difference in ADR identification between the three investigators, there were no ADRs identified in a senior investigator review of 217 cases deemed not to be ADRs by the data collection team. The differences in ADR identification between the members of the data collection team is unexplained but may have occurred because of daily variation in numbers and types of admission to the study hospital: the research nurse assessed fewer patient admissions to oncology despite approximately equal numbers of data collection days between the three investigators.

The ADRs reported in this study highlight some of the adverse consequences of drugs in children. A limitation of this study is that we have not taken into account the benefits of these medications. Furthermore, we cannot be certain of the aetiological fraction (the risk of an event occurring in the presence of a risk factor) for some of the drugs in our study, for example immunosuppressants, in their contribution to the stated reactions. For these drugs, more research is needed to accurately assess their contribution to ADRs and the ill-health of children, to allow for more detailed risk-benefit evaluation.

In this study, we have not considered ADRs caused by medications during inpatient stay in hospital. This aspect of drug reactions is likely to add greatly to the burden of ill-health to children and requires investigation of paediatric inpatient ADRs using a similar prospective study design to accurately identify the epidemiology of the problem. The first systematic review of ADRs in children by Impicciatore estimated the incidence of ADRs among paediatric hospital inpatients to be 9.53% (95% CI 6.81,12.26), with 12.3% of the total reported as severe reactions. The more recent comprehensive systematic review by Smyth et al did not provide a pooled estimate from the 51 inpatient ADR studies included (due to the varying sample size and incidence rates) but almost half of the studies had an incidence of more than 10%. Both these reviews provide evidence that ADRs among paediatric inpatients is a significant problem. A proportion of these ADRs are likely to be serious due to the types of medicine prescribed in inpatients vs those in outpatients and some of them may lead to an increase in length of stay. The associated financial costs are likely to be substantial.

The cost of ADRs causing paediatric admission to the NHS in England was calculated using knowledge of the cost of admissions to the study hospital, our estimate of the incidence of ADRs causing admission and an estimate of total paediatric admissions annually to hospitals in England. Information regarding total UK annual paediatric admissions, obtained using Hospital Episode Statistics, does not include emergency paediatric admissions from other specialties, thereby underestimating the total number of emergency paediatric admissions to hospitals in England. Although the ADR admission incidence from this study includes oncology cases, which is not included in the total annual admissions number used for our cost calculation, our estimate of costs of paediatric ADR admissions may be an underestimation.

The cost estimates provided in this study are rudimentary and are reported only to highlight that there is likely to be a significant cost to healthcare from ADRs causing admission in children. Our estimate takes no account of indirect costs associated with ADRs and does not consider ADRs occurring in other settings. There is likely to be a greater burden to healthcare from inpatient ADRs amongst hospitalised children and, therefore, our crude cost reporting is likely to reflect the tip of the iceberg economically in relation to ADRs in children. Future work in this area would need specific evaluation by investigators with specialist expertise in the field assessing both direct and indirect costs. This work could also allow us to more fully understand any economic impact from interventions aimed at reduction in harm from ADRs in children.

Clarification of the ethical aspects to this study was sought by written communication and occurred simultaneously to the funding application. After consideration, the National Research Ethics Service considered this study should be described as audit, due to the study collecting information routinely captured during clinical care (demographics, clinical presentation, medication history, etc.). The obvious advantage of this is the negation of need for individual patient/guardian consent, a task which would likely be almost impossible for a study of this magnitude without a significant increase in resources. A significant disadvantage was encountered when considering publication of results and the depth with which data about ADR cases could be described, due to patient confidentiality and the necessity to guard patient identifiable information. Another potential disadvantage may have occurred when seeking approval from the host hospital research governance processes, as a perceived lack of weight from the study being deemed audit by a national body may have led to increased scrutiny and an increase in workload for the study team from those processes.

Several sources of bias are likely to occur in this large study despite the prior undertaking of a pilot study. Some of these sources of bias are likely to represent the inexact science of identifying and attributing causality of ADRs. There is likely to have been some recall difficulties in parent/carer histories of both symptoms in the children and drugs taken. An illness in a child and subsequent admission to hospital can be a stressful event for any family and this may add to recall difficulties.

In a study of this nature, when investigators are collecting data and assigning outcome (ADR occurrence vs non-occurrence), there is likely to be some element of interviewer bias. This occurs because there is no gold standard for identification of an ADR and no standardisation for causality assessment. This may represent the apparent difference in numbers of identified ADRs for one of the investigators compared to the other two. Also, there is a risk of misclassification due to lack of standardisation of some assessments, e.g. causality, and unreliable assessment methods, e.g. avoidability. This might lead to over-estimation of the severity and burden of the problem of ADRs.

Although the findings from this large study are likely to resonate with many paediatric settings caution should be exercised in assessing the generalizability of the results and conclusions. The children's hospital within which the study took place provides secondary and tertiary level paediatric care, a feature which is not replicated across all child healthcare settings in the UK. The hospital provides tertiary specialty care for most, but not all, specialties and, therefore, alternative tertiary care settings will have specific differences in their patient case mix and medication use. The hospital is host to the busiest children's AED in the UK and the increased volume of patients exposed to healthcare and medicines may play a part in risk of occurrence of ADRs. The local population is known to suffer from higher than average (UK) levels of deprivation, and worse health outcomes in many conditions, and, whilst not investigated in this study, this may be a risk factor for occurrence of ADR. Internationally, patterns of populations, disease and drug use are different than in the UK and this is likely to add to variability in ADR occurrence, nature and impact. Nonetheless, our study highlights

the problem posed by ADRs associated with hospital admissions and this is a problem both in the UK and internationally.

The results of this study will be used to inform paediatric pharmacovigilance practice. We have demonstrated that ADRs cause admissions to a paediatric hospital and some of these are serious and potentially avoidable. Strategies to reduce the burden of ill-health from these ADRs are needed. Prevention will depend on whether an ADR is avoidable or not. ADRs that are avoidable by applying existing knowledge require efforts to implement good prescribing practice. The vast majority of ADRs identified were Type A (predictable or dose related). Some dose-related ADRs may reflect a lack of knowledge about pharmacokinetics and pharmacodynamics in children and may be amenable to prevention through personalised dosage regimens (for example by developing better pharmacokinetic models). Other ADRs that are currently unavoidable may be ameliorated by co-medication, for example concomitant use of laxatives to prevent constipation. Since many ADRs are unavoidable in the light of current knowledge, there is likely to be a continuing burden of ADRs in paediatric hospitals and further research is needed. Consideration should also be given to how suspected ADRs are handled in hospitals to improve identification of, and communication about, ADRs.

CHAPTER 5 SUMMARY, DISCUSSION AND FURTHER WORK

ADRs causing hospital admission are a considerable burden to the paediatric population, the extent of which has not been studied in detail in the UK (Smyth et al. 2012). Chapter 2 of this thesis describes a pilot study, which aimed to inform a much larger prospective study providing more detailed evidence of the burden of ADRs in children. The information obtained from analysis of the methodological difficulties encountered, such as defining what constitutes an admission, identifying admissions, data collection and the assessment of patient information and ADRs, all contributed toward the design of a larger study.

Given the problems of assessing ADRs in children in the observation area, where children stayed within the hospital for less than 4 hours, these patients were not included in our larger study. Short-stay paediatric assessment wards/units, used for assessment, investigation, observation and treatment of children with acute (or acute on chronic) conditions, are now very commonplace in the UK. In our pilot study, a small but significant number of patients in the observation ward had experienced ADRs as a probable cause for their attendance and their investigation and treatment may be a significant burden to the AED department. Undoubtedly, as these patients were not admitted to a hospital ward, some of these reactions could have been assessed and treated (or reassurance given) in a primary care setting. This aspect of ADRs in

children warrants further investigation as to the frequency, nature, cost and avoidability of these reactions.

Assessing the causality of ADRs using the Naranjo ADR probability scale during the pilot study, and early phase of data collection and assessment in our larger study of ADRs causing paediatric hospital admissions, proved to be unreliable according to expert group consensus opinion. Our group included experts in pharmacology, paediatrics, neonatology, pharmacy and statistics. Many ADRs that were thought to be clear-cut 'definite ADRs', such as those with a positive re-challenge with oncological cytotoxic chemotherapy, were assigned a category of 'probable', when using the Naranjo scale. This was due to some questions in the scale being redundant in the context of current medical practice (e.g. use of a placebo), or being rarely answered positively, thereby lowering the total achievable score and sensitivity of the tool.

Chapter 3 of this thesis details these difficulties and describes the development and evaluation of a new algorithmic causality tool, to more accurately describe the causality of the ADRs within our research programme. This new method, the Liverpool ADR CAT, was shown to have moderate to good inter-rater reliability. It performed as well as the Naranjo tool with the first set of study cases that were assessed, and better with a second set. When used in a large prospective study of paediatric ADRs, the new Liverpool ADR tool assigned a broader range of causality categories than the Naranjo tool. This was thought to be advantageous and more appropriate for the assessed case mix by the consensus group.

The study described in Chapter 4 of this thesis, which assessed the incidence and nature of ADRs causing admission to a UK paediatric hospital, showed that 2.9% of acute admissions over the course of one year were associated with an ADR. The drug classes most commonly associated with ADR admissions were cytotoxics (110 admissions), corticosteroids (102), NSAIDs (31), vaccines (22), immunosuppressants (18) and anti-bacterials (16). The most common ADRs were immunosuppression (98) and cytotoxic chemotherapy related reactions, in the form of neutropenia (89) and thrombocytopenia (55).

Almost half of the acute ADR admissions occurred in children receiving cytotoxic chemotherapy for malignancy. The children affected had received intravenous chemotherapy as inpatients, before being discharged from hospital, only to be re-admitted subsequently for treatment of the adverse reactions caused by their oncological therapy. The adverse reaction most commonly requiring treatment was febrile neutropenia. This is in keeping with other paediatric admission studies in tertiary children's hospitals from other countries, and suggests that this group of patients still suffer from troublesome ADRs, despite many years of evidence of the problem (McKenzie et al. 1976; Mitchell et al. 1988). The treatment of febrile neutropenia causes a significant burden to children undergoing cytotoxic therapy (Lau, Stewart & Dooley 2004).

Although paediatric oncology patients are known to be at significant risk of serious ADRs, this study also highlighted some of the ADRs that occur commonly in other children. Of note, NSAIDs and vaccines were commonly implicated drug classes,

causing ADR-related admissions during this study. These are both classes of drugs used frequently in children (DoH 2012; Neubert et al. 2010). Of the non-oncology patients, about two thirds of the causative drug prescriptions had a hospital origin. This is likely due to the severity of illness of children being treated by secondary care, as opposed to primary care, and the drugs necessary in treating severe acute or chronic childhood conditions.

The studies in this thesis investigated ADRs causing admission of children to a tertiary paediatric hospital. We have shown that a small, but significant, percentage of acute paediatric admissions are associated with ADRs. This is an important finding but is only one piece of a pharmacovigilance jigsaw. Children who are admitted to hospital invariably receive more medicines and are, therefore, at further risk of ADRs. The systematic reviews published by Impicciatore, Clavenna and Smyth highlight the increased incidence of ADRs occurring in children within the hospital setting after admission (Clavenna & Bonati 2009; Impicciatore et al. 2001). The incidence of ADRs among inpatients is likely to be of a magnitude of three to four times that of ADRs causing admission. However, there is little detailed research evidence of the burden of this problem within the UK paediatric population.

ADRs causing admission can be assessed at one point in time and cases need a limited amount of follow-up to collect data to aid in causality assessment. However, patients can stay many days, weeks or months when admitted to hospital and may have many ADRs, occurring at different times during the admission. This poses a different set of problems for data collection, case assessment and data analysis for an inpatient study

and needs an alternative methodology. A large inpatient study of ADRs has been undertaken by the ADRIC research group.

There are other settings where ADRs are likely to cause a significant burden to patients. Clinicians caring for neonatal patients use medicines, often off-label, in a very vulnerable patient group in whom signs and symptoms are often vague (e.g. vomiting, crying, unsettled, irritable, etc.) and difficult to identify. A similar picture may be viewed in both surgical theatres and paediatric intensive care where patients are likely to be sedated and have an altered conscious level. In addition, patients may be very unwell with life-threatening illness, requiring intensive support with vast amounts of medication use, which may pre-dispose them to an increased risk of ADRs. The methodology to assess the frequency and nature of ADRs among these inpatients would need to take account of these difficulties and assessment tools would need to address the uncertainty of clinical signs in some patients.

There are likely to also be a large number of patients being seen for relatively less severe ADRs in outpatient settings, daycare wards and in primary care settings (both in and out-of daytime working hours). Whilst these patients may not have such serious reactions they are likely to pose a significant burden to healthcare settings. Also, even the most minor ADR can cause concern amongst patients and carers and there may be indirect costs to the economy from the time needed to seek medical attention for these problems.

5.1 IDENTIFYING ADRS

The methodology used in the large prospective study in this thesis was labour intensive and comprehensive; three full-time multidisciplinary research fellows (a paediatric registrar, a pharmacist and a paediatric nurse) assessed all acute admissions each day for one year for occurrence of ADRs causing admission in children. There is a need for ongoing pharmacovigilance within healthcare settings to monitor drug-related harms but this methodology is unlikely to be acceptable for individual settings, due to the time needed and cost. Also, our study methodology did not investigate ADRs occurring in inpatients, or adverse drug events in admissions or inpatients, both of which are likely to cause significant harm to patients and burden to the setting. A study of inpatient ADRs would no doubt require an alternative methodology in comparison to an admission study e.g. patients can be subject to multiple admissions with potentially more than one ADR occurring during each admission.

Others have used alternative methodology such as nurse assessment of randomly selected cases (Mitchell et al. 1979) or information technology systems (Dormann et al. 2004), combined with laboratory results, to identify cases, or signals for occurrence, of possible ADRs. Dormann et al showed their computerised ADR signal detection method, using lab parameters in adult patients, was better than clinician spontaneous reporting but did not compare computerised signal detection against systematic case analysis (Dormann et al. 2000). These methods still need clinical input from experienced physicians, with an interest in ADRs, to assess the cases identified.

In the study in Chapter 4, the doctor (85/ 2634, 3.2%) and pharmacist (96/2969, 3.2%) identified a similar number of ADRs and both identified significantly more than a nurse investigator (59/2742, 2.2%). Although no false negative cases were identified from a senior investigator review of a random selection of cases, this difference in detection rates remains unexplained. It is possible that the nurse investigator had a lower sensitivity for identifying ADR cases. This difference may be an individual clinical difference but may need further investigation in other settings to optimise data collection methodology, should future investigators wish to replicate this study.

5.2 ASSESSMENT OF ADRS

Assessments of type of reaction, severity, causality and avoidability were undertaken for the ADRs investigated in the studies contained within this thesis. There is ongoing debate as to the best methods for assessing and describing ADRs, with no universally accepted methods for any of the assessments (Smyth et al. 2012). Type of reaction and severity assessments can be classified succinctly using structured guidance. However, assessment of causality and avoidability is not so straightforward. There are many causality tools used by different research groups and regulatory authorities with no consensus as to which is best.

5.2.1 Causality assessment

In this thesis, we present an alternative quick and reliable causality assessment algorithm (the Liverpool ADR CAT). This tool underwent an extensive internal

validation using spontaneous ADR reports and published case reports. The assessment tool has been published in an open access journal in the hope that other investigators use it to undertake external validation studies (Gallagher et al. 2011). This could happen in the following ways:

- Researchers could assess using the tool for spontaneous reports from their own studies or settings, evaluating cases in different populations (paediatric vs. adult), to assess inter-rater reliability among the investigating group.

- The tool could be used to assess published ADR case reports from the literature, instead of spontaneous reports, in the same manner as above.

- The tool could be compared to other methods for assessing causality, with investigators assessing which tool may be more suitable for assessing causality of ADR cases in certain populations or in particular clinical settings (i.e. general medical vs. specialty vs. clinical scenario). Evaluation of the tool in specific clinical scenarios should be approached with caution (for example teratogenicity or hepatotoxicity) as there may be well validated tools more suited for use in those areas.

- The tool could be used to evaluate ADR cases rated by a specific investigator types. For example, the tool was internally evaluated by a multi-disciplinary group. However, it could also be used by a group of pharmacists, doctors (GP or hospital generalists/specialists) or nurses and tested for its reliability within

that group using the methodology outlined in Chapter 3 to assess inter-rater reliability.

- Investigators could also investigate the reliability of the tool between different types of investigator (e.g. nurse vs. pharmacist) or between different grades of investigator of one type (e.g. medical student vs. junior doctor vs. consultant). This type of validation study would likely need an investigator-defined 'gold standard' set of results to define the causality of the cases, as the results of the participants in such a study may show positive inter-rater reliability and agree with each other but not be consistent with an experienced rater, or group of raters.

In evaluating the tool, it was noted that the inter-rater reliability of the Liverpool tool increased upon its use in a second set of cases when assessed by the same investigators, in comparison to Naranjo where there was no increase in inter-rater reliability. One possible explanation for this increase in inter-rater reliability may be due to a learning effect within the group. It is possible that assessors learned to use the tool more effectively and answer questions more appropriately. This effect may be better understood if it were to be repeated in external validation studies of the tool.

Another way to investigate this effect would be to use a RCT methodology; investigators could compare users who have had training in use of the Liverpool causality tool, but were previously naive to ADR assessment methods, against users who are naive to formal ADR structured causality assessment methods and have not had training. Investigators could use similar methodology and analyses to those

described in Chapter 3. This trial is planned as part of the end-stages of the ADRIC programme.

Two groups of clinicians, naive to using causality assessment methods, could rate a number of ADR case reports for causality using the Liverpool assessment tool. The number of cases can not be too high, due to the time required to complete assessments, but should probably number more than 20 to provide a reliable indicator of inter-rater reliability. Clinicians could be randomised to either receiving training in use of the tool, or not, at the beginning of the study. After a short break, perhaps a month or so, training in use of the tool could then be provided to the appropriate group of clinicians and the process could be repeated with a second different set of ADR cases.

Inter-rater reliability could be assessed between the groups before and after the training intervention. The participants' results, before and after training (or not), could also be assessed against a 'gold standard' set of results as defined by the investigating group. The training might be best delivered in an electronic format as it may be difficult to get all the participants in the 'training' arm of the study together at the same time to deliver face-to-face training. Also, if the training has a positive effect on clinician's ability to perform ADR causality assessment effectively, it could easily be disseminated through a variety of electronic media and targeted at many groups (e.g. student and post-graduate doctors, pharmacists and nurses).

Such a trial would require expert statistical input into the design of the study. Several variables are unknown, namely; the number of cases to be assessed by each participant, the number of participants needed to provide a reliable indicator of inter-rater

reliability and the definition of a significant increase in inter-rater reliability. The above suggested number of cases 'should probably number more than 20 to provide a reliable indicator of inter-rater reliability' is derived from personal discussion with statistical expertise. An increase in inter-rater reliability of 'good' to 'very good' may only need a difference of 0.01 in score, whereas an increase from 0.41 to 0.59 would still remain a 'moderate' inter-rater reliability. These are questions which would need answering with a well-thought out methodology and study protocol.

5.2.2 Avoidability assessment

Assessment of avoidability of the ADR cases in our large prospective study was undertaken, using the definitions of Hallas, with a non-structured group consensus approach. The methodology used in assessing avoidability in this study may be improved in several ways. Firstly, a more structured approach to gaining consensus, such as Nominal Group Technique, rather than open discussion, could be used. This would be, with little doubt, a more lengthy process but might yield more valid results regarding consensus avoidability assessments. Secondly, more expert opinion could be added to the investigating group for the assessment of certain cases e.g. a paediatric oncologist presence may have aided in the assessment of the large number of childhood oncology ADRs.

Evaluation of structured ADR avoidability assessment methods suffer from the same difficulty as when evaluating assessment of causality tools; namely, the lack of a gold-standard for comparison. Several methods for assessing avoidability exist. Ferner and

Aronson reviewed these and came to the conclusion that there is no universally accepted method for assessing avoidability and none of the previously published methods were adequate (Ferner & Aronson 2010b). Concurrently, the authors published a new algorithmic method for assessing preventability based on their own mechanistic ADR classifications (Aronson & Ferner 2010). This method looks comprehensive but there is no evidence base, as yet, compelling investigators to use this new tool in place of another.

Indeed, there is scarcely any evidence-base comparing any of these methods using measurable outcomes such as inter-rater reliability, or comparison of appropriateness of results. There is a need for an evidence base in this area, assessing the reliability of avoidability assessment tools. Future investigators, wishing to produce an avoidability assessment method for use in research studies or every-day clinical use, would do well to not only systematically create a user-friendly method but also provide evidence-based justification for the use and dissemination of their method. Investigators in the ADRIC programme are assessing this issue in the context of the difficulties with avoidability assessments during the observational studies. A more reliable avoidability tool is being formulated and evaluated.

5.3 PREVENTION OF ADRS

The avoidability of the ADR cases in our study of paediatric admissions is detailed in Chapter 4. Although case information is provided to highlight the reasons for our

assessment of some cases as possibly and definitely avoidable, there is, unfortunately, a limit to the data that can be published regarding these cases, due to concern regarding the safeguarding of patient identifiable information. However, this study is the first to publish such data in some detail, providing insight into possible areas for intervention for reduction in harm to children from ADRs. We concluded "that more careful attention to practical aspects of care, such as improved monitoring, following prescribing guidelines, improved patient education, and heightened suspicion about potential adverse reactions could lead to a reduction in the frequency of ADRs causing admission."

Evidence of specific interventions in adult populations cannot be extrapolated and applied directly to the paediatric population due to differences in the developing physiology of children, the pharmacokinetics/dynamics of drugs in children, the formulation of paediatric medicines, and differences in disease and ADR presentation. There is a need for systematic evaluation of interventions aimed at reducing the incidence of ADRs in the paediatric population.

We assessed 55 of the ADRs in our larger study to have been possibly or definitely avoidable. It is obvious to state that we think these ADR admissions may have been potentially avoidable. However, it is probably untrue to comment that the remainder of the ADRs are therefore unavoidable by definition. It is probably more accurate to comment that the remainder of the ADR cases were deemed to be unavoidable, in the context of present day knowledge of good medical practice. This definition of

'unavoidable' ADRs allows us to think forward. Some of the ADRs in our study that were deemed unavoidable may be amenable to prevention in the future. This may occur because of change in knowledge of improved therapy regimes with improved risk-benefit profiles, improvements in patient-tailored therapy (personalised medicine) or improved ability to ameliorate adverse reactions and prevent morbidity. Some ADR admissions may be preventable with improved ADR identification. There are several examples of these potential scenarios in our study:

- Oncology patients are at high risk of recurrent ADRs and warrant further evaluation into tailored therapy, and targeted symptom prevention, to prevent ADRs.

- The risk of post-tonsillectomy bleeding in relation to steroids and NSAIDs has not yet been defined and needs further evaluation with either a RCT or well-designed case-control study. There may be safer anaesthetic or treatment regimens with equal, or greater, effectiveness at preventing PONV.

- Many infants are admitted to hospital after routine immunisation with fever. Investigations for infection are undertaken and patients are treated empirically with intravenous antibiotics until the investigations, usually two days later, reveal no evidence of infection having been present. This is a common scenario. Research aimed at improving the identification of bacterial sepsis may have an impact on the assessment and treatment of these infants.

The majority of ADRs in our study were assessed as ‘unavoidable’. If the major burden of ADRs causing admission in children is to be addressed, it is with the current ‘unavoidable’ ADRs that research must now be focussed.

5.4 THESIS CONCLUSION

ADRs causing admission of children to hospital are an important public health problem. Thankfully, no children died as a result of ADRs in our study. However, some of the ADRs were serious and needed intensive care. ADRs cause a significant level of morbidity in children and pose a significant cost burden to the NHS. Almost a quarter of the ADRs were assessed as possibly or definitely avoidable. Interventions are needed to reduce the burden of these ADRs urgently. ADRs that are currently 'unavoidable' may be amenable to prevention with increasing advancements in medical knowledge. Future research should be targeted at increasing knowledge of how to prevent ADRs.

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APPENDICES

APPENDIX A PILOT STUDY MEDICATION HISTORY PROFORMA

Medication History (ADRIC project: Adverse Drug Reactions in Children)

Do not complete this form if the child is an elective surgical admission or is being admitted because of taking an intentional drug overdose or a substance of abuse.

Please inform the carer **"Currently at Alder Hey there is some research about the medicines children take and the best way to detect side effects of medicines: the ADRIC study. People working on the study may ask you some more questions during this admission."**

Tick here when you have told the patient / carer ☐

Child's name	
Child's hospital number	
Child's Date of Birth	
Source of referral	

Has the child had any medicinal products (Prescribed, Over the Counter (OTC), Immunisations, Complementary medicines) in the 2 weeks prior to this admission?
YES ☐ NO ☐ *If No, go no further. If yes, please complete below.*

Clinician #1 is the first person who clerks in the patient
Clinicians 2&3 clinicians updating medication history

	Name	Date	Time	Do you suspect an adverse drug reaction? (Please tick one response) Yes	No
Clinician #1					
Clinician #2					
Clinician #3					

Please record all medication taken by the child in the 2 weeks before admission including ALL complementary therapies (herbal, homeopathy, Chinese etc.), immunisations and over the counter (OTC) remedies.

Clinician Number	Medication Name Route	Date Started (–/–/–)	Date Stopped (–/–/–)	Dose	Frequency	Prescribed (Px) Or OTC	Indication

APPENDIX B ADRIC STUDY 1 MEDICATION HISTORY PROFORMA

Royal Liverpool Children's NHS
NHS Trust

Medication History Proforma

All hospital admissions should have a structured medication history taken by a clinician.

This should detail all medicinal products including:

- *prescribed medications*
- *over the counter drugs*
- *Immunisations*
- *Creams/topical remedies*
- *herbal or complementary medicines*

(Please affix a patient label if available)

Name

Unit Number

D.O.B.

Date of admission_____

Has the patient taken any medicinal products in the 2 weeks prior to this admission?

YES ☐ **NO** ☐

Please record all medication taken by the child in the 2 weeks before admission

Medication Name	Dose	Frequency	Route	Indication	Tick if Prescription	Tick if current

Name_____ **Signature**_____ **Date** _____

Allergies
Comments (notes relevant to Adverse Drug Reactions or medication history)

APPENDIX C ADR ADMISSIONS STUDY ALTERED MEDICATION HISTORY EMBEDDED IN HOSPITAL DOCUMENTATION

HISTORY (continued) **Page 2**

Has the patient taken any medicinal products in the 2 weeks before admission? Y / N (*record details below):*

Medication Name *(including prescribed, over the counter, immunisations, herbal or complementary)*	Dose	Frequency	Route	Indication	Tick if prescription	Tick if current

Allergies

Immunisations up to date YES / NO
If NO: Details:

EXAMINATION

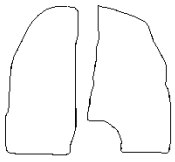
Weight: _____ kg Centile: _____ % Height: _____ cm Centile: _____ %

BMI: _____ Centile: _____ % OFC: _____ cm Centile: _____ %

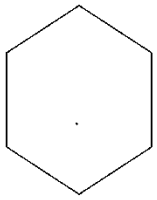
General impression:

CVS: HR: BP: CRT:
Heart sounds / murmurs

Respiratory: RR:



Abdomen:

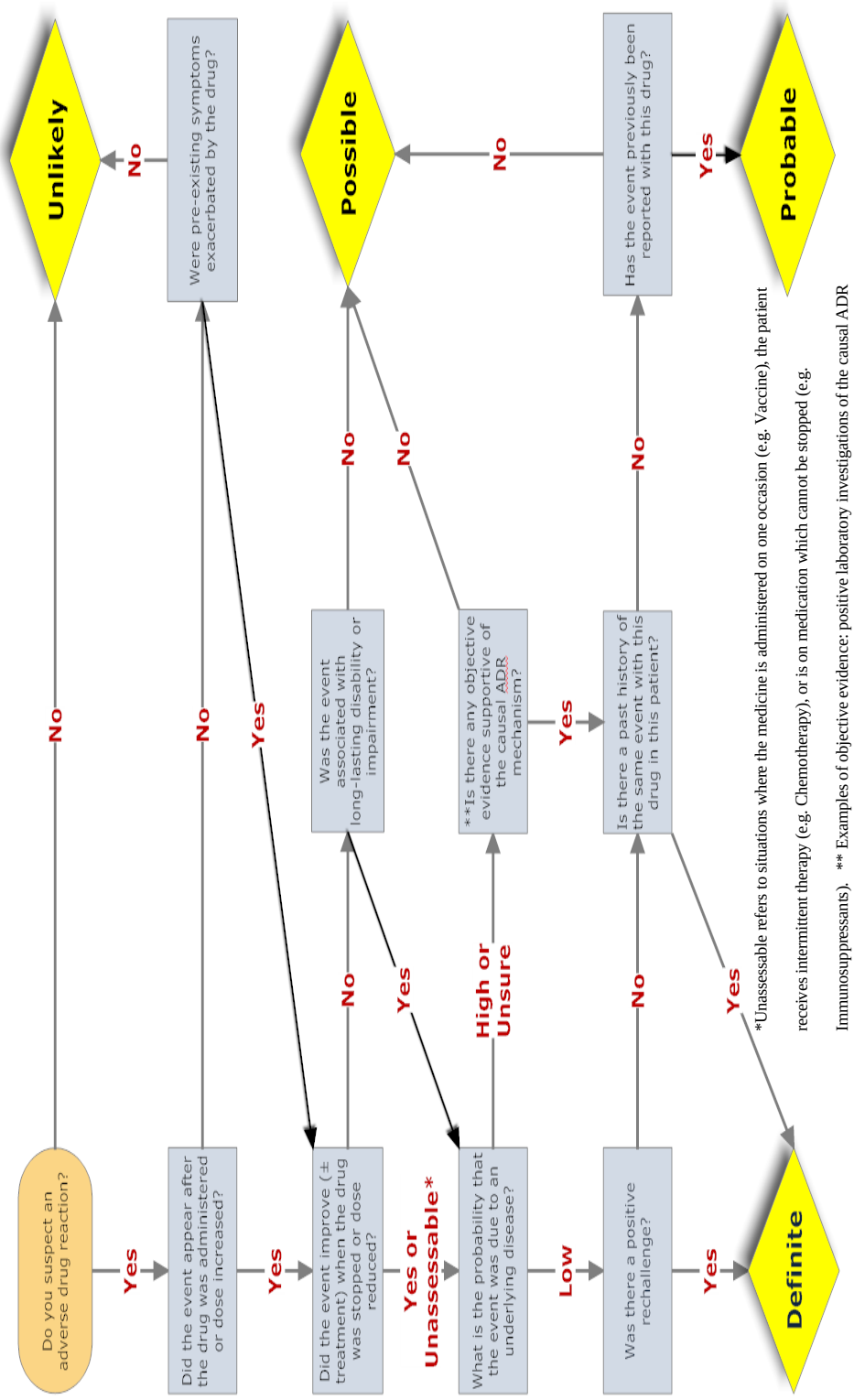


ENT: Ears: Right: Left:

Throat: Nose:

Cervical lymph nodes:

APPENDIX D LIVERPOOL ADR CAUSALITY ASSESSMENT TOOL



*Unassessable refers to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. Chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressants). ** Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient

APPENDIX E PUBLISHED ADVERSE DRUG REACTION CASE REPORTS ASSESSED USING THE LIVERPOOL ADR CAUSALITY ASSESSMENT TOOL

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APPENDIX F COPY OF PUBLICATIONS ARISING FROM THE WORK IN THIS THESIS

Journal of Clinical Pharmacy and Therapeutics (2010) doi:10.1111/j.1365-2710.2010.01194.x

ORIGINAL ARTICLE

Adverse drug reactions causing admission to a paediatric hospital: a pilot study

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SUMMARY

What is known and Objective: **It is known that adverse drug reactions (ADRs) cause admission to hospital in adults and children. A recent adult study showed that ADRs are an important and frequent cause of hospital admission. The objective of this study is to develop methodology to ascertain the current burden of ADRs through a prospective analysis of all unplanned admissions to a paediatric hospital.**

Methods: **Prospective observational study over a 2-week period.**

Results and Discussion: **There were 19 admissions to the main hospital wards related to an ADR, giving an estimated incidence of 4%, with the ADR directly leading to the admission in 71% of cases. There were no deaths attributable to ADR. 33% of the reactions were possibly avoidable. The drugs most commonly implicated in causing admissions were anti-neoplastic agents. The most common reactions were neutropenia, vomiting and diarrhoea. The health burden of ADRs in the paediatric population is likely to be significant. This pilot study will be used to inform a much larger prospective study providing more detailed evidence of the burden of ill-health from ADRs in children. This larger study will add to a body of research aiming to identify drug-related problems within children to aid paediatric pharmacovigilance.**

What is new and Conclusion: **This study provides knowledge regarding the methodology to be used for a larger study investigating ADRs in children. The study will allow authors who wish to replicate the study in their own populations (internationally) to avoid some of the pitfalls in planning a large epidemiological study of paediatric ADRs. The study also provides an estimate of the incidence and problem of admissions caused by ADRs in a UK paediatric population.**

Key words: **admission to hospital, adverse drug reactions, children**

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WHAT IS KNOWN AND OBJECTIVE

Children are vulnerable to adverse drug reactions (ADRs) (1–9) but have been under-represented in studies (1). In 2007, the UK National Institute for Health Research funded the Adverse Drug Reactions in Children (ADRIC) research programme (10), aiming to develop clinical tools to identify, prevent and manage ADRs in children. The first step in this process was to investigate the epidemiology of ADRs which may contribute to acute hospital admissions in the UK. The present study provides an evaluation of the feasibility of the methods required to conduct a larger definitive

study and a preliminary assessment of the proportion of acute admissions that were associated with ADRs.

Spontaneous reporting systems, such as the UK yellow card scheme (11) under report ADRs (12). To obtain reliable information about the incidence of ADRs prospective studies are needed. A study in an adult population showed as many as 6·5% of admissions were caused by ADRs (13). A systematic review of studies of ADRs estimated the rate of paediatric admissions due to ADRs to be 2·09% (95%CI 1, 3·8) (1). There are no recent large studies of the incidence and nature of ADRs causing admission of children to hospital in the UK.

The aim of the first study of the ADRIC programme is the prospective identification of ADRs in children causing admission to hospital to quantify the burden and identify key features. We plan to use a similar approach to Pirmohamed *et al.* (13) who showed an ADR incidence of 6·5% (95% CI: 6·2–6·9%) in an adult population.

We have conducted a pilot study to develop the methodology to address questions such as what constitutes an admission (which would allow comparison with other UK hospitals providing paediatric healthcare), and to assess feasibility of improving medication histories by use of a specific proforma.

METHODS

Preparation

An awareness-raising programme was undertaken within the hospital. The study team met with clinical teams and attended educational meetings to highlight the study and the importance of Hospital documentation was altered with introduction of a medication history proforma to highlight the elucidation of recently taken medication (in the preceding 2 weeks). A 2-week medication history was chosen as the time in which most important reactions causing admission were likely to have occurred after drug exposure.

Categories of admissions

There are many types of admission to the hospital. Many admissions are planned and were not included. Other exclusions were patients admitted with accidental or intentional overdose.

Unplanned admissions to the main hospital and the Accident and Emergency (A&E) observation ward were included. The intention was to include unplanned admissions to main hospital wards in the larger study. We were initially uncertain whether to include admissions to the observation ward, who were discharged without admission to the main hospital. The observation ward is an area within the A&E department where patients can be managed within a 4 h time limit and are either admitted to a main hospital ward or discharged home.

Assessment of admissions

The study was deemed to be audit after written communication with the National Research Ethics Service. All unplanned admissions to a large tertiary paediatric hospital were prospectively screened daily for ADR over a 2-week period including weekend days and a bank holiday. The definition of ADR used was that of Edwards and Aronson (14). Unplanned admissions in the previous 24 h were identified on a daily basis from computer systems. The study team collected information from the case notes on each patient including age, sex, presenting complaint, summary of clinical history, diagnosis (if available at the time of admission), and medications taken in the preceeding 2 weeks. If information on medication history for the preceding 2 weeks was not available, or if clinical information needed to be clarified, the study team interviewed the child/parents/carers to confirm the history. To identify possible ADRs, one investigator screened main hospital ward admissions, and a second screened case notes of patients admitted to the observation ward but subsequently discharged without admission to a main ward. The A&E case notes are routinely electronically scanned from paper notes and stored on a protected database.

Presenting symptoms/signs were cross-referenced against the medication history for each patient using the adverse drug reaction profile for relevant drugs from the Summary of Product Characteristics (15) or, if not available, the British National Formulary (16). The study team identified possible ADRs using this information combined

with clinical history and temporal relationships of the medication taken. All possible ADRs were reported to the clinicians. Assessment of causality was performed for all cases using the method of Naranjo *et al.* (17). We determined type of ADR (18), severity (19) and avoidability (20). One of the lead investigators, MP, had final decision regarding ADR case assessments. These final decisions took place at a meeting between investigators and MP at the end of the study.

Assessment of methodological issues

The following were assessed during the pilot study:

- Whether to include patients admitted to the A&E observation ward. The organization of acute paediatric services varies considerably in different UK hospitals. One feature of our service is the A&E observation ward. We needed to define what constitutes an admission, so that it would be applicable in a variety of settings. During this pilot study, our intention was to identify ADRs occurring during admissions to both the main hospital wards and the A&E observation ward in patients who were not subsequently admitted to a main ward. This would enable us to make a decision about whether it was worthwhile and feasible to include children admitted to the observation ward our definitive study.
- The feasibility of asking clinicians to complete a medication proforma The workload was assessed to identify whether it was achievable to screen both main ward and observation ward patients on a daily basis including weekends.

Analysis

Analyses of the rates of ADRs were expressed as number per 100 admissions with 95% confidence intervals. Other results were stated as raw numbers or tabulated.

RESULTS AND DISCUSSION

Preliminary estimates of incidence of ADRs

Over 2 weeks, 28th April to 12th May 2008, there were 847 admissions. Twenty-two of these were elective admissions and three were adverse drug events (one accidental overdose, two accidental poisoning). Therefore, there were 822 acute admissions to the hospital; 473 (57·5%) to the main hospital wards and 349 (42·5%) to the observation ward subsequently discharged home. Twenty-six patients had two admissions and one had three admissions during the study.

There were 27 admissions identified as being complicated by an ADR. The 27 admissions occurred in 25 patients, with two patients in the main hospital ward group admitted twice with an ADR during the study period. There were 19 admissions in main hospital ward patients and eight in the observation ward. This gives an incidence of four ADRs/100 admissions (95% CI 2·2–5·8) in the main hospital wards and 2·3 ADRs/100 admissions (95% CI 0·7–3·9) in the observation ward. Twenty of the 27 (74%) admissions were deemed to have been directly caused by ADRs. In six cases (22%), an ADR was deemed to be a co-factor for the admission. In one case (4%), the ADR was deemed to be incidental. Twenty-two (81%) of the ADRs were classified as type A (predictable from the known pharmacology) with five (19%) being type B (not predictable).

The main cause of ADR-related admissions (n = 10; 37%) were anti-neoplastic drugs. Immunosuppressants, antibiotics and analgesics were the next most commonly implicated drug groups in causing admission to the main wards (Table 1). There were 25 ADRs identified in these 19 cases.

Assessment of causality showed the majority of cases to be in the 'possible' classification (17/27, 63%). Some were classified probable (10/27, 37%) but none definite. Investigators reported the Naranjo tool difficult to use due to the nature of some of the questions and their relevance to current practice.

All of the ADRs were classified as grade 3 ('required treatment, or drug administration discontinued') according to the Hartwig severity scale. We defined anyone requiring admission to hospital as 'needing treatment'. No ADRs contributed to death. Investigators reported that the severity tool was easy to use. However, it may need modifying for a paediatric population as not all children admitted with an ADR needed active treatment or drug withdrawal. In two instances, observation was undertaken until symptoms abated.

Table 1. Adverse drug reactions in patients admitted to main hospital wards

ADR	Occurrences	Drugs identified
Neutropenia	6	Etoposide, carboplatin, vincristine, cytarabine, daunorubicin
Vomiting	5	Tacrolimus, prednisolone
Diarrhoea	4	Cefaclor, mycophenylate mofetil
Immunosuppression	2	Tacrolimus
Thrombocytopenia	2	Etoposide
Altered conscious level	1	Peg Asparaginase
Anaemia	1	Cyclophosphamide, doxorubicin
Rash	1	Amoxicillin
Constipation	1	Buscopan, ondansetron, tramadol
Haematemesis	1	Diclofenac
Impaired renal function	1	Cyclosporin

Table 2. ADRs in observation ward patients not admitted to a main hospital ward

ADR	Occurrences	Drugs identified
Rash	3	Paracetamol, cefaclor, MMR vaccine, pneumococcal vaccine
Irritability	2	DTaP/IPV/HIB vaccine, pneumococcal vaccine
Anaphylaxis	1	Mefloquine
Fever	1	MMR vaccine, pneumococcal vaccine
Vomiting	1	Cefaclor
Infection (cellulitis)	1	Hydrocortisone (cream)

ADRs, adverse drug reactions; MMR, measles, mumps, rubella; DTaP, diphtheria, tetanus, pertussis; IPV, inactivated polio vaccine; HIB, Haemophilus influenza type B.

We determined avoidability of admissions related to an ADR by the method of Hallas *et al.* Eighteen (67%) of the ADRs were assessed as unavoidable, whilst 9 (33%) were 'possibly avoidable'. None were classified as definitely avoidable. Investigators reported that the Hallas classification was easy to use but likely to be user-dependent given its broad classification terms.

Methodological issues

The majority of main hospital admissions (n = 473) came from A&E (n = 363, 77%). This included clinical areas within A&E and all GP acute referrals (all of whom are seen in A&E before admission). Hospital transfers and self-referrals of children with known chronic disease accounted for the remainder of main hospital admissions (n = 110, 23%). Observation ward admissions (n = 349; 42·5%) included self-referrals and acute GP referrals. The proportion of admissions to the observation ward that yielded an ADR was 2·3%, detailed in Table 2. There were nine ADRs identified in eight observation ward cases.

Of the 473 admissions to the main hospital wards, the separate medication history proforma was used in 57 (12%). The use of the proforma was higher in the observation ward (60/349; 17%). All of the proformas were completed in A&E as this is the main route of admission. Feedback from clinicians revealed that the proforma was difficult to use. Clinicians commented that a medication history proforma would be more usable if embedded into existing documentation, e.g. care pathways.

There was an average of 34 unplanned admissions to review each day of the study. The morning was used to collect data and the afternoon to input data onto a password protected database on a secure hospital server. The investigator would also

have to return to patients whose notes were missing or who had left the ward temporarily for investigations. Follow-up of patients was necessary to complete the assessment of cases. In some instances, several days to weeks were required for follow-up.

The patients from the observation ward were not available for interview. Their case notes were the only source of information about symptoms, signs and medication. There were 349 admissions, of 344 patients, to the observation ward during the 2 weeks with five patients admitted twice. There were approximately 25 reviews of notes each day. Whilst the number of patients in this group was less than the main ward, the process of recording information from scanned electronic records to our database was time consuming.

The estimated incidence of ADRs causing admission to the main hospital wards in this pilot study was 4% (95% CI 2·2, 5·8). This figure is higher than that seen in other studies including a meta-analysis of ADRs (1). McKenzie *et al.* (2), in 1976, studying 3556 children for 3 years in the USA, found 2% of admissions were caused by ADRs. Easton *et al.* (3), in Australia, investigated 2933 paediatric admissions over 22 weeks showing 4·3% (95% CI 3·6, 5·0) of admissions due to a drug-related problem, with <25% of these being ADRs (29/2933, 1%). A study by Martínez-Mir *et al.* (4) in 512 consecutive admissions under 2 years of age in Spain found the incidence (4·3%) to be similar to our study. Clearly, ours is a pilot study designed to assess the feasibility of the methodology used, and as such the reported estimate of incidence of ADRs should be interpreted with caution.

Amongst the methodological questions to be addressed was the definition of an admission. We found that, although there were possible ADRs that occurred in patients admitted to the A&E observation ward, the adequacy of clinical information in some cases, the lack of information about clinical progression and the short duration of stay made it difficult to assess for the occurrence of an ADR. The methodology used to retrieve information, with retrospective note review, was different to the main hospital group where prospective note review and, if needed, interview was used. The workload for the investigators was significantly increased with inclusion of the observation ward patients. This was particularly evident at weekends when only one investigator was available. For these reasons, together with the fact that: (i) the incidence of ADRs was lower in observation ward patients than those admitted to the main ward; (ii) an ADR causing admission to a main ward is intuitively more severe than one that leads to discharge within 4 h; and (iii) many paediatric departments may not have observation wards which would make generalizability of our findings difficult, we elected not to include observation ward admissions in our definitive study.

Capturing information about drug history is crucial in studies such as this. We designed a proforma for clinicians, with education about its use, to record the medication history over a 2 week period before admission. This was a separate sheet to be collated with existing case note pathways and clinical history recording. We found that the use of this proforma was inadequate during the study leading to many parent/carer interviews for the investigators. We plan to embed a more user friendly proforma within existing admission documentation with collaboration from clinicians and the hospital Care Pathways Co-ordinator.

The majority of ADRs that were seen during our study were oncology related. These were mainly children admitted with a febrile illness who were neutropenic. This group of patients are often exposed to medications which cause expected ADRs, may require admission for management, and may be unavoidable given the nature of the underlying illness and treatment required. However, there may be unusual or serious ADRs which may be important to capture. Although these patients are often exposed to many medications in the preceding 2 weeks, making data collection time consuming, it was possible to capture accurately their medications and clinical problems and identify ADRs that had occurred. We found it easier in this group to apply causality assessments because of the hospital-intensive nature of treatment, for example with re-challenge to chemotherapy, and detailed records of the recent clinical history.

WHAT IS NEW AND CONCLUSION

This pilot study will be used to inform a larger study to research ADRs that cause admission to hospital in the paediatric population. We anticipate the larger study to have ~12 000 admissions which

will allow a more precise estimate of the incidence of ADRs and allow more detailed description. Given the problems encountered of capturing ADRs in children in the observation area, i.e. those that stayed within hospital premises for <4 h, this area will not be included in our larger study. This should not be taken to mean that we feel that this aspect of hospital attendance is unimportant with respect to ADRs. We feel that further investigation of ADRs is required in those attending A&E but the methodology would have to be altered to achieve this. This is something we are planning for the future.

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Development and Inter-Rater Reliability of the Liverpool Adverse Drug Reaction Causality Assessment Tool

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Abstract

Aim: To develop and test a new adverse drug reaction (ADR) causality assessment tool (CAT).

Methods: A comparison between seven assessors of a new CAT, formulated by an expert focus group, compared with the Naranjo CAT in 80 cases from a prospective observational study and 37 published ADR case reports (819 causality assessments in total).

Main Outcome Measures: Utilisation of causality categories, measure of disagreements, inter-rater reliability (IRR).

Results: The Liverpool ADR CAT, using 40 cases from an observational study, showed causality categories of 1 unlikely, 62 possible, 92 probable and 125 definite (1, 62, 92, 125) and 'moderate' IRR (kappa 0.48), compared to Naranjo (0, 100, 172, 8) with 'moderate' IRR (kappa 0.45). In a further 40 cases, the Liverpool tool (0, 66, 81, 133) showed 'good' IRR (kappa 0.6) while Naranjo (1, 90, 185, 4) remained 'moderate'.

Conclusion: The Liverpool tool assigns the full range of causality categories and shows good IRR. Further assessment by different investigators in different settings is needed to fully assess the utility of this tool.

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Competing Interests: RLS and MP are members of the Commission on Human Medicines. MP Chairs the Pharmacovigilance Expert Advisory Group, while RLS Chairs the Paediatric Medicines Expert Advisory Group.

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Introduction

Adverse drug reactions are a frequent source of morbidity and mortality [1,2]. Causality assessment of ADRs may be undertaken by clinicians, academics, pharmaceutical industry, regulators and in different settings, including clinical trials [3,4,5,6]. At an individual level, health care providers assess causality informally when dealing with ADRs in patients to make decisions regarding therapy. Regulatory authorities assess spontaneous ADR reports [4,5] where causality assessment can help in signal detection and aid in risk-benefit decisions regarding medicines [7,8].

An early paper by Sir Bradford Hill [9], describing minimum criteria for establishing causality of adverse events, pre-dates the earliest attempts to formulate ADR causality assessment tools. Bradford Hill set out criteria for establishing causality which included assessment of strength of the association, consistency of the association, specificity, temporal relationship, biological gradient (dose response), biological plausibility, coherence, experimental evidence, and reasoning by analogy. Although these criteria were not meant for ADRs, the elements have been adapted in ADR causality tools. Indeed, attempts to formalise causality assessment of ADRs into structured assessment tools have been ongoing for more than 30 years [10,11]. It is known that assessing ADR likelihood without a structure can lead to wide disagreements between assessors [12]. These disagreements may be the result of differing clinical backgrounds, specialties and experience. The causality tools thus aim to limit disagreement between assessors of ADR cases as to the likelihood that a reaction is related to a particular medication taken by the patient. A large number of causality tools have been developed ranging from the simple to the complex, but none have gained universal acceptance [13].

One of the most widely used causality assessment tools is the Naranjo tool [10]. This is a simple 10-item questionnaire that classifies the likelihood that a reaction is related to a drug using concepts such as timing, plausibility/evidence, de-challenge and re-challenge/previous exposure. Each element of the questionnaire is weighted and the total score used to categorise the event into unlikely, possible, probable and definite. The tool was developed 30 years ago by adult pharmacologists/physicians and psychiatrists. Published case reports were used to validate the

reliability of the tool in assessing causality. It has subsequently been widely used, including recently in two prospective observational studies of ADRs causing hospital admission and occurring in hospital in-patients [14,15]. However, the reliability of the Naranjo tool has been questioned by a number of investigators [3,8,16,17,18].

While undertaking a prospective observational study of ADRs in children (in preparation), we found several difficulties with using the Naranjo tool. When assessing this heterogeneous mix of potential ADR cases, the investigators found some questions were not appropriate, leading to many answers being categorised as "unknown". This led to lack of sensitivity as the overall score obtained for each causality assessment may be artificially lowered, which in turn underestimates the likelihood of an ADR. The investigators encountered several cases which were unanimously thought to be definite ADRs (e.g. repeated episodes of febrile neutropenia during oncological chemotherapy) but which did not reach the threshold for definite using the published Naranjo tool. Moreover, the weighting for each question and the ADR classification scoring boundaries used in the Naranjo tool were not justified in the original publication, or subsequently. Therefore, we undertook to develop a causality assessment tool that would overcome some of these issues, while at the same time (a) making it as easy, or easier, to use than the Naranjo tool; and (b) ensuring that the basic principles of assessing causality as defined by Bradford Hill were maintained.

Methods

Each of seven investigators (RG, JM, KB, MP, TN, RS, MT) independently assessed the first 40 consecutive case reports from a study of suspected ADRs causing hospital admission (ADRIC Study 1 – adverse drug reactions in children available at http://www.adric.org.uk/) using the Naranjo tool. The first 40 cases assessed using Naranjo were reviewed in terms of the results of the pair-wise agreements between the seven investigators. The cases where major discrepancies occurred, that is, where the range of causality probability differed by more than one category (e.g. possible and definite), and the cases where close to half of the raters differed from the others by one category were identified. The questions within the Naranjo tool which caused the discrepancies were identified and reviewed.

Each question in the Naranjo tool was reviewed by the investigators at a consensus meeting to assess whether it was appropriate to incorporate, discard or integrate with other questions into a new, more appropriate, causality tool (Table 1). A new causality tool was drawn up and modified through a consensus approach between the seven investigators. The format of the new tool was an algorithm, or flowchart, with dichotomous responses to each decision followed by routing to further, specific questions, rather than the weighted responses used in the Naranjo tool.

The new Liverpool ADR causality tool was then used to assess 20 new suspected ADR case reports from our observational study.

Table 1. Decisions made about questions within the Naranjo tool.

No.	Naranjo tool questions	Yes	No	Don't know	Outcome for Liverpool Tool
Q1	Are there previous *conclusive* reports on this reaction?	+1	0	0	**Retained** – knowledge of previous reports can be important when assessing if an adverse event is due to drug or disease.
Q2	Did the adverse event appear after the suspected drug was administered?	+2	−1	0	**Modified** – timing of event in relation to drug exposure is important when determining causality.
Q3	Did the adverse reaction improve when the drug was discontinued or *a specific* antagonist was administered?	+1	0	0	**Modified** – Knowledge of de-challenge, if available, may provide further evidence as to causality of an event. However, an event may have long-lasting sequelae. A new question was added to the Liverpool tool to cover this possibility.
Q4	Did the adverse reaction reappear after the drug was readministered?	+2	−1	0	**Combined** – Knowledge of re-challenge, if available, may add to the level of certainty regarding causality assessment. This question is combined with Naranjo Q8 regarding dose-response relationship to increasing dose. This can also provide evidence to support or refute causality.
Q5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	**Modified** – This question is replaced within the Liverpool tool by a question involving likelihood of alternative cause, with an option to answer 'unsure' (which prompts the user to seek further evidence of the reaction). Naranjo Q5 is worded such that it is difficult to answer No.
Q6	Did the reaction reappear when a placebo was given?	−1	+1	0	**Rejected** – With the exception of clinical trials, placebo use is not common practice and this question is no longer relevant.
Q7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**Modified** – Objective evidence of the ADR occurrence will already be taken in to account when the user is deciding whether the event is likely to be drug or disease related. A question in the Liverpool tool asks for objective evidence of likely ADR mechanism. If apparent, this may provide evidence of causality to an assessor.
Q8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	**Combined** – This question is combined with one addressing de-challenge in the Liverpool tool. The answer to this question may be important in establishing if there is a dose-response relationship between drug and adverse event.
Q9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	**Modified** – this is included in the Liverpool algorithm, in relation to the same drug(s) only, and given the same weighting as a positive re-challenge. This may provide evidence of susceptibility, and likelihood, of the event being related to a drug.
Q10	Was the adverse event confirmed by any objective evidence?	+1	0	0	**Modified** – see Q7

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All cases assessed from the ADRIC study contained a similar level of documentation. The collated causality categories for all seven assessors showed 1 (0.7%) unlikely, 18 (12.9%) possible, 2 (1.4%) probable and 119 (85%) definite. The assessors achieved moderate agreement with a kappa of 0.51 (95% CI 0.19, 0.82). However, there was an inappropriate bias towards the category of definite which was caused by decision paths leading to an answer of definite without the need for a positive re-challenge or previous reaction with exposure to the same drug. The assessment tool was reviewed again, and major discrepancies between scorers identified and each question within the algorithm reviewed to assess usefulness. Questions and decision pathways that caused major discrepancies were then modified. The new assessment tool was then tested on a further 20 case reports; ten from the ADRIC study and ten from an observational study of in-patient ADRs in an adult hospital. Collated causality categories for the ten ADRIC 1 cases showed 0 (0%) unlikely, 24 (34%) possible, 39 (56%) probable and 7 (10%) definite with a kappa of 0.27 (95% CI 0.11, 0.44). Collated causality categories for the ten adult cases showed 0 (0%) unlikely, 13 (19%) possible, 48 (69%) probable and 9 (13%) definite with a kappa of 0.13 (95% CI −0.14, 0.38).

The results of these assessments prompted another review of the appropriateness of the tool and questions. A third iteration was used so that the development and evaluation of tool prototypes was based on discussions in which 80 cases were used (Figure 1). After the third iteration the investigators were satisfied with the final version of the new tool (Figure 2) in terms of ease of use, lack of ambiguity, and appropriateness of the causality assignment. This was judged by expert opinion and consensus within the group.

The assessment process for the Liverpool causality assessment tool followed a step-wise procedure:

- The original 40 case reports (case reports of raw clinical data from an observational study) initially assessed with Naranjo were assessed by each of the seven investigators using the new assessment tool to provide a comparison of the inter-rater reliability between the two tools.
- In order to examine the tool using cases other than those collected in our observational study, 37 cases of ADRs were randomly selected from the Annals of Pharmacotherapy (Figure S1) and independently evaluated by the seven assessors using only the new tool. The Annals of Pharmacotherapy requires authors to apply a Naranjo assessment prior to publication of case reports.
- Since the original 40 cases from our observational study had been used in the design of the new tool, a further new set of 40 ADR case reports from our study were then used to compare inter-rater reliability using both the Naranjo and the Liverpool tools.

Categorical scores from both the Naranjo tool and the new tool take the same four point ordinal scale. The inter-rater agreements at each stage of the assessment process were assessed using a linear weighted kappa with 95% confidence intervals for ordered categories. Exact agreement percentages (%EA) were computed to measure the absolute concordances between assessor scores. The percentage of extreme disagreement (%ED), where the causality scores between two raters of the same case are wider than one causality interval apart (e.g. definite for 1 rater and possible for the other), were also computed to measure extreme disagreements between pair-wise rater assessments. To supplement the pair-wise kappas, a global kappa score measuring nominal scale agreement across multiple assessors was calculated with 95% confidence

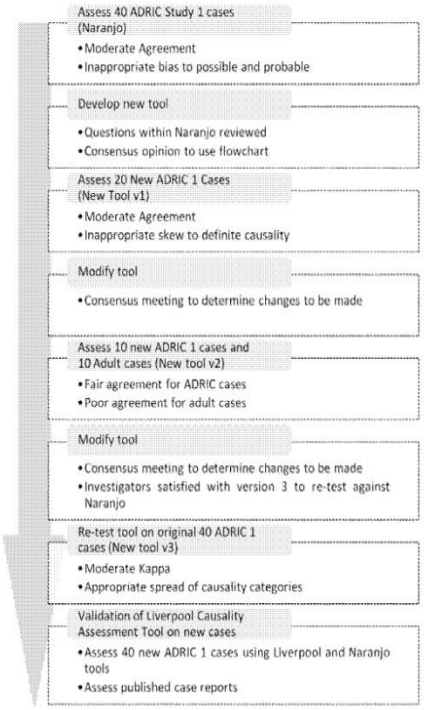

Figure 1. Flowchart of the development of the Liverpool ADR Causality Assessment Tool.
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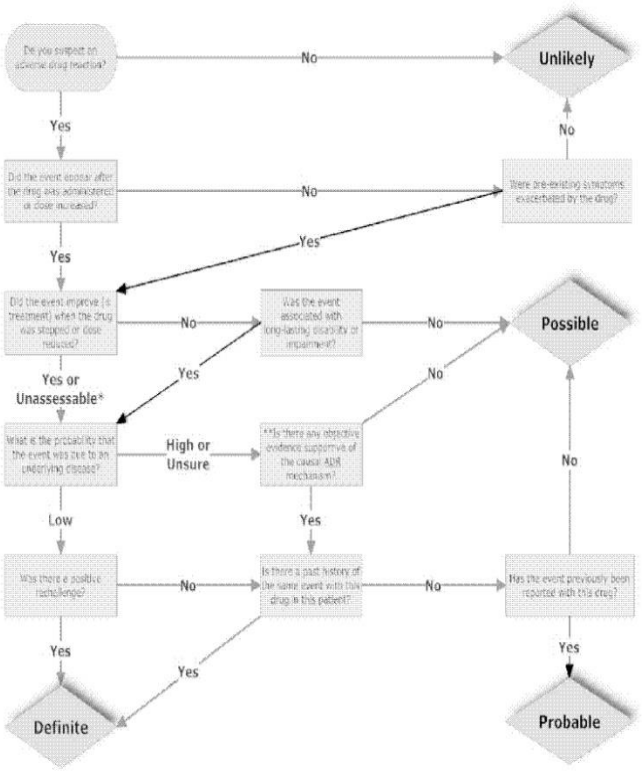
intervals [19]. The global kappa score provides a single statistic to quantify assessor agreement for each set of cases. Kappa values were interpreted according to the guidance from Altman [20]: poor <0.2; fair 0.21–0.40; moderate 0.41–0.60; good 0.61–0.80; and very good 0.81–1.00 agreement.

Ethics Statement

The observational study of paediatric ADR admissions (ADRIC) was conducted as a service evaluation and this aspect of the study was felt, after discussion with the relevant bodies, not to require an opinion from the Local Research Ethics Committee or the hospital management.

Results

Assessment of the original 40 consecutive ADR cases by the seven investigators using the Naranjo tool showed collated categorisation of causality scores for all assessors (n = 280 assessments) of 0 (0%) unlikely, 100 (36%) possible, 172 (61%) probable and 8 (3%) definite (Table 2). Exact agreement percentages for the pair-wise comparisons between raters ranged from 43%–93%. Percentage of extreme disagreement (%ED) was 2.5% for four of the twenty-one pair-wise comparisons. There were no extreme disagreements in 17/21 pair-wise comparisons. Pair-wise kappas ranged from 0.27 to 0.86 and the assessors achieved moderate inter-rater reliability with a global kappa of 0.45 (95% CI 0.35–0.54) (Table 3). The same cases



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

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

Figure 2. Liverpool ADR causality assessment tool.
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assessed using the new Liverpool tool showed collated causality categories of 1 (0.4%) unlikely, 62 (22%) possible, 92 (33%) probable and 125 (45%) definite. Exact agreement percentages ranged from 43–93%. All 21 pair-wise comparisons displayed extreme disagreement with percentages ranging from 5–20%. Pair-wise kappas ranged from 0.27 to 0.84 and the assessors achieved moderate inter-rater reliability with a global kappa score of 0.48 (95% CI 0.42–0.54) (Table 3).

The 37 randomly selected ADR case reports from the Annals of Pharmacotherapy assessed by the seven investigators using the Liverpool tool showed collated categorisation of causality scores (n = 259 assessments) of 1 (0.4%) unlikely, 67 (26%) possible, 136 (53%) probable and 55 (21%) definite. Exact agreement percentages ranged from 57%–97%. 18/21 pair-wise comparisons between raters showed some extreme disagreement, with the percentage ranging from 5–11%, while three showed no extreme disagreements. Pair-wise kappas ranged from 0.31 to 0.96 and the assessors achieved moderate inter-rater reliability with a global kappa of 0.43 (95% CI 0.34–0.51) (Table 4). These case reports were not assessed by the investigators using the Naranjo tool as The Annals of Pharmacotherapy requires authors to apply a Naranjo assessment prior to publication of case reports in the journal. The collated categorization of the case report author assessments for the 37 cases showed 0 unlikely, 5 (14%) possible, 29 (78%) probable and 3 (8%) definite.

The 40 newly selected ADR cases assessed by the seven investigators using the Naranjo tool showed collated categorisation of causality scores (n = 280 assessments) of 1 (0.4%) unlikely, 90 (32%) possible, 185 (66%) probable and 4 (1%) definite. Exact agreement percentages ranged from 63%–90%. Percentage of extreme disagreement was 2.5% for four pair-wise comparisons. There were no extreme disagreements in 17/21 comparisons. The

Table 2. Causality category assignments of investigators.

		ADRIC Original (N = 40)				Annals of Pharmacotherapy (N = 37)				ADRIC New (N = 40)			
		Unlikely	Possible	Probable	Definite	Unlikely	Possible	Probable	Definite	Unlikely	Possible	Probable	Definite
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Assessor	Tool												
RG	Naranjo	0 (0.0)	18 (45.0)	22 (55.0)	0 (0.0)	NA	NA	NA	NA	0 (0.0)	18 (45.0)	21 (52.5)	1 (2.5)
	Liverpool	0 (0.0)	7 (17.5)	23 (57.5)	10 (25.0)	0 (0.0)	11 (29.7)	18 (48.7)	8 (21.6)	0 (0.0)	11 (27.5)	12 (30.0)	17 (42.5)
JM	Naranjo	0 (0.0)	17 (42.5)	22 (55.0)	1 (2.5)	NA	NA	NA	NA	0 (0.0)	19 (47.5)	21 (52.5)	0 (0.0)
	Liverpool	0 (0.0)	15 (37.5)	8 (20.0)	17 (42.5)	0 (0.0)	11 (29.7)	20 (54.1)	6 (16.2)	0 (0.0)	14 (35.0)	8 (20.0)	18 (45.0)
KB	Naranjo	0 (0.0)	18 (45.0)	21 (52.5)	1 (2.5)	NA	NA	NA	NA	0 (0.0)	15 (37.5)	25 (62.5)	0 (0.0)
	Liverpool	0 (0.0)	18 (45.0)	4 (10.0)	18 (45.0)	0 (0.0)	12 (32.4)	19 (51.4)	6 (16.2)	0 (0.0)	13 (32.5)	10 (25.0)	17 (42.5)
MT	Naranjo	0 (0.0)	14 (35.0)	24 (60.0)	2 (5.0)	NA	NA	NA	NA	1 (2.5)	9 (22.5)	27 (67.5)	3 (7.5)
	Liverpool	1 (2.5)	5 (12.5)	17 (42.5)	17 (42.5)	0 (0.0)	10 (27.0)	18 (48.7)	9 (24.3)	0 (0.0)	8 (20.0)	9 (22.5)	23 (57.5)
TN	Naranjo	0 (0.0)	10 (25.0)	29 (72.5)	1 (2.5)	NA	NA	NA	NA	0 (0.0)	13 (32.5)	27 (67.5)	0 (0.0)
	Liverpool	0 (0.0)	3 (7.5)	15 (37.5)	22 (55.0)	1 (2.7)	10 (27.0)	20 (54.1)	6 (16.2)	0 (0.0)	8 (20.0)	12 (30.0)	20 (50.0)
MP	Naranjo	0 (0.0)	12 (30.0)	27 (67.5)	1 (2.5)	NA	NA	NA	NA	0 (0.0)	12 (30.0)	28 (70.0)	0 (0.0)
	Liverpool	0 (0.0)	7 (17.5)	12 (30.0)	21 (52.5)	0 (0.0)	10 (27.0)	17 (46.0)	10 (27.0)	0 (0.0)	9 (22.5)	13 (32.5)	18 (45.0)
RS	Naranjo	0 (0.0)	11 (27.5)	27 (67.5)	2 (5.0)	NA	NA	NA	NA	0 (0.0)	4 (10.0)	36 (90.0)	0 (0.0)
	Liverpool	0 (0.0)	7 (17.5)	13 (32.5)	20 (50.0)	0 (0.0)	3 (8.1)	24 (64.9)	10 (27.0)	0 (0.0)	3 (7.5)	17 (42.5)	20 (50.0)
Totals	Naranjo	0 (0.0)	100(35.7)	172 (61.4)	8 (2.9)	0* (0)	5* (13.5)	29* (78.4)	3* (8.1)	1 (0.36)	90 (32.1)	185 (66.1)	4 (1.4)
	Liverpool	1 (0.36)	62 (22.1)	92 (32.9)	125(44.6)	1 (0.39)	67 (25.9)	136 (52.5)	55 (21.2)	0 (0.0)	66 (23.6)	81 (28.9)	133 (47.5)

*It is a journal requirement for authors of case reports in Annals of Pharmacotherapy to complete a Naranjo causality assessment. **Author identification for tables:** Gallagher RM (RG), Mason J (JM), Bird K (KB), Nunn AJ (TN), Turner MA (MT), Smyth RL (RS), Pirmohamed M (MP).

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Table 3. Naranjo and Liverpool tool assessment of 40 original ADR cases from an observational study.

			Assessor 2						
			RG	JM	KB	MT	TN	MP	RS
Assessor 1	RG	%EA/ED		*57.5/0%*	*42.5/0%*	*55.0/0%*	*52.5/0%*	*62.5/0%*	*55.5/0%*
		Kappa (95%CI)		*0.52 (0.27,0.77)*	*0.47 (0.21,0.73)*	*0.44 (0.19,0.69)*	*0.45 (0.21,0.69)*	*0.36 (0.09,0.62)*	*0.29 (0.04,0.54)*
	JM	%EA/ED	57.5/5%		***92.5/0%***	*70.0/0%*	*77.5/0%*	*72.5/0%*	*70.0/2.5%*
		Kappa (95%CI)	0.46 (0.26,0.67)		***0.86 (0.71,1.00)***	*0.46 (0.22,0.69)*	*0.56 (0.34,0.78)*	*0.47 (0.19,0.75)*	*0.40 (0.15,0.65)*
	KB	%EA/ED	42.5/10%	**75.0/5%**		***77.5/0%***	*70.0/0%*	*70.0/0%*	*77.5/2.5%*
		Kappa (95%CI)	0.28 (0.08,0.49)	**0.69 (0.52,0.87)**		***0.60 (0.39,0.81)***	*0.43 (0.19,0.66)*	*0.43 (0.15,0.71)*	*0.55 (0.32,0.77)*
	MT	%EA/ED	55.0/7.5%	**70.0/5%**	57.5/7.5%		*72.5/0%*	*62.5/0%*	*70.0/2.5%*
		Kappa (95%CI)	0.31 (0.06,0.56)	**0.62 (0.45,0.80)**	0.49 (0.31,0.67)		*0.45 (0.20,0.70)*	*0.37 (0.11,0.62)*	*0.48 (0.23,0.73)*
	TN	%EA/ED	52.5/7.5%	62.5/15%	52.5/20%	70.0/7.5%		*70.0/0%*	*72.5/2.5%*
		Kappa (95%CI)	0.27 (0.07,0.46)	0.42 (0.21,0.62)	0.30 (0.10,0.50)	0.49 (0.26,0.72)		*0.33 (0.05,0.62)*	*0.35 (0.06,0.63)*
	MP	%EA/ED	62.5/5%	**77.5/7.5%**	67.5/12.5%	**80.0/5%**	**80.0/7.5%**		*70.0/0%*
		Kappa (95%CI)	0.47 (0.25,0.69)	**0.68 (0.49,0.86)**	0.54 (0.33,0.74)	**0.69 (0.49,0.89)**	**0.62 (0.39,0.84)**		*0.38 (0.11,0.65)*
	RS	%EA/ED	55.5/10%	70.0/12.5%	62.5/15%	**80.0/7.5%**	75.0/10%	**92.5/5%**	
		Kappa (95%CI)	0.30 (0.05,0.55)	0.54 (0.32,0.76)	0.46 (0.24,0.67)	**0.66 (0.44,0.87)**	0.52 (0.27,0.76)	**0.84 (0.66,1.00)**	

%EA/ED and Kappa scores in italics represent Naranjo tool analyses.
%EA/ED and Kappa scores in normal font represent Liverpool ADR causality tool analyses.
Kappa scores outlined in bold demarcate either a good or very good level of agreement.
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pair-wise kappas ranged from 0.19 to 0.81 with moderate inter-rater reliability and global kappa of 0.44 (95% CI 0.33–0.55) (Table 5). The same cases assessed using the Liverpool tool showed collated causality categories of 0 (0%) unlikely, 66 (24%) possible, 81 (29%) probable and 133 (48%) definite. Exact agreement percentages ranged from 65%–88%. Percentage of extreme disagreement ranged from 2.5–7.5% for 14 pair-wise comparisons. There were no extreme disagreements in 7/21 comparisons. Pair-wise kappas ranged from 0.51 to 0.85 and the assessors achieved good inter-rater reliability with a global kappa of 0.60 (95% CI 0.54–0.67) (Table 5).

Discussion

A recent systematic review of studies assessing the reliability of causality assessments concluded that "no causality assessment method has shown consistent and reproducible measure of causality."[3] We are currently undertaking a comprehensive assessment of adverse drug reactions in children [21]. As part of this, we had initially decided to use the Naranjo tool to assess causality in our patients admitted with ADRs, and those who developed ADRs as in-patients. In order to do this, we planned to have assessments conducted independently by seven assessors.

Table 4. Liverpool ADR Causality tool assessment of 37 randomly selected published ADR case reports.

			Assessor 2						
			RG	JM	KB	MT	TN	MP	RS
Assessor 1	RG	%EA/ED		62.2/10.8%	64.9/10.8%	**73.0/0%**	56.8/8.1%	59.5/5.4%	67.6/5.4%
		Kappa (95% CI)		0.307 (0.03,0.58)	0.38 (0.10,0.65)	**0.65 (0.44,0.85)**	0.32 (0.05,0.59)	0.41 (0.16,0.66)	0.46 (0.22,0.69)
	JM	%EA/ED			**97.3/0%**	62.2/10.8%	64.9/8.1%	56.8/8.1%	64.9/8.1%
		Kappa (95% CI)			**0.93 (0.82,1.00)**	0.31 (0.04,0.59)	0.34 (0.06,0.61)	0.29 (0.02,0.57)	0.33 (0.09,0.57)
	KB	%EA/ED				59.5/10.8%	67.6/8.1%	59.5/8.1%	62.2/8.1%
		Kappa (95% CI)				0.31 (0.03,0.59)	0.41 (0.13,0.68)	0.36 (0.10,0.63)	0.34 (0.10,0.58)
	MT	%EA/ED					64.9/8.1%	64.9/5.4%	**78.4/5.4%**
		Kappa (95% CI)					0.40 (0.13,0.66)	0.48 (0.23,0.72)	**0.61 (0.38,0.84)**
	TN	%EA/ED						62.2/8.1%	67.6/5.4%
		Kappa (95% CI)						0.38 (0.11,0.64)	0.42 (0.19,0.65)
	MP	%EA/ED							70.3/0%
		Kappa (95% CI)							0.58 (0.38,0.77)
	RS								

Kappa scores outlined in bold demarcate either a good or very good level of agreement.
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Table 5. Naranjo and Liverpool tool assessment of 40 new ADR cases from an observational study.

		Assessor 2						
		RG	**JM**	**KB**	**MT**	**TN**	**MP**	**RS**
Assessor 1 **RG**	%EA/ED		***90.0/0%***	***80.0/0%***	*70.0/2.5%*	*75.0/0%*	*72.5/0%*	*62.5/0%*
	Kappa (95%CI)		***0.81 (0.64,0.98)***	***0.61 (0.38,0.84)***	*0.46 (0.25,0.66)*	*0.51 (0.26,0.75)*	*0.46 (0.20,0.71)*	*0.23 (0.03,0.42)*
JM	%EA/ED	**70.0/5%**		*75.0/0%*	*67.5/0%*	*80.0/0%*	*77.5/0%*	*62.5/0%*
	Kappa (95%CI)	**0.62 (0.43,0.81)**		*0.49 (0.23,0.76)*	*0.45 (0.25,0.64)*	*0.59 (0.35,0.83)*	*0.54 (0.29,0.79)*	*0.22 (0.02,0.41)*
KB	%EA/ED	**65.0/0%**	**77.5/2.5%**		*70.0/2.5%*	*80.0/0%*	*77.5/0%*	*67.5/0%*
	Kappa (95%CI)	**0.62 (0.44,0.79)**	**0.73 (0.57,0.90)**		*0.40 (0.16,0.63)*	*0.56 (0.29,0.83)*	*0.50 (0.22,0.78)*	*0.19 (−0.06,0.44)*
MT	%EA/ED	**70.0/2.5%**	**75.0/5%**	**75.0/7.5%**		*70.0/2.5%*	*70.0/2.5%*	*72.5/0%*
	Kappa (95%CI)	**0.63 (0.45,0.81)**	**0.70 (0.52,0.88)**	**0.64 (0.45,0.84)**		*0.367 (0.12,0.62)*	*0.40 (0.15,0.65)*	*0.25 (0.003,0.50)*
TN	%EA/ED	**82.5/2.5%**	**77.5/2.5%**	**70.0/2.5%**	**82.5/0%**		*77.5/0%*	*77.5/0%*
	Kappa (95%CI)	**0.77 (0.61,0.93)**	**0.73 (0.57,0.88)**	**0.61 (0.43,0.79)**	**0.79 (0.64,0.93)**		*0.48 (0.18,0.77)*	*0.38 (0.09,0.66)*
MP	%EA/ED	**70.0/2.5%**	**80.0/2.5%**	**72.5/2.5%**	**80.0/0%**	**87.5/0%**		*80.0/0%*
	Kappa (95%CI)	**0.63 (0.44,0.81)**	**0.75 (0.59,0.91)**	**0.64 (0.46,0.82)**	**0.76 (0.61,0.91)**	**0.85 (0.73,0.97)**		*0.41 (0.12,0.71)*
RS	%EA/ED	**70.0/2.5%**	70.0/5%	65.0/5%	**80.0/0%**	**82.5/0%**	**75.0/0%**	
	Kappa (95%CI)	**0.60 (0.42,0.78)**	0.57 (0.40,0.74)	0.50 (0.31,0.69)	**0.73 (0.58,0.88)**	**0.77 (0.62,0.91)**	**0.67 (0.51,0.84)**	

%EA/ED and Kappa scores in italics represent Naranjo tool analyses.
%EA/ED and Kappa scores in normal font represent Liverpool ADR causality tool analyses.
Kappa scores outlined in bold demarcate either a good or very good level of agreement.
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Initial assessments revealed some significant issues with the Naranjo tool (as outlined in the introduction above), which led us to develop the Liverpool Causality Assessment Tool.

The development of the Liverpool Causality Assessment Tool involved an iterative process conducted by a multidisciplinary team using raw case data and published case reports. The clinical team included nurses, pharmacists and physicians, including those working with adults and children. Previous experience with formal ADR assessment ranged from minimal to advanced. The assessment team comprised medical statisticians who focused discussion on how to classify cases and monitored progress using standard tools for inter-rater agreement. This approach has the strength of timeliness but the potential weaknesses of "group-think", in which independent thinking and expression of differences may be lost in the pursuit of group cohesiveness.

We believe that the Liverpool Causality tool has several advantages over the Naranjo tool. First, it performed as well as the Naranjo tool with the first set of cases that were assessed. The inter-rater reliability improved over time with the new tool, whereas the inter-rater reliability when using Naranjo remained similar, despite the fact that there was as much exposure to this tool within the assessing group. The improved inter-rater reliability with the new tool may be explained by increasing experience of its use.

The proportion of exact agreements between assessors was comparable between the two tools for both sets of cases despite the improvement in the global kappa for the new tool. This is because it is difficult to achieve a 'definite' category using the Naranjo tool and assessors mainly scored cases as 'possible' or 'probable.' Therefore, the chances of exact agreement between two assessors of the same case using the Naranjo tool are likely to be falsely elevated compared to the kappa scores which adjust for chance agreement. This paradox has been discussed previously in the literature [22,23,24].

The percentage of extreme disagreement between raters was higher for the Liverpool tool, when compared to Naranjo. Due to the difficulty in achieving a 'definite' score with Naranjo the chances of finding extreme disagreement, when comparing pair-wise assessments, is likely to be falsely low. The observed percentage of extreme disagreements decreased when using the Liverpool tool from the first set of 40 cases to the last set. This may also be explained by increasing experience of its use.

Second, the inter-rater reliability on assessing published case reports with the new tool was similar to that when we assessed our observational study cases with the Naranjo tool. Five of the seven assessors work in paediatric practice and the published case reports were adult cases. This perhaps provides an indication, albeit indirectly, of the robustness of the tool in assessing a range of case reports, even when used by assessors for cases from unfamiliar clinical settings.

Third, in the Naranjo tool, almost all cases were categorised as possible or probable. With the new tool, the range of categorisations was broader with some cases judged as being definite. A novel aspect of the tool which made this possible was that prior exposure that led to the same ADR, for example during a previous course of chemotherapy, was included and was thus judged as being equivalent to a prospective re-challenge. The high proportion of definite causality assessments can be explained by the fact that our study contained a large number of children with malignancies who had repeated courses of chemotherapy. It is also important to note that the cases were extracted from an observational study of suspected ADRs in children, and thus some case selection had occurred *a priori* making it improbable to record a score of 'unlikely' when assessing with either tool.

Fourth, a flow diagram rather than scoring system was used in the new tool for causality assessment and was felt by assessors to be easy to follow and quick to complete. We used a classification approach based on binary decisions (taking account of "don't know" responses). In this case, it is important to ensure that the binary decisions are robust. Once this has been done, then the instrument should be relatively context-independent. A weighted scoring system, such as the Naranjo tool, however will give more

influence to some variables than others. A weighting scheme requires the validation of both the items in the tool and the weightings themselves. Ideally, the weightings need to be developed and validated in a context that is similar to the context in which they are applied. Thus a weighting scheme is more likely to be sensitive and specific within a defined context (as long as you have a gold standard) but is more likely to be context-dependent. Thus we would conclude, that for ADRs where many different drugs can cause reactions in different settings, and where the patient's ADR may be assessed by healthcare professionals from a variety of backgrounds, it is more important to develop a tool that is context-independent.

Not unexpectedly, we were unable to achieve complete agreement about causality assessment for a minority of suspected ADRs. Most likely, this reflects underlying uncertainty arising from issues such as the perceived likelihood of alternative explanations. These perceptions will vary between raters depending on their experience or professional backgrounds.

In summary, we present a new causality assessment tool, developed by a multi-disciplinary team, which performed better than the Naranjo tool. We believe the new tool to be practicable and likely to be acceptable for use by healthcare staff in assessing ADRs. We have undertaken a validation of the tool, with a total of 819 causality assessments by seven investigators, using investigators within our ADRIC research programme. Although this validation is equivalent, if not better, than that undertaken for many other tools [10,25,26], one limitation is that the increase in IRR for the second set of 40 case reports using the new tool remains unexplained. We plan to investigate this using external validation in a randomised clinical trial. Another limitation is that the validation has been undertaken internally and not independently by other investigators. However, we feel that the tool shows promise, and by publishing it, we hope it will allow other investigators to undertake independent assessments of the usefulness of this tool in other populations (e.g. using data from adult or elderly care settings), not only for spontaneous reports but also for adverse events occurring within trials.

Supporting Information

Figure S1 Annals of Pharmacotherapy published adverse drug reaction case reports assessed using the Liverpool ADR Causality Assessment Tool.
(DOC)

Author Contributions

Conceived and designed the experiments: RMG JJK PRW RLS MP. Performed the experiments: RMG JRM KAB AJN MAT RLS MP. Analyzed the data: JJK RMG. Wrote the paper: RMG JJK PRW MAT RLS MP.

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Adverse Drug Reactions Causing Admission to a Paediatric Hospital

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Abstract

Objective(s): To obtain reliable information about the incidence of adverse drug reactions, and identify potential areas where intervention may reduce the burden of ill-health.

Design: Prospective observational study.

Setting: A large tertiary children's hospital providing general and specialty care in the UK.

Participants: All acute paediatric admissions over a one year period.

Main Exposure: Any medication taken in the two weeks prior to admission.

Outcome Measures: Occurrence of adverse drug reaction.

Results: 240/8345 admissions in 178/6821 patients admitted acutely to a paediatric hospital were thought to be related to an adverse drug reaction, giving an estimated incidence of 2.9% (95% CI 2.5, 3.3), with the reaction directly causing, or contributing to the cause, of admission in 97.1% of cases. No deaths were attributable to an adverse drug reaction. 22.1% (95% CI 17%, 28%) of the reactions were either definitely or possibly avoidable. Prescriptions originating in the community accounted for 44/249 (17.7%) of adverse drug reactions, the remainder originating from hospital. 120/249 (48.2%) reactions resulted from treatment for malignancies. The drugs most commonly implicated in causing admissions were cytotoxic agents, corticosteroids, non-steroidal anti-inflammatory drugs, vaccines and immunosuppressants. The most common reactions were neutropenia, immunosuppression and thrombocytopenia.

Conclusions: Adverse drug reactions in children are an important public health problem. Most of those serious enough to require hospital admission are due to hospital-based prescribing, of which just over a fifth may be avoidable. Strategies to reduce the burden of ill-health from adverse drug reactions causing admission are needed.

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Introduction

Children are vulnerable to adverse drug reactions (ADRs). [1,2,3,4,5,6] Spontaneous reporting systems, such as the UK Yellow Card scheme, [7] are subject to under reporting of ADRs, even those which are severe. [8] To obtain reliable information about the incidence of ADRs prospective studies are needed. A systematic review of observational studies of ADRs causing paediatric hospital admissions, between 1976 to 1996, estimated the rate of ADR admissions to be 2.1% (95% CI 1.0, 3.8). [9] A further review of prospective paediatric studies published between 2001 and 2007 did not identify any large studies of the incidence and nature of ADRs causing hospital admission. [10]

Some results of the present study, prior to publication, were included in a recent systematic review by Smyth et al in 2011 [11]. The authors reviewed prospective studies researching ADRs in three settings; ADRs in-patients, those causing acute admission to hospital and those occurring in out-patients. Incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of

Table 1. Univariate analyses of ADRs by age.

Age (years, months) [Median; Q1, Q3]	All	No ADR	ADR	Mann–Whitney U	P–value
All	[3y 1m; 9m, 9y] (n = 4656)	[3y 0m; 9m, 9y] (n = 4514)	[6y 0m; 2y 4m, 11y] (n = 142)	244161	<0.001
Oncology	[6y; 3y 6m, 12y] (n = 74)	[6y; 3y 6m, 13y] (n = 33)	[6y; 3y 0m, 10y] (n = 41)	580.5	0.296
Non–Oncology	[3y; 9m, 9y] (n = 4582)	[2y 11m; 9m, 9y] (n = 4481)	[6y; 1y 7m, 11y] (n = 101)	178319.5	<0.001

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all children (pooled estimate of 2.9% (2.6%, 3.1%)). Only 19/102 studies, from all three settings, assessed avoidability.

The aim of this study was to prospectively identify ADRs in children causing hospital admission during a one year period in order to quantify the burden of ADRs and characterise their features. The investigators aimed to determine the avoidability of identified ADRs and detail the reasons for determining reactions as avoidable. This aspect of ADRs causing admission in children has not been fully addressed in previous studies.

Methods

We prospectively screened all unplanned admissions to a tertiary paediatric hospital for ADRs over a one year period, including weekends and holidays, from 1st July 2008 to 30th June 2009. Admissions were excluded if they were planned, or occurred as a result of accidental or intentional overdose. Patients admitted to an Accident and Emergency (A&E) department short-stay 'observation ward' were not included. [12] The definition of ADR used was that of Edwards and Aronson which is "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." [13] This definition was chosen as it describes only clinically significant adverse reactions that cause harm and it includes the concept of preventive action.

Before the study began, an educational program was undertaken amongst clinicians of all grades to raise awareness about the importance of taking detailed medication histories. A structured medication history section was added to medical admission documentation to ensure details were taken about medication in the preceding two weeks. We identified all unplanned admissions in the previous 24 hours daily from hospital information systems. The study team collected the following information from case notes: age, sex, presenting complaint, clinical history, diagnosis (if available), and medications, including over-the-counter drugs, taken in the preceding two weeks. If any information was unclear, study team members interviewed the family to clarify the history.

We cross-referenced presenting symptoms/signs against the medication history for each patient using the ADR profile for relevant drugs from the Summary of Product Characteristics (SPC) [14] in the Medicines Compendium or, if not available, the British National Formulary (BNF) [15]. We identified possible ADRs using this information combined with the clinical history and temporal relationships of the medication(s) taken. We reported all possible ADRs to the responsible clinicians and to the Yellow Card scheme.

Table 3. Multivariate logistic regression analysis for risk factors for occurrence of ADR admission.

Parameter	Odds Ratio (OR)	95% CI for OR	P–value
Gender	0.77	0.52, 1.12	0.17
Age	1.04	1, 1.08	0.03
Oncology	29.71	17.35, 50.88	<0.01
Number of medicines	1.24	1.19, 1.29	<0.01

[a]Variable(s) entered on step 1: Gender (Male), Age, Oncology, Number of medicines.

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We assessed the origin of prescription for drugs thought to be associated with ADRs using classifications of:

- *Community* – drugs where prescriptions originated in community settings, for example general practice, or where administration took place prior to hospital admission (e.g. paramedic administered)
- *Hospital* – drugs where the prescription originated, or administration took place, in hospital and then may or may not have been continued in community or outpatient settings
- *Oncology* – all drugs prescribed, or administered, from the oncology ward.

Drug class, according to BNF classification, was recorded for drugs implicated in causing ADRs. We performed assessment of causality using the Liverpool ADR Causality Assessment Tool, an algorithm developed by the investigators. [16] A novel aspect of the tool, which allows for a case to be classified as 'definite'

Table 2. Univariate analyses of ADRs by number of medicines taken.

Drug Count [Median; Q1, Q3]	All	No ADR	ADR	Mann–Whitney U	P–value
All	[2;1,3] (n = 4656)	[2;1,3] (n = 4514)	[6;3,9] (n = 142)	115391.5	<0.001
Oncology	[6;4,9] (n = 74)	[4;3,7] (n = 33)	[8;5,10] (n = 41)	380.5	0.001
Non–Oncology	[2;1,3] (n = 4582)	[2;1,3] (n = 4481)	[5;3,9] (n = 101)	100371.5	<0.001

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Table 4. Classification of drugs associated with ADR admissions.

Drug class (No' of cases)	No of drugs	Drugs	ADRs
Cytotoxics (110)	275	Vincristine 51, Doxorubicin 38, Methotrexate 35, Etoposide 30, Mercaptopurine 27, Cytarabine 24, Ifosfamide 18, Cyclophosphamide 15, Carboplatin 7, Vinblastine 5, Pegasparaginase 5, Dactinomycin 5, Daunorubicin 4, Cisplatin 3, Irinotecan 3, Temozolomide 2, Fludarabine 1, Amsacrine 1, Imatinib 1	Neutropenia 89, Thrombocytopenia 55, Anaemia 38, Vomiting 8, Mucositis 8, Deranged Liver Function Tests 7, Immunosuppression 7, Diarrhoea 5, Nausea 4, Constipation 3, Headache 2, Abdominal pain 1, Back pain 1, Haematuria 1, Leukencephalopathy 1, Deranged renal function 1
Corticosteroids (102)	107	Dexamethasone 68, Prednisolone 33, Hydrocortisone 2, Betamethasone 1, Mometasone 1, Methylprednisolone 1, Fluticasone 1	Immunosuppression 71, Post-op bleeding 23, Hyperglycaemia 3, Hypertension 1, Gastritis 1, Increased appetite 1, Impaired healing 1, Adrenal suppression 1
NSAIDs (31)	43	Ibuprofen 28, Diclofenac 15	Post-op bleeding 27, Haematemesis 2, Constipation 1, Abdominal pain 1
Vaccines (22)	37	Diphtheria Tetanus Pertussis Inactivated polio Haemophilus Influenza vaccine 11, Pneumococcal conjugate 9, Meningococcal C 8, MMR 7, Haemophilus Influenza B 1, Influenza 1	Fever 8, Rash 5, Irritability 4, Seizure 4, Vomiting 3, Pallor 1, Apnoea 1, Limb swelling 1, Lethargy 1, Thrombocytopenia 1, Diarrhoea 1, Abdominal pain 1, Respiratory distress 1, Kawasaki disease 1
Drugs affecting the immune response (18)	26	Tacrolimus 15, Mycophenolate 7, Azathioprine 2, Methotrexate 1, Infliximab 1	Immunosuppression 18
Anti-bacterial (16)	17	Co-amoxiclav 4, Penicillin V 3, Amoxicillin 3, Flucloxacillin 2, Cefaclor 1, Cefalexin 1, Cefotaxime 1, Teicoplanin 1, Erythromycin 1	Diarrhoea 7, Rash 4, Vomiting 4, Lip swelling 1, Deranged LFTs 1, Thrush 1
Drugs used in diabetes (9)	13	Insulin detemir 4, Insulin aspart 3, Isophane insulin 2, Biphasic isophane 2, Human insulin 2,	Hypoglycaemia 9
Drugs used in status epilepticus (8)	12	Lorazepam 5, Diazepam 5, Midazolam 2	Respiratory depression 8
Opioid analgesia (6)	7	Dihydrocodeine 3, Codeine phosphate 3, Fentanyl 1	Constipation 4, Ileus 1, Decreased conscious level 1
Drugs used in nausea (4)	4	Ondansetron 4	Constipation 4
Anti-epileptic drugs (2)	2	Carbamazepine 1, Nitrazepam 1	Constipation 1, Respiratory depression 1
Drugs that suppress rheumatic disease (2)	2	Methotrexate 1, Anakinra 1	Immunosuppression 2
Other (16)	4	Calcium carbonate and Amlodipine 1, Oxybutynin 1, Baclofen 1	Constipation 3
	2	Dimeticone 1, Carbocysteine 1	Rash 2
	2	Desmopressin acetate 1, Alimemazine 1	Seizure 2
	10	Glucose and Dextrose 1, Propanolol 1, Acetazolomide 1, Spironolactone 1, Loperamide 1, Macrogols 1, Captopril 1, Alfacalcidol 1, Ethinylestradiol 1	Hyperglycaemia 1, Wheeze/Difficulty in breathing 1, Headache 1, Hyperkalaemia 1, Intestinal obstruction 1, Diarrhoea 1, Renal dysfunction 1, Hypercalcaemia 1, Inter-menstrual bleed 1

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causality, is that prior drug exposure that led to the same ADR was judged as being equivalent to a prospective re-challenge. Three investigators (RG, MT, AN) independently assessed causality for all ADR cases. Agreement on causality between all three investigators was taken as accepted consensus. Where the investigators did not achieve consensus, a fourth investigator (MuP) assessed cases to decide on causality.

The investigating group met to assess avoidability of the ADRs by consensus using the definitions developed by Hallas et al. [17] We determined the type of ADR (using the Rawlins and Thompson classification) [18] and severity using the Hartwig scale. [19] We chose these assessment tools to describe the ADRs in our study as they have been used in ADR studies by other investigators and can be completed quickly. Three investigators (AN, MuP, RLS) independently assessed 217/4514 (4.8%) reports of admissions exposed to medication, but deemed not to have had an ADR, to assess for occurrence of possible ADR cases wrongly classified by the study team.

We calculated the mean cost of ADR admissions to the study hospital, using information provided by the finance department for the cost of each case. Paediatric emergency admission data from the Health and Social Care Information Centre (National Health Service (NHS)), between 2009/2010, was used to estimate the total cost of ADR admissions annually in England.

Ethics Statement

The Liverpool Paediatric Research Ethics Committee issued a formal opinion that this study was audit and informed consent from individual patients was not necessary.

Statistical Analysis

Analyses of the rates of ADRs were based on the number of admissions with the rate expressed as ADR per 100 admissions, together with 95% confidence intervals. Other results are presented as medians and interquartile ranges or percentage frequencies and 95% percent confidence intervals. The formal statistical analysis was based on the data obtained at the first admission for patients exposed to a medication. Univariate statistical analyses were performed using the Mann-Whitney U test except for frequency data, which were analysed using a chi-square test. A multivariate logistic regression analysis was undertaken to calculate odds ratios for possible risk factors for ADR.

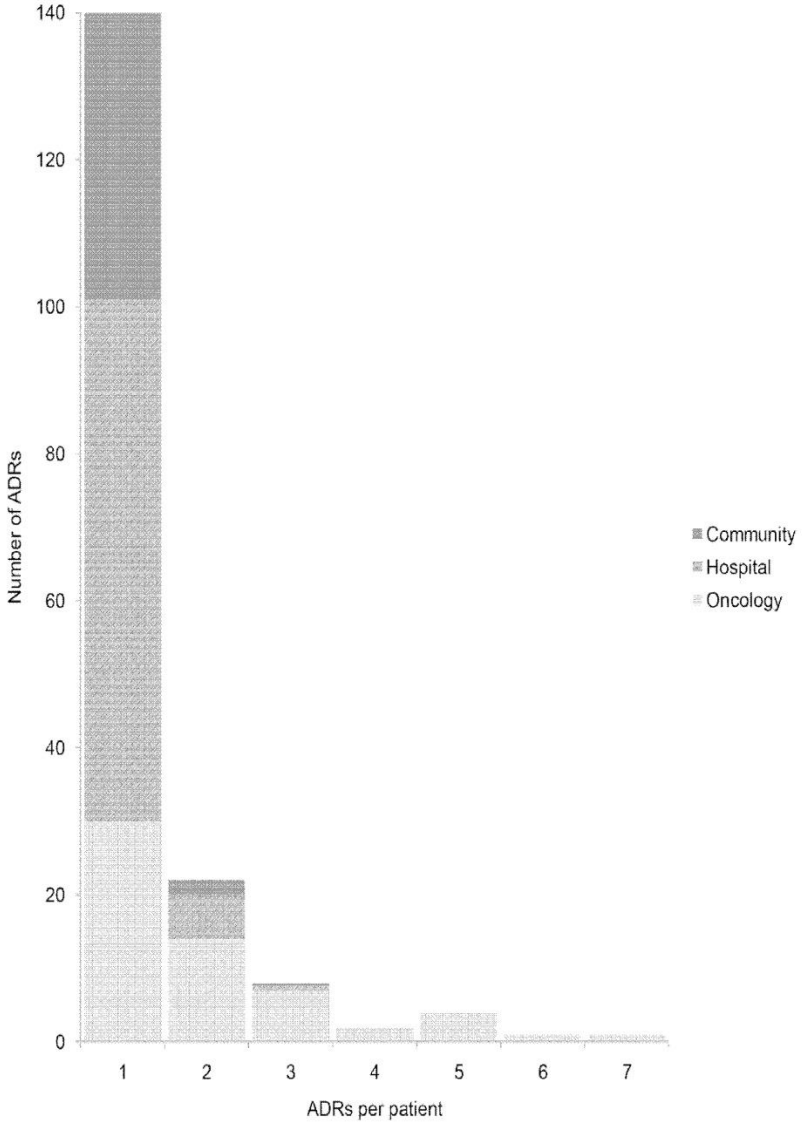

Figure 1. Number of ADRs per patient with ≥ one ADR according to origin of prescription.
doi:10.1371/journal.pone.0050127.g001

A P-value <0.05 was regarded as being significant. All data were analyzed anonymously.

Results

Over the study period, there were 6821 patients (3961 boys and 2860 girls) admitted 8345 times to the study hospital. The median number of admissions per patient was one, with 932 patients having more than one acute admission, up to a maximum of fifteen. 178 patients (94 boys, 84 girls) experienced 240 admissions with an ADR. This gives an incidence of 2.9 ADRs per 100 admissions (95% CI 2.5, 3.3). In 233 of 240 (97.1%) admissions an ADR was deemed to have directly caused, or contributed to, admission. There were 249 ADRs in 240 admissions, with nine admissions having two separate ADRs. 35/178 (19.7%) patients

Table 5. Possibly and definitely avoidable cases and explanation of assessment result.

Avoidable	Frequency	ADR(s)	Drug Classes	Reason for potential avoidability
Definitely	3	Diarrhoea and/or vomiting	Anti-bacterial	Inappropriate indication, signs/symptoms of viral illness
Definitely	2	Constipation	Cytotoxics, Drugs used in nausea, Opioid analgesia	Appropriate prophylaxis not used
Definitely	1	Lip swelling, rash	Anti-bacterial	Same ADR previously to same medication
Definitely	1	Seizure	Antihistamine	Same ADR previously to similar medication
Definitely	1	Adrenal suppression	Corticosteroids	Avoidable with more rational prescribing (prolonged use of drugs) and improved monitoring
Definitely	1	Intestinal obstruction	Anti-motility drugs	Could be prevented by improved parent/ patient education
Definitely	1	Deranged renal function	Drugs affecting the renin-angiotensin system	Avoidable with improved monitoring
Possibly	9	Hypoglycaemia	Drugs used in diabetes	Avoidable with improved patient education (e.g. insulin use when unwell) and more rational prescribing
Possibly	8	Respiratory depression	Drugs used in status epilepticus, Hypnotics	Alternative medicine available, Multiple doses given - avoidable with more rational prescribing
Possibly	6	Diarrhoea/vomiting	Anti-bacterial	Inappropriate indication, symptoms suggested viral infection
Possibly	5	Constipation	Antiepileptic drugs, Opioid analgesia, Drugs used in nausea, NSAIDs, Cytotoxics, Calcium-channel blockers, Calcium supplements	Prophylaxis not used
Possibly	4	Immunosuppression	Drugs affecting the immune response, Corticosteroids	Possibly Avoidable with improved monitoring of drug levels, Avoidable with more rational prescribing
Possibly	2	Haematemesis	NSAIDs	Avoidable with improved patient education/ more rational prescribing (less NSAID use)
Possibly	1	Neutropenia	Cytotoxics	Same ADR previously at same dose of medication
Possibly	1	Neutropenia, thrombocytopenia, anaemia	Cytotoxics	Superficial infection after recent admission with febrile neutropenia. Possibly avoidable by prolonging antibiotic use or commencing GCSF
Possibly	1	Hyperglycaemia	Corticosteroids	Avoidable with more rational prescribing (prolonged course steroids used)
Possibly	1	Hyperglycaemia	Parenteral preparations	Avoidable with more rational prescribing (more judicial use) or improved monitoring
Possibly	1	Seizure	Posterior pituitary hormones	Possibly inappropriate medication used for a patient with seizures
Possibly	1	Diarrhoea	Laxatives	Avoidable with improved patient education
Possibly	1	Ileus	Opioid analgesia	Avoidable with more rational prescribing (possibly use alternative analgesia)
Possibly	1	CNS depression	Opioid analgesia	Avoidable with improved patient education
Possibly	1	Vomiting	Cytotoxics	Possibly avoidable with more appropriate anti-emetic prophylaxis
Possibly	1	Gastritis	Corticosteroids	Previous gastritis. Possibly avoidable with improved prophylaxis
Possibly	1	Hypercalcaemia	Vitamins	Avoidable with improved monitoring

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had more than one admission (maximum seven) with an ADR. Assessment of a sample of non-ADR cases (n = 217) confirmed that no admissions were due to ADRs.

There were 4656 patients exposed to medication in the two weeks prior to acute hospital admission. Of these, 142 (3%) had a suspected ADR on their first hospital admission. There was no significant difference between the proportion of boys (76/2677, 2.8%) and girls (66/1979, 3.3%) experiencing an ADR on their first admission, for the group as a whole or oncology patients studied separately. For non-oncology patients, there was a slightly higher proportion of girls admitted with an ADR (boys 48/2627

(1.8%), girls 53/1955 (2.7%), P = 0.044), although overall more boys than girls were admitted.

The median age of the 4656 patients who had been exposed to a drug on their first admission was 3 years 1 month (IQR 9 months, 9 years). Patients with an ADR (6y; 2y 4m, 11y) were significantly older (P<0.01) than those without (3y; 9m, 9y) (Table 1). There was no age difference between 41 oncology patients admitted with an ADR (6y; 3y, 10y) and 33 oncology patients admitted without an ADR (6y; 3y 6m, 13y). There was a significant age difference (P<0.01) between 101 non-oncology patients admitted with ADR (6y; 1y 7m, 11y) and 4481 admitted without ADR (2y 11m; 9m, 9y).

Patients admitted with an ADR had taken a greater number of drugs than those admitted for other reasons (Table 2). For patients admitted with an ADR (n = 142), the number of medicines taken was higher (6; 3, 9, P<0.001) than those for other reasons (n = 4514) (2; 1, 3). The number of medicines taken by oncology patients admitted with an ADR (8; 5, 10) was higher than those admitted without an ADR (4; 3, 7) and this difference was also found for non-oncology patients (with ADR 5; 3, 9: without ADR 2; 1, 3).

Logistic regression analysis showed a trend towards boys being less likely to experience an ADR than girls, with an odds ratio (OR) of 0.77 (95% CI 0.52, 1.12, P = 0.17) (Table 3). There was an increased likelihood of ADRs with increasing age (OR 1.04, 95% CI 1.003, 1.08, P = 0.03). No children were admitted with an ADR in the first month of life. Oncology patients were much more likely to have an ADR causing admission (OR 29.71, 95% CI 17.35, 50.88, P<0.001). The likelihood of a child being admitted with an ADR increased with the number of medicines taken (OR 1.24, 95% CI 1.19, 1.29, P<0.001). Therefore, for each additional medicine taken the risk of an ADR occurring increases by almost 25%.

Drug Class

The main class of drugs contributing to ADR-related admissions (n = 110; 44.2%) was cytotoxic drugs (Table 4). Corticosteroids (n = 102, 41%), non-steroidal anti-inflammatory drugs (NSAIDs) (n = 31, 12.4%), vaccines (n = 22, 8.8%) and immunosuppressants (n = 18, 7.2%) were the next most commonly implicated drug classes causing ADR-related hospital admissions.

ADRs

The most common ADRs were oncology related including neutropenia (89), thrombocytopenia (55) and anaemia (38). The next most common ADR was immunosuppression (74), occurring in both oncology and non-oncology patients. Post-operative bleeding, linked to peri-operative corticosteroid administration and/or NSAIDs, caused 28 admissions (26 post-tonsillectomy). Vomiting (15), diarrhoea (14), rash (11) and constipation (9) were all common ADRs causing admission. Hypoglycaemia in diabetic patients treated with regular insulin caused nine admissions. Respiratory depression following treatment for status epilepticus caused eight admissions to the hospital's paediatric intensive care unit (PICU).

Origin of Prescriptions

44/249 (17.7%) of ADRs were associated with prescriptions from the community, 85/249 (34.1%) with prescriptions originating in hospital for treatment of conditions other than oncology; 120/249 (48.2%) with prescriptions originating from oncology. Of the patients with one ADR (n = 140) in the study period, 39 (27.9%) occurred with community prescriptions, 71 (50.7%) with hospital prescriptions and 30 (21.4%) with oncology prescriptions; hospital-based prescriptions, particularly oncology, predominated in patients who had more than one ADR (Figure 1).

ADR Assessments (Reaction Type, Causality, Severity, Avoidability)

238/249 (95.6%) ADRs were classified as type A (predictable from the known pharmacology) with 11/249 (4.4%) being type B (not predictable). Assessment of causality showed the majority of cases (94/249, 37.8%) to be in the 'definite' category. Oncology cases accounted for 80 of these 94 definite cases (Table S1). 92/238 (39.1%) type A reactions were assessed to be of definite causality. 8/11 (72.7%) type B reactions were assessed to be 'possible.'

223/249 (89.6%) of the ADRs were classified as grade 3 ('required treatment or drug administration discontinued') according to the Hartwig severity scale, as we defined anyone requiring admission to hospital as 'needing treatment.' 14 (5.6%) were classified as grade 4 ('resulted in patient transfer to higher level of care') including respiratory depression (8), immunosuppression (4), neutropenia (1), fever/seizure (1) and leukencephalopathy (1). Three ADRs were classified as grade 5 ('caused permanent harm or significant haemodynamic instability'). Two of these most severe ADRs occurred in oncology patients with febrile neutropenia and septicaemia and the remaining case was a child who required bowel resection for ileus following treatment with loperamide. No ADRs contributed to death. The majority (16/17, 94.1%) of the more severe reactions (≥ Grade 4 Hartwig severity score) were assessed to have definite or probable causality.

We determined 112/120 (93.3%) of the oncology patient admission ADRs to be unavoidable, with a further six being possibly avoidable and two definitely avoidable. These 'definitely avoidable' cases were oncology patients with constipation following treatment with vincristine and ondansetron (with one also having dihydrocodeine) without laxative prophylaxis.

Of the ADR admissions not associated with oncology patients, 82/129 ADRs (63.6%) were classified as unavoidable, 39 (30.2%) as possibly avoidable (14/39 prescribed from the community) and 8 (7.6%) as definitely avoidable (5/8 prescribed from the community). The eight 'definitely avoidable' comprised four patients prescribed antibiotics where the antibiotic choice or indication was deemed to be inconsistent with good practice, one patient with intestinal obstruction being treated with loperamide who had not passed stool for two days prior to admission, one patient who had a seizure after alimemazine having had two previous occurrences of seizure following anti-histamine use, one patient with deranged renal function which improved after cessation of captopril where improved renal function monitoring may have avoided the ADR, and one patient who presented with adrenal suppression following two years of continuous treatment with intranasal corticosteroids. The possibly avoidable cases and the reasons for their allocation are summarised in Table 5. 41/55 (74.5%) of possibly or definitely avoidable cases were classified as 'definite' or 'probable' causality.

Cost of ADRs

We calculated the mean cost of 238/240 ADR admissions to the study hospital, using information provided by the finance department, to be £4753 per admission (95% CI £3439, £6066). Cost data were missing for two ADR admissions. Data from the Health and Social Care Information Centre (National Health Service (NHS)) [20] showed, in one year between 2009/2010, the total number of paediatric emergency admissions in England was approximately 597,800 (includes paediatrics and paediatric surgery, cardiology and neurology). We estimate the annual mean

cost of ADR admissions to the NHS in England to be £82.4M. Using the upper and lower confidence intervals for our estimate of ADR incidence (2.5%, 3.3%), and study hospital costs, we estimate the cost to the NHS in England to be between £51.4–119.7M.

Discussion

This prospective observational study is the largest of its kind in children and the only one to comprehensively assess causality, type of reaction, severity, avoidability and risk factors. In our setting, the majority of admissions associated with ADRs in children occurred as a result of prescriptions originating in hospital. Potential preventative strategies for ADRs causing admission in children should therefore be targeted at hospital prescribing. Our analysis of the 'definitely avoidable' ADRs in our study suggests careful attention to practical aspects of care, such as improved monitoring, following prescribing guidelines, patient education, and heightened suspicion about potential reactions could lead to a reduction in the frequency of this important problem.

This study gave an estimated ADR admission incidence of 2.9% (95% CI 2.5, 3.3), which is similar to a pooled estimate of 2.9% (2.6%, 3.1%) from a recent comprehensive systematic review. [11] The incidence of ADRs in this study was significantly less than that of a large US study published in 1988 (3.96%, 95%CI 3.52, 4.43). [2] In that study the top three drugs causing ADRs were phenobarbital, aspirin and phenytoin, all of which are used in children much less now because of safety concerns and because better alternatives are available. The majority of ADRs that were seen during our study were oncology related. Oncology patients are often exposed to medications causing ADRs, including neutropenia, nausea, vomiting, diarrhoea and thrombocytopenia, all of which may require admission. [21] These ADRs are expected and may be unavoidable given the underlying illness and the treatment options available. Although several studies have evaluated a potential preventative strategy for neutropenia [22], no definite evidence exists regarding the use of granulocyte-colony stimulating factors (GCSF) to prevent such ADRs [23].

Steroids, along with other immunosuppressants, increase risk of infection. [24] These ADR admissions were children taking steroids, admitted with proven bacterial, or viral infections associated with immunosuppression, such as shingles. Although such infections occur in healthy children, immunosuppressive therapy may be causal and this may be an under-recognised ADR.

The majority of admissions for post-operative bleeding (23/28) occurred in patients exposed to intravenous dexamethasone for anti-emetic prophylaxis, and non-steroidal anti-inflammatory drugs (NSAIDs). A few patients received either steroid or NSAIDs. Dexamethasone has been linked to post-tonsillectomy bleeding [25] but its role, and the role of NSAIDs, in causing secondary haemorrhage is yet to be determined. [26,27] However, intra-operative steroids have played a major role in improving post-operative nausea and vomiting in children. [26,28]

Respiratory depression following treatment of seizures with benzodiazepines, a well recognised event, [29] was the cause of eight PICU admissions, some of whom were transfers from other district general hospitals. Some occurred as a result of rectal diazepam used by paramedics in out-of-hospital care. The benefit/risk ratio of drugs used to treat seizures has been the objective of a number of clinical studies [30,31], and there may be better drugs to treat seizures in children. [32]

Assessment of avoidability was undertaken by consensus approach using the definitions by Hallas. The definitions, which are based on avoidability linked to standards of care, are wide and may lead to variability in assessor rating. The Hallas criteria are less prescriptive than some other avoidability tools but there is little evidence to suggest preference for the use of any one avoidability tool. [33]

While this study has highlighted important ADRs, we cannot be certain of the aetiological fraction (the risk of an event occurring in the presence of a risk factor) for some of the drugs in their contribution to the ADRs. Further prospective, cohort studies that capture benefits and harms using validated tools and all medication exposures with adequate sample size are needed to assess this accurately and to estimate more precisely risks compared to benefits.

We calculated the cost of ADRs to the NHS in England using knowledge of the cost of admissions to the study hospital, our estimate of the incidence of ADRs causing admission and an estimate of total paediatric admissions annually to hospitals in England, although this may be an underestimate, as the multiplier which we used (total paediatric emergency admissions), did not include admissions of children from other specialities.

Conclusion

We have demonstrated that ADRs cause a small but substantial proportion of admissions to hospital and some of these are serious and potentially avoidable. The results of this study should be used to inform paediatric pharmacovigilance practice. Preventing avoidable ADRs will require careful attention to good prescribing practice.

Supporting Information

Table S1 Origin of prescription of ADR drugs by type of reaction, severity score, avoidability and causality assessment. (DOCX)

Author Contributions

Conceived and designed the experiments: RMG JRM KAB JJK M. Peak PRW AJN MAT M. Pirmohamed RLS. Performed the experiments: RMG JRM KAB AJN MAT M. Pirmohamed RLS. Analyzed the data: RMG JJK PRW. Wrote the paper: RMG JRM KAB JJK M. Peak PRW AJN MAT M. Pirmohamed RLS.

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