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Rosalind L Smyth,[1,2*] Matthew Peak,[3†] Mark A Turner,[4] Anthony J Nunn,[5] Paula R Williamson,[6] Bridget Young,[7] Janine Arnott,[7] Jennifer R Bellis,[3] Kim A Bird,[3] Louise E Bracken,[3] Elizabeth J Conroy,[6] Lynne Cresswell,[6] Jennifer C Duncan,[3] Ruairi M Gallagher,[1] Elizabeth Gargon,[6] Hannah Hesselgreaves,[7] Jamie J Kirkham,[6] Helena Mannix,[3] Rebecca MD Smyth,[8] Signe Thiesen[1] and Munir Pirmohamed[9]

[1]Institute of Child Health, University of Liverpool, Liverpool, UK
[2]Institute of Child Health, University College London, London, UK
[3]Alder Hey Children's National Health Service Foundation Trust, Liverpool, UK
[4]Institute of Translational Medicine, Liverpool Women's National Health Service Foundation Trust and University of Liverpool, Liverpool, UK
[5]National Institute for Health Research Medicines for Children Research Network, University of Liverpool, Liverpool, UK
[6]Department of Biostatistics, University of Liverpool, Liverpool, UK
[7]Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK
[8]School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, UK
[9]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK

*Corresponding author
†Corresponding author

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Abstract

ADRIC: Adverse Drug Reactions In Children – a programme of research using mixed methods

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[1]Institute of Child Health, University of Liverpool, Liverpool, UK
[2]Institute of Child Health, University College London, London, UK
[3]Alder Hey Children's National Health Service Foundation Trust, Liverpool, UK
[4]Institute of Translational Medicine, Liverpool Women's National Health Service Foundation Trust and University of Liverpool, Liverpool, UK
[5]National Institute for Health Research Medicines for Children Research Network, University of Liverpool, Liverpool, UK
[6]Department of Biostatistics, University of Liverpool, Liverpool, UK
[7]Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK
[8]School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, UK
[9]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK

*Corresponding author rosalind.smyth@ucl.ac.uk
†Corresponding author matthew.peak@alderhey.nhs.uk

Aims: To comprehensively investigate the incidence, nature and risk factors of adverse drug reactions (ADRs) in a hospital-based population of children, with rigorous assessment of causality, severity and avoidability, and to assess the consequent impact on children and families. We aimed to improve the assessment of ADRs by development of new tools to assess causality and avoidability, and to minimise the impact on families by developing better strategies for communication.

Review methods: Two prospective observational studies, each over 1 year, were conducted to assess ADRs in children associated with admission to hospital, and those occurring in children who were in hospital for longer than 48 hours. We conducted a comprehensive systematic review of ADRs in children. We used the findings from these studies to develop and validate tools to assess causality and avoidability of ADRs, and conducted interviews with parents and children who had experienced ADRs, using these findings to develop a leaflet for parents to inform a communication strategy about ADRs.

Results: The estimated incidence of ADRs detected in children on admission to hospital was 2.9% [95% confidence interval (CI) 2.5% to 3.3%]. Of the reactions, 22.1% (95% CI 17% to 28%) were either definitely or possibly avoidable. Prescriptions originating in the community accounted for 44 out of 249 (17.7%) of ADRs, the remainder originating from hospital. A total of 120 out of 249 (48.2%) reactions resulted from treatment for malignancies. Off-label and/or unlicensed (OLUL) medicines were more likely to be implicated in an ADR than authorised medicines [relative risk (RR) 1.67, 95% CI 1.38 to 2.02;

$p < 0.001$]. When medicines used for the treatment of oncology patients were excluded, OLUL medicines were not more likely to be implicated in an ADR than authorised medicines (RR 1.03, 95% CI 0.72 to 1.48; $p = 0.830$). For children who had been in hospital for > 48 hours, the overall incidence of definite and probable ADRs based on all admissions was 15.9% (95% CI 15.0 to 16.8). Opiate analgesic drugs and drugs used in general anaesthesia (GA) accounted for > 50% of all drugs implicated in ADRs. The odds ratio of an OLUL drug being implicated in an ADR compared with an authorised drug was 2.25 (95% CI 1.95 to 2.59; $p < 0.001$). Risk factors identified were exposure to a GA, age, oncology treatment and number of medicines. The systematic review estimated that the incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children [pooled estimate of 2.9% (95% CI 2.6% to 3.1%)] and from 0.6% to 16.8% of all children exposed to a drug during hospital stay. New tools to assess causality and avoidability of ADRs have been developed and validated. Many parents described being dissatisfied with clinician communication about ADRs, whereas parents of children with cancer emphasised confidence in clinician management of ADRs and the way clinicians communicated about medicines. The accounts of children and young people largely reflected parents' accounts. Clinicians described using all of the features of communication that parents wanted to see, but made active decisions about when and what to communicate to families about suspected ADRs, which meant that communication may not always match families' needs and expectations. We developed a leaflet to assist clinicians in communicating ADRs to parents.

Conclusion: The Adverse Drug Reactions In Children (ADRIC) programme has provided the most comprehensive assessment, to date, of the size and nature of ADRs in children presenting to, and cared for in, hospital, and the outputs that have resulted will improve the management and understanding of ADRs in children and adults within the NHS. Recommendations for future research: assess the values that parents and children place on the use of different medicines and the risks that they will find acceptable within these contexts; focusing on high-risk drugs identified in ADRIC, determine the optimum drug dose for children through the development of a gold standard practice for the extrapolation of adult drug doses, alongside targeted pharmacokinetic/pharmacodynamic studies; assess the research and clinical applications of the Liverpool Causality Assessment Tool and the Liverpool Avoidability Assessment Tool; evaluate, in more detail, morbidities associated with anaesthesia and surgery in children, including follow-up in the community and in the home setting and an assessment of the most appropriate treatment regimens to prevent pain, vomiting and other postoperative complications; further evaluate strategies for communication with families, children and young people about ADRs; and quantify ADRs in other settings, for example critical care and neonatology.

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List of abbreviations

%EA	exact agreement percentages
%ED	percentage of extreme disagreement
A&E	accident and emergency
AAT	avoidability assessment tool
ADE	adverse drug event
ADR	adverse drug reaction
ADRIC	Adverse Drug Reactions In Children
AE	adverse event
Alder Hey	Alder Hey Children's NHS Foundation Trust
BNF-C	*British National Formulary for Children*
BTS	British Thoracic Society
CAMHS	Child and Adolescent Mental Health Services
CAT	causality assessment tool
CI	confidence interval
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EU	European Union
FDA	US Food and Drug Administration
GA	general anaesthesia
HDU	high-dependency unit
HR	hazard ratio
IMD	Index of Multiple Deprivation
IQR	interquartile range
IRR	inter-rater reliability
LCAT	Liverpool Causality Assessment Tool
LOS	length of stay
MA	marketing authorisation
MCRN	Medicines for Children Research Network
MDT	multidisciplinary team
MeSH	medical subject heading
MHRA	Medicines and Healthcare products Regulatory Agency
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSAID	non-steroidal anti-inflammatory drug
OLUL	off-label and/or unlicensed
OR	odds ratio
PICU	paediatric intensive care unit
PK/PD	pharmacokinetic/ pharmacodynamic
PONV	postoperative nausea and vomiting
RR	relative risk
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	summary of product characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCU	transitional care unit
WHO	World Health Organization

Plain English summary

Many common medicines have not been tested on children either properly or at all. We wanted to improve the safety of medicines used in children by investigating their side effects [adverse drug reactions (ADRs)].

We showed that three out of every 100 children admitted to hospital experienced an ADR due to a medicine taken at home. One out of five times this might have been avoidable. Nearly half of all ADRs were due to anticancer medicines.

We found that one in six children experienced an ADR while in hospital. More than half were due to medicines used in general anaesthesia and to treat pain after an operation. We used the results of these studies to develop tools to assess the likelihood of symptoms resulting from an ADR (causality) and whether an ADR was avoidable (avoidability).

We reviewed the literature on previous studies of ADRs in children and found that most studies had flaws in design and reporting, and lacked essential information, such as the name of the drugs causing ADRs and whether they were avoidable.

We interviewed children, parents and clinicians about ADRs. Many children and parents thought that communication about medicines could be improved, whereas parents of children with cancer were generally happy about the way clinicians communicated. Clinicians often made decisions about when and what to tell families but this did not always match what parents needed or expected. To address this, we developed information leaflets for parents and children to support communication between clinicians and families about ADRs.

Scientific summary

Background

Drug safety is an important issue in all medical disciplines but in paediatrics this is compounded by the fact that medicines are often not tested in children, and therefore at the time of licensing there is no indication for use in children. This leads to off-label and/or unlicensed (OLUL) prescribing, estimated to occur in 25% of paediatric inpatient prescriptions. It is clear that extrapolation of efficacy, dosing regimens and adverse drug reactions (ADRs) from adult data to children is inappropriate owing to size differences, developmental changes in physiology and drug handling. Taken together with the fact that the pattern of diseases in children is different from that in adults, this puts them at high risk of serious and unpredictable ADRs. Much of the work to identify and address these problems was led from Liverpool, and this programme of research was conceived to address important gaps in the evidence.

Most studies to date have focused on individual aspects of ADRs, for example ADRs causing hospital admission, ADRs occurring within small, specialised units, etc. However, no previous programme of work has looked at the whole spectrum from when and where ADRs are occurring to developing solutions to reduce the burden of ADRs. Our research planned to focus on this spectrum and the clinical studies were conducted in the largest children's hospital in Europe, with between 12,000 and 13,000 admissions per annum. During the course of the programme, we found that none of the commonly used tools to assess causality and avoidability of ADRs was sufficiently reliable to be used in these studies. This led us to develop and validate new assessment tools (see objectives 4 and 5, below). We also wished to assess the impact of ADRs on families to identify any unmet communication needs. Because of the scale of the communication problems that we identified, the final objective of the programme was to develop strategies to improve communication between clinicians and families about ADRs.

Objectives

1. To determine the incidence of ADRs that were associated with admission to hospital in children; describe their causality, severity, avoidability and nature; and identify which children were particularly at risk of this complication.
2. To determine the incidence of ADRs that occurred in children in hospital; characterise them in terms of type, drug aetiology, causality and severity; and identify risk factors for the occurrence of ADRs in hospitalised children.
3. To conduct a systematic review of observational studies of ADRs in children in three settings: causing admission to hospital; occurring during hospital stay; and occurring in the community. We were particularly interested in understanding how these ADRs might be better detected, assessed and avoided.
4. To develop and validate a new ADR causality assessment tool (CAT) that would be easy to use and reliable.
5. To develop and validate a new ADR avoidability assessment tool (AAT) that would be generalisable and applicable to a variety of settings.
6. To identify any unmet information and communication needs described by families following a suspected ADR in a child.
7. To develop a strategy to support communication between families and clinicians by identifying any barriers to effective communication with families from the perspective of clinicians following a suspected ADR, and to develop information leaflets about ADRs for parents, children and young people to support their communication with clinicians.

Methods

All clinical studies were conducted in Alder Hey Children's NHS Foundation Trust (Alder Hey), a large children's hospital, with an accident and emergency department, providing local and specialist regional and national paediatric care in the north-west of England. Participants were aged between 0 and 16 years 11 months. Study 1 was a prospective observational study of all acute paediatric admissions, over a 1-year period, of all children who had taken any form of medication during the previous 2 weeks. The outcome measure was a suspected ADR. Study 2 was a prospective cohort study of children admitted over 48 hours; patients were not observed while admitted to the paediatric intensive care unit (PICU), the transitional care unit (TCU), theatre, recovery or the department of radiology. A nested case–control study within the cohort examined the impact of OLUL drug use on ADR risk.

The systematic review was conducted by searching 19 electronic databases using a comprehensive search strategy. The primary outcome was any clinical event described as an ADR to one or more drugs. Additional information relating to the ADR was collected: associated drug classification; clinical presentation; associated risk factors; methods used for assessing causality, severity and avoidability.

A new ADR CAT, the Liverpool Causality Assessment Tool (LCAT), and a new AAT were developed by the 'Adverse Drug Reactions In Children' (ADRIC) programme group to address the limitations of the widely used Naranjo CAT and the Hallas scale, respectively. The LCAT was compared with the Naranjo CAT in 80 cases from a prospective observational study and 37 published ADR case reports (819 causality assessments in total). The AAT development occurred in two phases: first defining the tool, modifying the tool and refining the tool, by a multidisciplinary team, and, second, the independent assessment of 50 ADR cases from study 2 by six different reviewers and a comparison of the results. Following the completion of phase 2, it was decided that further testing was needed and that perhaps the best way to assess avoidability is in a group setting. Agreement in phase 2 ranged from poor to good; possible reasons for this may be attributable to lack of experience in certain specialty areas or a possible training effect. The next step in the development process will be to carry out group assessments of additional cases and look for an improvement in the results. For both CAT and AAT, we assessed utilisation of categories, measure of disagreements and inter-rater reliability (IRR).

We conducted semistructured qualitative interviews with 20 children and young people, and the parents of 44 children and young people who had experienced a suspected ADR. Interviews were conducted face to face or by telephone; most were audio-recorded and transcribed. To develop a communication strategy about ADRs between clinicians and families, we conducted semistructured qualitative interviews with 42 clinicians about their experiences of ADRs in children. Face-to-face interviews were audio-recorded and transcribed. The parental leaflet on ADRs was developed based on feedback from a range of stakeholders, including parents and clinicians. The usefulness of the leaflet was further examined by conducting structured interviews with 17 clinicians after they had used the leaflet during routine parent–clinician discussions about suspected ADRs. Analysis of these parts of the programme was informed by the principles of the constant comparative method.

Findings

In study 1, 240 out of 8345 admissions in 178 out of 6821 patients admitted acutely to a paediatric hospital were thought to be related to an ADR, giving an estimated incidence of 2.9% [95% confidence interval (CI) 2.5% to 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 ADR. Of the reactions, 22.1% (95% CI 17% to 28%) were either definitely or possibly avoidable. Prescriptions originating in the community accounted for 44 out of 249 (17.7%) ADRs, the remainder originating from hospital. Of 16,551 prescription medicine courses, 11,511 (69.5%) were authorised, 4080 (24.7%) were off-label and 960 (5.8%) were unlicensed. Treatment for malignancies resulted in 120 out of 249 (48.2%) reactions. The drugs most commonly implicated in

causing admissions were cytotoxic agents, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), vaccines and immunosuppressant drugs. OLUL medicines were more likely to be implicated in an ADR than authorised medicines [relative risk (RR) 1.67, 95% CI 1.38 to 2.02; $p < 0.001$]. When medicines used to treat oncology patients were excluded, OLUL medicines were not more likely to be implicated in an ADR than authorised medicines (RR 1.03, 95% CI 0.72 to 1.48; $p = 0.830$). The most common reactions were neutropenia, immunosuppression and thrombocytopenia.

In study 2, over the 1-year period, 5118 children were admitted to hospital for > 48 hours. Of all children, 17.7% experienced at least one ADR. Opiate analgesic drugs and drugs used in general anaesthesia (GA) accounted for > 50% of all drugs implicated in ADRs. A total of 0.9% of ADRs caused permanent harm or required admission to a higher level of care. The hazard of an ADR for children after GA is more than six times that in children who had not received a GA [hazard ratio (HR) 6.38, 95% CI 5.30 to 7.68]. Other factors increasing the risk of an ADR were increasing age (HR 1.06 for each year, 95% CI 1.04 to 1.07), increasing number of drugs (HR 1.25 for each additional drug, 95% CI 1.22 to 1.28) and oncological treatment (HR 1.89, 95% CI 1.36 to 2.63). Our nested case–control study included 1388 patients. The odds ratio of an OLUL drug being implicated in an ADR compared with an authorised drug was 2.25 (95% CI 1.95 to 2.59; $p < 0.001$). Risk factors identified were exposure to a GA, age, oncology treatment and number of medicines.

One hundred and two studies were included in the systematic review. Seventy-one per cent (72/102) of studies assessed causality and 33% (34/102) performed a severity assessment. Only 19 studies (19%) assessed avoidability. Incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children [pooled estimate of 2.9% (95% CI 2.6% to 3.1%)] and from 0.6% to 16.8% of all children exposed to a drug during hospital stay. Anti-infective drugs and antiepileptic drugs were the most frequently reported therapeutic class associated with ADRs in children admitted to hospital (17 studies and 12 studies, respectively) and children in hospital (24 studies and 14 studies, respectively), whereas anti-infective drugs and NSAIDs were frequently reported as associated with ADRs in outpatient children (13 studies and 6 studies, respectively). Fourteen studies reported rates ranging from 7% to 98% of ADRs being either definitely or possibly avoidable.

The LCAT, 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 (κ) = 0.48] compared with Naranjo (0, 100, 172, 8) with 'moderate' IRR ($\kappa = 0.45$). In a further 40 cases, the LCAT (0, 66, 81, 133) showed 'good' IRR ($\kappa = 0.6$), whereas Naranjo (1, 90, 185, 4) remained 'moderate'.

In the qualitative study to assess the impact on families of their children experiencing an ADR, many parents described being dissatisfied with clinicians' communication about ADRs. In contrast, the accounts of parents of children with cancer emphasised confidence in clinicians' management of ADRs and the way clinicians communicated about medicines. The accounts of children and young people largely reflected parents' accounts. Families were positive about the Yellow Card Scheme and felt recording and reporting ADRs was important. Parents, children and young people linked symptoms to medicines using a similar reasoning as clinicians use to evaluate the possibility of an ADR.

Clinicians reported all of the features of communication about ADRs that parents wanted to see. However, clinicians made active decisions about when and what to communicate to families about suspected ADRs. These decisions mean that communication may not always match families' needs and expectations. Clinicians describe a number of complexities with effective communication, some of which are unique to paediatric settings. The complexities perceived by clinicians may explain, at least in part, the discordance between clinician and family perspectives. Clinicians found the leaflet useful in supporting discussions with parents about a suspected ADR in their child.

Conclusions

1. 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 one-fifth may be avoidable.
2. ADRs are as common in hospitalised children as in hospitalised adults. A concerning aspect of our findings was that GA agents and opiate analgesic drugs were the most important causes. OLUL drugs are more likely to be implicated in an ADR than authorised drugs. It is important to develop strategies to reduce the burden of ADRs occurring in hospitalised children and these areas merit particular attention.
3. Our systematic review found that although there is extensive literature that investigates ADRs in children, studies are heterogeneous and generally not well reported. Further work is needed to address how ADRs in children may be prevented.
4. The LCAT 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.
5. The Liverpool ADR AAT showed mixed IRR in the individual assessment phase therefore further testing in a group setting is required to develop and validate the tool.
6. Most parents felt clinicians' communication about ADRs was poor, suggesting that improvements are needed. The accounts of parents of children with cancer indicate that prospective explanation about ADRs can be effective. Convergence between parents and clinicians in their reasoning for linking children's symptoms to medicines could be a starting point for improved communication.
7. The parent leaflet was useful in supporting discussions between parents and clinicians about suspected ADRs. Further strategies to improve communication between families and clinicians should focus on aligning clinicians' decision-making about what and when to communicate with the priorities of families following a suspected ADR.

Funding

Funding for this study was provided by the Programme Grants for Applied Research programme of the National Institute for Health Research.

Chapter 1 Introduction

Drug safety is an important issue in all disciplines. The World Health Organization's (WHO) stated definition of an adverse drug reaction (ADR) is 'A response to a drug which is noxious, and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function'.[1]

The problem of drug safety in paediatrics is compounded by the fact that medicines are often not tested in children, and therefore at the time of licensing there is no indication for use in children. For example, in 2006 around 75% of all 317 centrally licensed medicines were relevant for children but only half (34%) had a paediatric indication.[2] This leads to off-label and/or unlicensed (OLUL) prescribing: this has been estimated to occur in 25%[3] of paediatric inpatient prescriptions and 65% of neonatal prescriptions.[4] It is clear that extrapolation of efficacy, dosing regimens and ADRs from adult data are inappropriate owing to developmental changes in physiology and drug handling.[5] Taken together with the fact that the pattern of diseases in children is different from that in adults, this puts them at high risk of serious and unpredictable ADRs from the use of medicines. As with any population, distinguishing between an ADR and non-drug-induced pathology is difficult but is further compounded in this age group. Important examples of ADRs in children include deaths associated with propofol used for paediatric intensive care unit (PICU) sedation,[6] acute adrenal crisis associated with inhaled corticosteroids,[7] grey baby syndrome in neonates associated with chloramphenicol,[8] the threefold increase in Stevens–Johnson syndrome with lamotrigine[9] and colonic strictures in cystic fibrosis owing to high-strength pancreatic enzymes.[10] The last of these examples was first reported at Alder Hey Children's NHS Foundation Trust (Alder Hey) in Liverpool; the primary author led the study confirming the association with pancreatic enzyme therapy and because of this, and subsequent regulatory measures, this problem is no longer reported in the UK. A trend towards more ADRs when OLUL medicines are prescribed in children and young people was first reported from this research group.[11] However, the recognition of serious new ADRs generally depends on a cluster of individuals presenting with a similar pattern of unexplained clinical features and there is no systematic, pre-emptive approach to this problem in children, largely because of the dearth of good-quality scientific evidence on this topic. The burden of ADRs in children has not been systematically assessed and the knowledge base of the impact of ADRs in children on morbidity, overall health economy and societal consequences is poorly understood. In addition, methods to detect and assess causality and avoidability of suspected ADRs have not been validated in children. Evidence suggests that patients are generally poorly informed about medicines and the systems to ensure drug safety.[12] There is a need to consider communication about ADRs as an integral component of medicine adherence as well as an important transaction in its own right. Particular concerns surround children's medicines; although health-care professionals have access to mechanisms to report and manage suspected ADRs, little is known about the understanding and experiences of families who experience a suspected ADR. Given the lack of robust evidence in the broad spectrum of ADR burden and characterisation in the population of children and young people, and the lack of knowledge and understanding of the interactions between health-care professionals and families whose child experiences a suspected ADR, Adverse Drug Reactions In Children (ADRIC) was designed to address this knowledge gap.

The regulatory and policy perspective of pharmacovigilance in children and young people

The Department of Health recognised the importance of the development of medicines and drug safety science in children by establishing the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) in 2006. Assessment of the harms of medicines is as important as assessment of their benefits and is integral to the proposals within the European regulation on medicines for children[13] and the guidance on pharmacovigilance in children. In July 2012, new pharmacovigilance legislation came into effect across the European Union (EU),[14] including centralised reporting by industry of ADRs to the

EudraVigilance database at the European Medicines Agency (EMA) and the inclusion of reports from patients as valid, reportable ADRs. The Children and Young People's Outcomes Strategy (commissioned by the Secretary of State for Health) identified the need to optimise the safe use of medicines.[15] In 2008, there were 33,000 safety incidents in children reported to the National Reporting and Learning System by health-care professionals, and of these 19% were for a medication problem. This led to a recommendation report that 'the Medicines and Healthcare Products Regulatory Agency (MHRA), with immediate effect, prioritises pharmacovigilance of children's medicines, including medication errors and off-label use, in line with the new EU legislation effective in July 2012'.[16]

The MHRA is responsible for monitoring the safety of medicines in the UK.[17] The collection and analysis of reports of ADRs is critical to the MHRA's responsibility to monitor the safety of medicines in practice: this is achieved through the submission of spontaneous reports of suspected ADRs by health-care professionals and the public through the Yellow Card Scheme.[18] The Yellow Card Scheme is designed to detect signals that may indicate a potential hazard with a medicine, leading to further investigations that may result in withdrawal of the medicine or changes in prescribing recommendations and restrictions in its use. Signal detection from spontaneous reports of ADRs and subsequent guidance in risk–benefit decisions is highly dependent on the availability of reliable instruments to assess ADR causality, which presents difficulties in paediatric pharmacovigilance. There is considerable variation in reporting of ADRs by practitioners and the potential for under-reporting and, partly in response to these concerns, the Yellow Card Scheme was extended to patients and families in 2005. The detail of individual ADR reports from patients is generally superior to those of health-care professionals, contributing to the EU pharmacovigilance legislation.[16] There is a clear statement through legislation, regulation and policy recommendations that the framework for pharmacovigilance in children is suboptimal and that a broader understanding of the assessment and improvement in the systems and quality of reporting of ADRs in this age group is urgently needed.

Burden of adverse drug reactions in children and young people

Given the stated importance of medicines for children by the Department of Health and the EMA, as well as other international authorities, it is important that we perform robust studies to fill knowledge gaps in the burden of ADRs in children and young people. Drugs are the mainstay of treatment in paediatric practice, yet a high proportion of drugs have not been tested in children. This leads to OLUL prescribing, the use of inappropriate doses, the use of age-inappropriate formulations, which may result in underdosing or overdosing, and drug development without due regard for the processes that are vital for normal development of a child into an adult. There are data showing that the current practice of drug development and drug use in paediatrics leads to avoidable adverse effects, which lead to morbidity and mortality. There is a need to identify the burden of ADRs in children; this has been emphasised by recent documents from the EMA and the US Food and Drug Administration (FDA), and is one of the important aims of the MCRN.

A number of studies have been performed in children to determine the incidence of ADRs; however, there are deficiencies in the evidence available at present. There is a lack of reliable and contemporary data estimating how frequently ADRs are causing admissions, how frequently they occur in general paediatric wards, how frequently they are life-threatening or cause death, and how often they could have been avoidable by better prescribing, better information in summary of product characteristics (SmPC) or better monitoring. Additionally, we do not have the tools to prevent these reactions. A number of studies have attempted to estimate the incidence of ADRs in children and have reported data on ADR rates causing admission to hospital, within inpatients and in the outpatient setting. The summary data confirmed that ADRs in children are a considerable burden. However, studies to date have varied considerably in their methodological rigour,[19] including the definition of an ADR used, the age range of the study population and the clinical settings for data collection. Similarly, systematic reviews and meta-analyses of studies of ADRs in children also demonstrate methodological limitations, including the source bibliographical databases, definitions of ADRs to include adverse events (AEs) and exclusion of paediatric data from

studies that included both adults and children. For example, a previous systematic review pointed out that there was substantial heterogeneity in the incidence estimates in the different studies reflecting differing, and often inadequate, methodologies that were used. Often the severity of the ADR was not reported, and patient age, diagnosis and drug prescription patterns were often not reported, and thus could not be considered in determining factors associated with ADRs in children. The need to conduct rigorous, prospective studies of ADRs in children, both which cause hospital admission[20,21] and within the inpatient setting,[22] was clearly needed. In addition, a methodologically rigorous systematic review incorporating the findings of these novel prospective studies was required.[19]

Assessment of causality and avoidability of adverse drug reactions in children and young people

In addition to the overall burden of ADRs, the characterisation of individual ADRs provides essential information in the context of drug safety science: two important factors are assessment of causality and avoidability. Causality assessment estimates the strength of the relationship between drug exposure and the occurrence of an ADR. Assessment of ADR avoidability, or preventability, does not have a universally accepted definition, but there are two conventionally recognised principles: whether in the absence of error an event is preventable, and, if so, whether the event can be prevented. The concepts of causality and avoidability are relevant to health-care professionals, regulators, the pharmaceutical sector and the academic community, although the context may vary among these constituencies. Regardless of the reason or motivation to undertake causality or avoidability assessments, the availability of reliable and valid instruments to generate meaningful data is essential. Given the difficulties in distinguishing between ADRs and non-drug-induced pathology in children, these aspects are of particular importance in this population.

The Naranjo ADR probability scale[23] is most widely used and reported causality assessment tool (CAT). This instrument contains 10 weighted items that generate a construct to produce a total score resulting in categorisation of the event as either unlikely, possible, probable or definite. Each item is based on concepts including temporal relationships, biological plausibility and rechallenge/previous exposure. The instrument was developed by adult physicians and psychiatrists using published case reports to validate instrument reliability. The validity and reliability of the Naranjo tool has been subject to challenge and, in addition, the use of the instrument to assess causality of ADRs in children is questionable given that individual items were developed and validated using adult case reports.[24]

There is currently no standardised method for determining ADR avoidability and many of the established tools are not suitable for use in paediatric practice. A number of instruments have been developed for assessment of ADR avoidability and a systematic review found that several definitions exist for the preventability of drug-related harm as a consequence of the variability in methodological approaches to assessment of avoidability, and none fits all circumstances.[25] The authors of the systematic review proposed an approach to preventability, based on analysis of the mechanisms of ADRs and their clinical manifestations. Some authors have proposed a methodological framework for future studies of ADR avoidability and the development of valid instruments.[26] This includes reliability and validity testing, standardisation of the measurement processes, description of assessor training and experience in assessing preventability, details of independent or consensus assessments and rationalisation of assessor disagreement. These authors recommend that there is a need to modify existing instruments or develop novel instruments for use in different settings and populations.

The available instruments for assessment of causality and avoidability of ADRs vary in reliability and validity.[19] In particular, the assessment of avoidability is compromised by a lack of consensus on the definition of avoidability and associated heterogeneity in underpinning methodology for instrument development. No instruments are available specifically for characterisation of ADRs in children and young people, and there is a requirement to develop such instruments.

Communication about drug safety in children and young people

Previous literature on communication concerning medicines highlights the benefits of open discussion between health-care professionals and patients, at the time of prescribing, on their potential risks and the importance of supplementary written information in conveying key messages about drug safety.[12,27] Despite the movement towards patient reporting of ADRs and changes in EU legislation on pharmacovigilance in children,[16] patients and their families are generally poorly informed about ADRs and pharmacovigilance systems to optimise safety of medicines. Other than in the context of understanding parental beliefs and attitudes to childhood vaccination, very little is known about the experiences of parents whose child has experienced a suspected ADR.[28] As a consequence, health-care professionals have no approriate evidence base from which to inform either generic or individualised communication strategies with the family when a child experiences a suspected ADR. In addition, there is little knowledge and documentary evidence of the experience of health-care professionals in the same circumstances. The perspectives of health-care professionals regarding what information parents require during episodes of suspected ADRs, have not been described and the mechanisms for decision analysis and motivations which underpin the timing, content and narrative of communication by clinicians has not been explored. In addition, there has been no attempt to identify if there are barriers to effective communication with families from the perspective of clinicians following a suspected ADR. More fundamentally, we did not know if the nature of the communication by health-care professionals about ADRs meets the needs and expectations of parents. Despite the beneficial impact of written supplementary information on the understanding of drug safety at the point of prescribing, this paradigm has not extended into circumstances when there is a suspected ADR in children. There are no customised written materials, generated with the involvement of relevant stakeholders, which provide a framework within which communication between health-care professionals and parents can be guided, and, in particular, documentation intended for parents, which allows enquiry and dialogue to be initiated and led from their perspective. Beyond this, it is important that further materials to guide communication pay adequate attention to key principles of transaction and process, including what and when to communicate to families, as opposed to developing and modifying the communication skills of clinicians.[29]

The Adverse Drug Reactions In Children programme

Most studies of pharmacovigilance in children and young people to date have focused on individual aspects of ADRs, for example ADRs causing hospital admission and ADRs occurring within small specialised units. However, no programme of work has investigated a broad spectrum incorporating when and where ADRs occur, characterising the nature of ADRs in this age group, developing instruments customised for assessment of casuality and avoidability of ADRs in paediatric practice, and understanding the narratives and communications between families and health-care professionals during episodes of suspected ADRs. ADRIC was designed to undertake a comprehensive and coherent suite of studies aiming to add significantly to the existing evidence base and to generate outputs that can be adopted into both clinical practice and further research to improve methodologies for our understanding and management of pharmacovigilance in this vulnerable age group.

The ADRIC research strategy comprised the following component parts, which logically follow on from each other:

- *Quantification* To estimate the incidence of ADRs in children, causing admission to hospital, and to estimate the burden to the health-care economy; to estimate the incidence of ADRs in hospitalised children.

- *Evaluation* To identify risk factors for ADRs in causing admission to hospital and for causing ADRs in hospitalised children, and to characterise these ADRs in terms of type, drug aetiology, causality, avoidability and severity. To identify the unmet communication needs of parents whose child has experienced a suspected ADR.
- *Instrument development* To develop and validate instruments to improve the assessment of causality and avoidability of ADRs in children.
- *Intervention* To develop written materials that will guide the communication between parents and health-care professionals following an episode of a suspected ADR(s).

The methodologies used to undertake the above aims included two large and comprehensive single-centre prospective observational studies; a systematic review; reliability and validity testing of novel ADR assessment instruments; qualitative enquiry; structured interviews and evaluation of intervention implementation.

The ADRIC team was assembled with the necessary expertise to achieve the aims set out above. The Senior Investigator Team comprised paediatricians and neonatologists, a clinical pharmacologist with extensive experience in leadership and design of studies of assessment of ADRs in the adult population, experienced secondary researchers, a senior paediatric pharmacist, a senior academic psychologist with experience in qualitative methodologies for understanding the experience of children and families, and a NIHR Paediatric Clinical Research Network Director. Members of the team also hold executive positions within the NIHR MCRN and membership of expert committees, including the EMA and the UK Commission on Human Medicines.

The ADRIC study was supported by a steering group to provide an independent strategic overview of the programme. The steering group was overseen by an independent chairperson (Professor Sir Alisdair Breckenridge, Chairman, MHRA) and included senior representation from the MHRA (Director of Vigilance and Risk Management), US FDA, international academic paediatric pharmacovigilance expertise, and the chairperson of the NIHR Research Methods programme. A management group, comprising ADRIC senior investigators and members of the research team, was responsible for the design, implementation, analysis and reporting of each study within the overall of the programme.

A multidisciplinary research team comprised paediatric research nurses, research pharmacists, paediatric medical research fellows and research associates in qualitative methodologies. The setting for the ADRIC study was Alder Hey, widely recognised as the largest specialist children's health-care provider in Western Europe, serving a population of children and young people in excess of two million and acting as a tertiary referral centre for much of the north-west of England and north Wales. Alder Hey provides general and all specialist paediatric services at local, regional and national levels. Community child health services are provided alongside Child and Adolescent Mental Health Services (CAMHS) over a large geographical footprint. The full range of paediatric services is provided at a single site with 325 beds and typically there are annually 120,000 outpatient episodes, 26,000 inpatient admissions including day case episodes, 70,000 accident and emergency (A&E) attendances, 1000 critical care admissions and 13,000 CAMHS episodes at Alder Hey (with 14,400 CAMHS outpatient episodes in community teams). ADRIC was conducted over a 5-year period, between May 2008 and April 2013.

Chapter 2 Adverse drug reactions causing admission to a paediatric hospital

Abstract

Objective(s)
To determine the incidence of ADRs, which were associated with admission to hospital in children, describe their causality, severity, avoidability and nature, and identify which children were particularly at risk of this complication. To identify potential areas where intervention may reduce the burden of ill health.

Design
Prospective observational study.

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

Participants
All acute paediatric admissions over a 1-year period.

Main exposure
Any medication taken in the 2 weeks prior to admission.

Outcome measures
Occurrence of ADR.

Results
In total, 240 out of 8345 admissions in 178 out of 6821 patients who were admitted acutely to a paediatric hospital were thought to be related to an ADR, giving an estimated incidence of 2.9% [95% confidence interval (CI) 2.5% to 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 ADR. Overall, 22.1% (95% CI 17% to 28%) of the reactions were either definitely or possibly avoidable. Prescriptions originating in the community accounted for 44 out of 249 (17.7%) of ADRs, the remainder originating from hospital. Of 16,551 prescription medicine courses, 11,511 (69.5%) were authorised, 4080 (24.7%) were off-label and 960 (5.8%) were unlicensed. A total of 120 out of 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 (NSAIDs), vaccines and immunosuppressants. OLUL medicines were more likely to be implicated in an ADR than an authorised medicines [relative risk (RR) 1.67, 95% CI 1.38 to 2.02; $p < 0.001$]. When medicines used for the treatment of malignancies were excluded, OLUL medicines were

not more likely to be implicated in an ADR than authorised medicines (RR 1.03, 95% CI 0.72 to 1.48; $p = 0.830$). 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 one-fifth may be avoidable. Strategies are needed to reduce the burden of ill health from ADRs causing admission.

Introduction

Children are vulnerable to ADRs.[32–37] A recent retrospective study by Hawcutt *et al.*[38] identified 31,726 of 222,755 (14.2%) ADR reports received by the UK MHRA through the Yellow Card Scheme, from 2000 to 2009, concerned children of < 17 years of age.[38] However, it is well recognised that spontaneous reporting systems, such as the Yellow Card Scheme in the UK,[39] are subject to under-reporting of ADRs, even those that are severe.[40] 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 problem in the UK.

Hospital-based ADRs can be identified by retrospective studies using case note review; such studies, however, are likely to be less reliable than prospective studies in estimating the frequency with which ADRs occur owing to the inadequacy of recorded information. 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 and 1996, estimated the overall rate of paediatric hospital admissions due to ADRs in children to be 2.1% (95% CI 1.0% to 3.8%).[34] This review included five prospective observational studies investigating ADRs causing admission in children.[32,33,41–43] Three of the studies were large, including > 1000 admissions each.[32,33,41] Three of the studies used published measures to assess causality of ADRs,[41–43] whereas the two largest studies in the review used self-derived definitions for assessing causality.[32,33] Only one of the studies,[41] with a low comparative reported ADR incidence of 10 out of 1682 admissions (0.6%), reported on avoidability of the cases using an adapted version of a published method[44] but did not detail which ADRs were deemed avoidable or the reasons for assessing ADRs as being avoidable. The other studies did not report avoidability of the admissions associated with ADRs.

A further systematic review of prospective studies published between 2001 and 2007 included four studies[37,45–47] but did not identify any large significant studies detailing the incidence and nature of ADRs causing admission of children to hospital.[35] Three studies[37,45,46] included < 1000 admissions and the remaining study[47] included a study population of 39,625 admissions but resulted in an ADR admission rate of only 0.16%. All four studies[37,45–47] assessed causality using a published algorithm. However, only one study reported the avoidability of the ADR cases.[46] This study[46] did not give detail of the method used for assessing avoidability, nor did the investigators detail the reasons for assigning cases as avoidable.

There have been no large paediatric studies that have looked at ADRs leading to hospital admission and then gone on to consider the influence of OLUL medicine use. There is one small pilot study[48] that included ADRs to medicines administered before admission and recorded whether or not the medicines implicated were off-label. Of the 41 ADRs detected in 41 out of 1619 patients, 12 were attributed to medicines administered before admission and 29 were attributed to medicines administered in the hospital. In 16 out of the 41 patients experiencing an ADR, an off-label medicine was implicated; five of these were patients who experienced an ADR due to medicines administered before admission.

The aim of this study was to prospectively identify ADRs in children causing admission to hospital during a 1-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. In addition, the impact of OLUL medicine use on ADR risk in this context was examined.

Methods

The study hospital had an induction programme that was delivered to new members of staff to educate them about the hospital and some aspects of specific practice within the setting. This 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 programme was undertaken within the hospital among 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. First, 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. Second, 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 2 weeks. A 2-week medication history was chosen as the time when reactions causing admission were most likely to have occurred following exposure to a drug. A 2-week pilot study to develop and refine the methodology for this larger study was conducted prior to the commencement of this study.[20]

The study team prospectively screened all unplanned admissions to a large paediatric centre (which provides local and specialist regional and national services) for ADRs over a 1-year period, including weekends and public holidays, from 1 July 2008 to 30 June 2009. 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 overdose. The definition of ADR used was that of Edwards and Aronson,[49] 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, for the patients coded as having an emergency admission, from the hospital computer system to a password-protected Microsoft Access 2007 database (Microsoft Corporation, Redmond, WA, USA) stored on a secure hospital hard drive. Only the study team had access to the database and the patient information recorded within.

Members of the study team, consisting of a paediatric registrar (RMG), a research pharmacist (JRB) and a research nurse (KAB) collected the following information from the case notes of each patient: presenting complaint, summary of clinical history and diagnosis (if available at the time of admission). The details of any medication taken at any time during the 2 weeks before admission were recorded, specifically drug name, route, dose, frequency, duration, indication (if this required clarification) and whether it was a prescription or non-prescription medicine. The data on prescription medicine use were scrutinised in order

to define each medicine course as either authorised, off-label, unlicensed or unknown. Authorised use was defined as the use of a medicine with a UK marketing authorisation (MA), within the terms of that MA. The terms of the MA were found in the SmPC available online from the Electronic Medicines Compendium (EMC).[50] If no SmPC was available, the *British National Formulary for Children* (BNF-C)[51] was consulted for details of the product MA. If neither reference source provided adequate clarity of information, the manufacturer of the medicine was contacted. Off-label use was defined as the use of a medicine with a UK MA, outside the terms of that MA. According to the definitions described by Turner *et al.*,[52] unlicensed medicines were defined as those without a UK MA, and an 'unknown' category was reserved for medicine courses for which inadequate detail was available to decide whether use was authorised or OLUL. 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 SmPC[50] in the EMC or, if not available, the BNF-C.[51] 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 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:

1. ***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).
2. ***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.
3. ***Oncology*** All drugs administered, or prescribed, from the oncology ward. These drugs may or may not be cytotoxic in nature.

We performed assessment of causality for all cases using the Liverpool Causality Assessment Tool (LCAT).[53] Three investigators (RMG, JRB, KAB) independently assessed causality for all possible ADR cases. Agreement on causality category between all three investigators was taken as accepted consensus. In cases when the three investigators did not achieve consensus, a fourth investigator assessed cases to decide on causality (MPir).

Avoidability of the ADR cases was assessed by consensus meeting between the investigators, using the definitions developed by Hallas *et al.*[54] 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[55] as either Type A (predictable from the known pharmacology) or Type B (not predictable). Severity was determined using an adapted Hartwig scale.[56] This adapted scale is shown in *Table 1*. Grades 3 and 4 are adapted from the original schema, as not all ADR admissions necessitate cessation of the causative drug(s).

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 out of 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 (AJN, MPir, MAT).

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% CIs. Other results are presented either as medians and interquartile ranges (IQRs) or percentage frequencies and 95% CI, as appropriate. The formal statistical

TABLE 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

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-squared test. Multivariate logistic regression analysis was undertaken to calculate odds ratios (ORs) for possible risk factors for ADR. The RR (with 95% CI) for OLUL medicines being implicated in an ADR was calculated for prescription medicines. A p-value of < 0.05 was regarded as being significant.

Ethics

This study used routinely collected clinical data in an anonymised format. The chairperson of Liverpool Paediatric Local Research Ethics Committee informed us that this study did not require individual patient consent or review by an ethics committee.

Results

Over the study period, there were 6821 patients admitted acutely to the study hospital, accounting for 8345 unplanned admissions. Boys accounted for 3961 out of 6821 (58.1%) patients and 4793 out of 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 15. A total of 178 patients experienced 240 admissions with an ADR. This gives an incidence of 2.9 ADRs per 100 admissions (95% CI 2.5 to 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 out of 178 (19.7%) patients had more than one admission with an ADR, up to a maximum of seven.

There were 4656 patients exposed to a medication in the 2 weeks prior to acute admission to the hospital. Of these patients, 142 (3%) had a suspected ADR on their first hospital admission within the study period. 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 2*). 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.

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 to 9 years). Patients with an ADR (6 years, IQR 2 years 4 months to 11 years) were significantly older ($p < 0.001$) than those without (3 years, IQR 9 months to 9 years) (*Table 3*). There was no age difference between the 41 oncology patients admitted with an ADR (6 years, IQR 3–10 years) and the 33 oncology patients admitted without an ADR (6 years, IQR 3 years 6 months to 13 years). There was a significant age difference ($p < 0.001$) between 101 non-oncology patients admitted with ADR (6 years, IQR 1 year 7 months to 11 years) and 4481 admitted without ADR (2 years 11 months, IQR 9 months to 9 years).

TABLE 2 Univariate analyses of ADRs by gender

Gender		All	No ADR	ADR	Chi-squared test	*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
	Girls	24	11 (45.8%)	13 (54.2%)		
Non-oncology	Boys	2627	2579 (98.2%)	48 (1.8%)	4.062	0.044
	Girls	1955	1902 (97.3%)	53 (2.7%)		

TABLE 3 Univariate analyses of ADRs by patient age

Age (years, months); median: quartile 1, quartile 3	All	No ADR	ADR	Mann–Whitney *U*-test	*p*-value
All	3 years 1 month; 9 months, 9 years ($n = 4656$)	3 years 0 months; 9 months, 9 years ($n = 4514$)	6 years 0 months; 2 years 4 months, 11 years ($n = 142$)	244,161	< 0.001
Oncology	6 years; 3 years 6 months, 12 years ($n = 74$)	6 years; 3 years 6 months, 13 years ($n = 33$)	6 years; 3 years 0 months, 10 years ($n = 41$)	580.5	0.296
Non-oncology	3 years; 9 months, 9 years ($n = 4582$)	2 years 11 months; 9 months, 9 years ($n = 4481$)	6 years; 1 year 7 months, 11 years ($n = 101$)	178,319.5	< 0.001

Patients admitted with an ADR had taken a greater number of drugs than those admitted for other reasons (*Table 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).

Logistic regression analysis showed a trend towards boys being less likely to experience an ADR than girls, with an OR of 0.77 (95% CI 0.52 to 1.12; $p = 0.17$) (*Table 5*). There was an increased likelihood of ADRs with increasing age (OR 1.04, 95% CI 1.003 to 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 to 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 to 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 Univariate analyses of ADRs by number of medicines taken

Drug count	All (median; IQR)	No ADR	ADR	Mann–Whitney *U*-test	*p*-value
All	2 (1–3) ($n = 4656$)	2 (1–3) ($n = 4514$)	6 (3–9) ($n = 142$)	115,391.5	< 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) ($n = 101$)	100,371.5	< 0.001

TABLE 5 Multivariate logistic regression analysis

Parameter[a]	OR	95% CI for OR	*p*-value
Gender (male)	0.77	0.52 to 1.12	0.17
Age	1.04	1 to 1.08	0.03
Oncology	29.71	17.35 to 50.88	< 0.01
No. of medicines	1.24	1.19 to 1.29	< 0.01

a Variable(s) entered on step 1: gender (male), age, oncology, no. of medicines.

A further univariate analysis was carried out which included only patients on their first admission who had received at least one prescription medicine in the 2 weeks prior to admission ($n = 3869$). This analysis compared each continuous variable in the group of patients who had experienced at least one ADR with those who had not in three subpopulations: all patients, patients who had been exposed to at least one OLUL medicine and patients who had received only authorised medicines. There was no significant difference in the proportion of each gender in any of the subpopulations. The median age and median number of medicines was greater in patients who had experienced at least one ADR; however, within the population of patients exposed to authorised medicines only there was no difference. The median number of medicines was significantly greater in children who experienced an ADR for all subpopulations. Oncology patients and patients exposed to OLUL medicines were significantly more likely to experience an ADR (*Table 6*). Multivariate analysis indicated oncology patients were more likely to have experienced an ADR: OR 25.70 (95% CI 14.56 to 45.38; $p < 0.001$). The number of authorised medicines courses administered in the 2 weeks before admission was a significant ADR risk factor (OR 1.25, 95% CI 1.16 to 1.35; $p < 0.001$) but so was the number of OLUL medicines administered (OR 1.23, 95% CI 1.10 to 1.36; $p < 0.001$). In addition, increasing age was associated with an increased risk of ADR; OR 1.04 (95% CI 1.00 to 1.08; $p = 0.045$). There was a trend towards females being more likely to experience an ADR: OR 0.74 (95% CI 0.51 to 1.09; $p = 0.130$) (*Table 7*).

TABLE 6 Univariate analyses of ADRs for all first admissions who received at least one prescription medicine in the 2 weeks before admission by gender, age and number of medicines taken ($n = 3869$)

Variable		All	No ADR	ADR	*p*-value
Gender					
All boys		2247	2172 (96.7%)	75 (3.3%)	0.271[a]
All girls		1622	1557 (96.0%)	65 (4.0%)	
OLUL exposed	Boys	869	812 (93.4%)	57 (6.6%)	0.982[a]
	Girls	627	585 (93.3%)	42 (6.7%)	
Authorised only	Boys	1321	1303 (98.6%)	18 (1.4%)	0.063[a]
	Girls	953	930 (97.6%)	23 (2.4%)	
Age (years, months): median; quartile 1, quartile 3					
All		3 years 1 month; 8 months, 9 years ($n = 3869$)	3 years; 8 months, 9 years ($n = 3729$)	6 years; 2 years 4 months, 11 years ($n = 140$)	< 0.001[b]
OLUL exposed		2 years 5 months; 3 months, 8 years ($n = 1595$)	2 years 1 month; 3 months, 7 years ($n = 1496$)	7 years; 3 years 7 months, 12 years ($n = 99$)	< 0.001[b]
Authorised only exposed		3 years 8 months; 1 year, 10 years ($n = 2274$)	3 years 8 months; 1 year, 10 years ($n = 2233$)	3 years 9 months; 8 months; 8 years 6 months ($n = 41$)	0.968[b]
No. of medicines: median; quartile 1, quartile 3					
All		2; 1, 4 ($n = 3869$)	2; 1, 4 ($n = 3729$)	6; 3, 9 ($n = 140$)	< 0.001[b]
OLUL exposed		3; 2, 6 ($n = 1565$)	3; 2, 5 ($n = 1496$)	8; 5, 10 ($n = 99$)	< 0.001[b]
Authorised only exposed		2; 1, 3 ($n = 2274$)	2; 1, 3 ($n = 2233$)	3; 2, 6 ($n = 41$)	0.003[b]
Specialty					
Oncology		73	32 (43.8%)	41 (56.2%)	< 0.001[a]
Non-oncology		3796	3697 (97.4%)	99 (2.6%)	
OLUL exposure					
OLUL exposed		1595	1496 (93.8%)	99 (6.2%)	< 0.001[a]
Authorised only exposed		2274	2233 (98.2%)	41 (1.8%)	

a Chi-squared test.
b Mann–Whitney *U*-test.

TABLE 7 Multivariate logistic regression analysis for all first admissions who received at least one prescription medicine in the 2 weeks before admission ($n = 3869$)

Variable	OR (95% CI)	*p*-value
Gender (male)	0.74 (0.51 to 1.09)	0.130
Specialty (oncology)	25.70 (14.56 to 45.38)	< 0.001
No. of authorised medicines	1.25 (1.16 to 1.35)	< 0.001
No. of OLUL medicines	1.23 (1.10 to 1.36)	< 0.001
No. of unknown medicines	0.84 (0.59 to 1.18)	0.303
Age in years	1.04 (1.00 to 1.08)	0.045

Drug classes and drugs

The main class of drugs contributing to ADR-related admissions ($n = 110$; 44.2%) was cytotoxic drugs (*Table 8*). Corticosteroids ($n = 102$, 41%), NSAIDs ($n = 31$, 12.4%), vaccines ($n = 22$, 8.8%) and immunosuppressant drugs ($n = 18$, 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. A total of 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.

There were 17,758 prescription medicine courses given to 3869 patients in the 2 weeks prior to admission. Of these, 1207 (6.8%) could not be categorised, 11,511 (64.8%) were authorised, 4080 (23.0%) were off-label and 960 (5.4%) were unlicensed. OLUL medicines were more likely to be implicated in an ADR than authorised medicines [RR 1.67 (95% CI 1.38 to 2.02)]. In total, 14,923 out of 16,106 medicine courses administered to non-oncology patients could be categorised. Of these, 71% were authorised, 24% off-label and 5% unlicensed and OLUL medicines were not more likely to be implicated in an ADR than authorised medicines [RR 1.03 (95% CI 0.72 to 1.48)]. In comparison, among the 1652 medicine courses administered to oncology patients, 1628 could be classified and 57% were approved, 34% were off-label and 9% were unlicensed, and OLUL medicines were more likely to be implicated in an ADR than authorised medicines [RR 1.39 (95% CI 1.12 to 1.71)].

Nature of the adverse drug reactions

The most common ADRs were oncology related, including neutropenia ($n = 89$), thrombocytopenia ($n = 55$) and anaemia ($n = 38$). The next most common ADR was immunosuppression ($n = 74$), occurring in both oncology and non-oncology patients. Overall, 84 cases of neutropenia, thrombocytopenia, anaemia and/or immunosuppression among oncology patients involved at least one OLUL medicine, and 12 cases of immunosuppression among non-oncology patients involved at least one OLUL medicine. Postoperative bleeding, linked to perioperative corticosteroid administration and/or NSAIDs, caused 28 admissions (26 post tonsillectomy), and 21 of the post-tonsillectomy bleeds were attributed to at least one OLUL medicine. Vomiting ($n = 15$), diarrhoea ($n = 14$), rash ($n = 11$) and constipation ($n = 9$) were all common ADRs causing admission. Hypoglycaemia in diabetic patients treated with regular insulin caused nine admissions and none of the insulin prescriptions were off-label. Respiratory depression following treatment

TABLE 8 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; 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 liver function tests, 7; immunosuppression, 7; diarrhoea, 5; nausea, 4; constipation, 3; headache, 2; abdominal pain, 1; back pain, 1; haematuria, 1; leucoencephalopathy, 1; deranged renal function, 1
Corticosteroids (102)	107	Dexamethasone, 68; prednisolone, 33; hydrocortisone, 2; betamethasone, 1; mometasone, 1; methylprednisolone, 1; fluticasone, 1	Immunosuppression, 71; postoperative bleeding, 23; hyperglycaemia, 3; hypertension, 1; gastritis, 1; increased appetite, 1; impaired healing, 1; adrenal suppression, 1
NSAIDs (31)	43	Ibuprofen, 28; diclofenac, 15	Postoperative bleeding, 27; haematemesis, 2; constipation, 1; abdominal pain, 1
Vaccines (22)	37	Diphtheria, tetanus, pertussis, inactivated polio *Haemophilus influenzae* vaccine, 11; pneumococcal conjugate, 9; meningococcal C, 8; measles; mumps and rubella (MMR), 7; *Haemophilus influenzae* type 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
Antibacterial drugs (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
Antiepileptic 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

TABLE 8 Classification of drugs associated with ADR admissions (*continued*)

Drug class (no. of cases)	No. of drugs	Drugs	ADRs
Other (16)	4	Calcium carbonate and amlodipine, 1; oxybutynin, 1; baclofen, 1	Constipation, 3
	2	Dimethicone, 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; intermenstrual bleed, 1

LFT, liver function test.

for status epilepticus caused eight admissions to the hospital's PICU: unlicensed buccal midazolam liquid was implicated in two of these.

Origin of adverse drug reaction drug prescriptions

Prescriptions originating from community settings accounted for 44 out of 249 (17.7%) of the ADRs, and 85 out of 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 out of 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 out of 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.

Adverse drug reaction assessments (reaction type, causality, severity, avoidability)

A total of 238 out of 249 (95.6%) ADRs were classified as type A (predictable from the known pharmacology), with 11 out of 249 (4.4%) being type B (not predictable). Assessment of causality using the LCAT 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 9*). In total, 41 out of 55 (74.5%) of possibly or definitely avoidable cases were classified as 'definite' or 'probable', 92 out of 238 (39.1%) type A reactions were assessed to be of definite causality, and 8 out of 11 (72.7%) type B reactions were assessed to be 'possible'. The majority (16/17, 94.1%) of the more severe reactions (adapted Hartwig severity score of grade 4 or more) were assessed to have definite or probable causality.

A total of 223 out of 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'. Fourteen (5.6%) were classified as grade 4 ('resulted in patient transfer to higher level of care'), including respiratory depression ($n = 8$), immunosuppression ($n = 4$), neutropenia ($n = 1$), fever/seizure ($n = 1$) and leukoencephalopathy ($n = 1$). 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

TABLE 9 Origin of prescription of ADR drugs by type of reaction, severity score, avoidability and causality assessment

	Type of reaction		Severity score					Avoidability			Causality		
Origin of prescription	A	B	1	2	3	4	5	Unavoidable	Possibly	Definitely	Possible	Probable	Definite
Oncology (120)	119	1	5	0	111	2	2	112	6	2	9	31	80
Hospital (85)	85	0	1	2	74	8	0	57	25	3	51	24	10
Community (44)	34	10	1	0	38	4	1	25	14	5	23	17	4

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').

Of the ADRs, 194 out of 249 (78%) were assessed as 'unavoidable', whereas 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 drugs; 31 possibly avoidable cases were associated with hospital-prescribed drugs and 14 with community-prescribed drugs. A total of 114 (47.5%) of the ADR admissions occurred in oncology patients, accounting for 120 ADRs. Of the ADRs due to oncology drugs, 112 out of 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.

Of the ADR admissions not associated with oncology patients ($n = 126$ admissions and 129 ADRs), 82 out of 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 who were prescribed antibiotics, for whom 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 2 days prior to admission; one patient who had a seizure after alimemazine, having had two previous occurrences of seizure after the antihistamine; one patient with deranged renal function, which improved after cessation of captopril, for whom the ADR may have been avoided through improved renal function monitoring; and one patient who presented with adrenal suppression following 2 years of continuous treatment with intranasal corticosteroids. The possibly and definitely avoidable cases and the reasons for their allocation are summarised in *Table 10*.

TABLE 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	Antibacterial drugs	Inappropriate indication, signs/symptoms of viral illness
	2	Constipation	Cytotoxic drugs, drugs used in nausea, opioid analgesia	Appropriate prophylaxis not used
	1	Lip swelling, rash	Antibacterial drugs	Same ADR previously to same medication
	1	Seizure	Antihistamine	Same ADR previously to similar medication
	1	Adrenal suppression	Corticosteroids	Avoidable with more rational prescribing (prolonged use of drugs) and improved monitoring
	1	Intestinal obstruction	Antimotility drugs	Could be prevented by improved parent/patient education
	1	Deranged renal function	Drugs affecting the renin–angiotensin system	Avoidable with improved monitoring

continued

TABLE 10 Possibly and definitely avoidable cases and explanation of assessment result (*continued*)

Avoidable?	Frequency	ADR(s)	Drug classes	Reason for potential avoidability
Possibly	9	Hypoglycaemia	Drugs used in diabetes	Avoidable with improved patient education (e.g. insulin use when unwell) and more rational prescribing
	8	Respiratory depression	Drugs used in status epilepticus, hypnotic drugs	Alternative medicine available, multiple doses given; avoidable with more rational prescribing
	6	Diarrhoea/vomiting	Antibacterial	Inappropriate indication, symptoms suggested viral infection
	5	Constipation	Antiepileptic drugs, opioid analgesia, drugs used in nausea, NSAIDs, cytotoxic drugs, calcium channel blockers, calcium supplements	Prophylaxis not used
	4	Immunosuppression	Drugs affecting the immune response, corticosteroids	Possibly avoidable with improved monitoring of drug levels; avoidable with more rational prescribing
	2	Haematemesis	NSAIDs	Avoidable with improved patient education/more rational prescribing (less NSAID use)
	1	Neutropenia	Cytotoxic drugs	Same ADR previously at same dose of medication
	1	Neutropenia, thrombocytopenia, anaemia	Cytotoxic drugs	Superficial infection after recent admission with febrile neutropenia; possibly avoidable by prolonging antibiotic use or commencing granulocyte colony-stimulating factor
	1	Hyperglycaemia	Corticosteroids	Avoidable with more rational prescribing (prolonged course steroids used)
	1	Hyperglycaemia	Parenteral preparations	Avoidable with more rational prescribing (more judicial use) or improved monitoring
	1	Seizure	Posterior pituitary hormones	Possibly inappropriate medication used for a patient with seizures
	1	Diarrhoea	Laxatives	Avoidable with improved patient education
	1	Ileus	Opioid analgesia	Avoidable with more rational prescribing (possibly use alternative analgesia)
	1	CNS depression	Opioid analgesia	Avoidable with improved patient education
	1	Vomiting	Cytotoxic drugs	Possibly avoidable with more appropriate antiemetic prophylaxis

TABLE 10 Possibly and definitely avoidable cases and explanation of assessment result (*continued*)

Avoidable?	Frequency	ADR(s)	Drug classes	Reason for potential avoidability
	1	Gastritis	Corticosteroids	Previous gastritis; possibly avoidable with improved prophylaxis
	1	Hypercalcaemia	Vitamins	Avoidable with improved monitoring

CNS, central nervous system.

Drug exposure prior to acute admission

Of 8345 admissions, 6020 (72.1%) were exposed to medication in the 2 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 owing to an admission for cardiothoracic surgery in the 2 weeks prior to readmission. *Figure 1* shows the distribution of drugs per admission.

Children of < 1 year of age accounted for the most number of admissions: 1737 out of 2539 (68.4%) of < 1-year-olds had been exposed to medication prior to admission (*Figure 2*). 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 7 years were the least exposed to medication (163/245, 66.5%) prior to admission.

Of 6020 children exposed to at least one medicine prior to admission, those aged 16 years were exposed to the greatest number of drugs per admission, with a mean of 5.93 (95% CI 4.92 to 6.93) drugs. Children aged < 1 year were exposed to fewer medicines on average, with a mean of 2.82 (95% CI 2.71 to 2.93) drugs per admission (*Figures 3* and *4*).

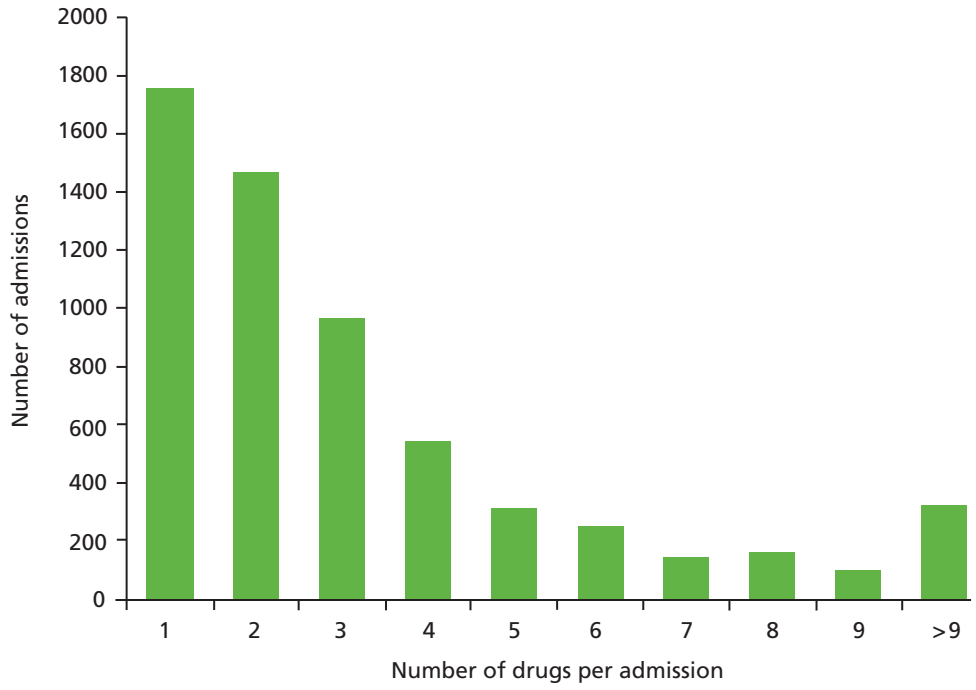


FIGURE 1 Number of drugs per admission.

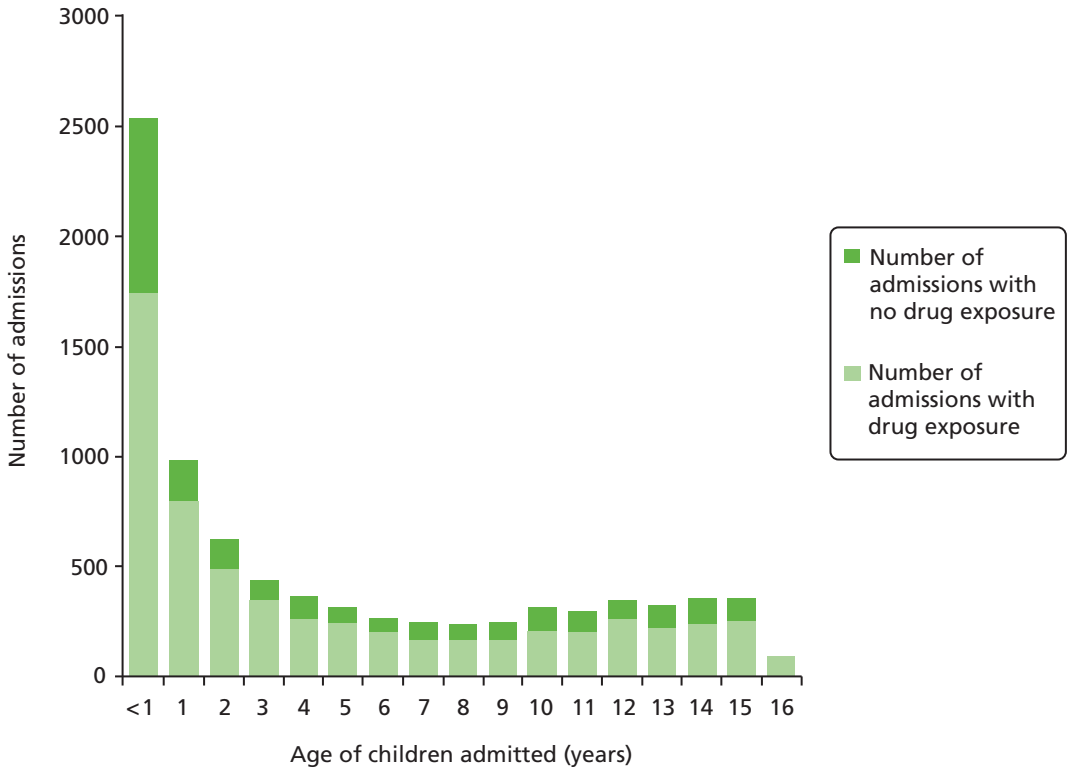


FIGURE 2 Age (1-year intervals) and number of children exposed to medication prior to admission.

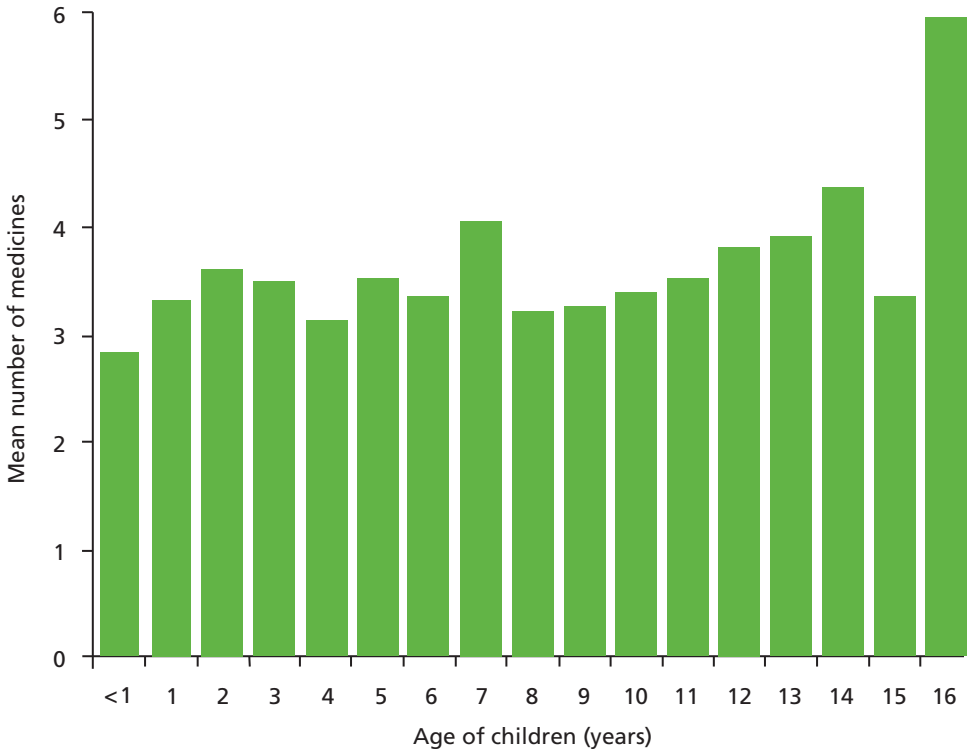


FIGURE 3 Mean number of drugs taken by each age group (1-year intervals).

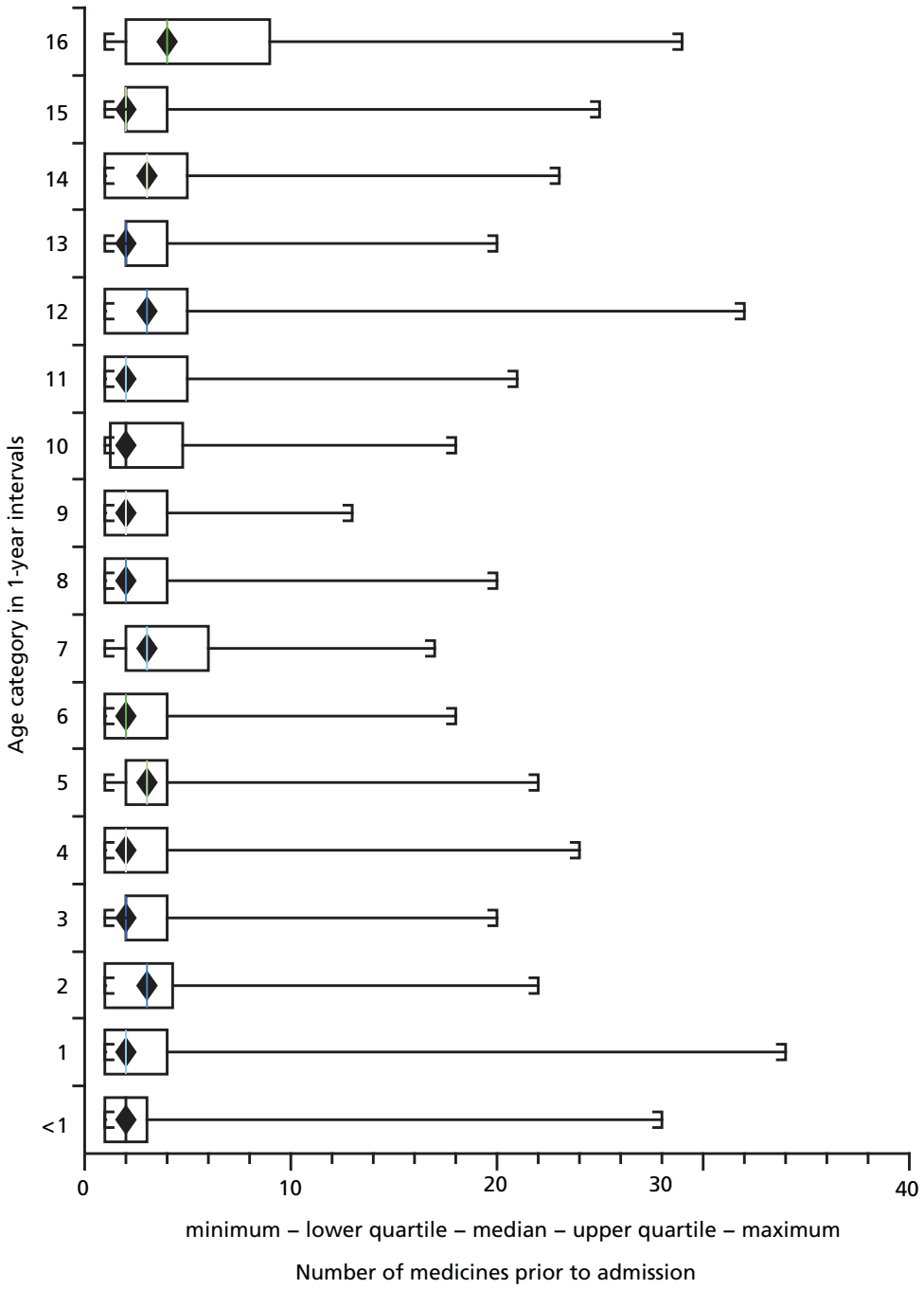


FIGURE 4 Box and whisker plot of number of medicines taken by age group.

Cost of adverse drug reactions and length of stay

The mean cost of 238 out of 240 ADR admissions to the study hospital, using information provided by the finance department, was calculated to be £4753 per admission (95% CI £3439 to £6066). Cost data were missing for two ADR admissions: one oncology admission 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 to £6816.58). The mean cost of 125 non-oncology admissions was £4141.40 (95% CI £1963.84 to £6318.95). The mean length of stay (LOS) of all 240 ADR admissions was 5.67 (95% CI 3.28 to 8.06) days. The mean LOS for the oncology admissions was 5.45 (95% CI 4.35 to 6.55) days, and 5.87 (95% CI 1.4 to 10.34) days for the non-oncology admissions.

Data from the Health and Social Care Information Centre[57] showed that in 1 year, between 2009 and 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 CIs 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 £51.4M and £119M.

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 inclusive of the use of OLUL medicines. 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 incidence of ADRs causing admission in this study (2.9%, 95% CI 2.5% to 3.3%) was similar to the incidence in two systematic reviews: 2.09% (95% CI 1.02% to 3.77%) and 1.8% (95% CI 0.4% to 3.2%) but was significantly less than that of a large US study published in 1988.[33] 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. As 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 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 2 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 the female gender has been described in studies in adult populations.[58,59] The number of authorised medicines and the number of OLUL medicines administered in the 2 weeks before admission were both significant predictors of ADR risk in this study, which supports the finding that the administration of multiple medicines increases ADR risk.

Causality was determined, of the ADR cases, using a novel CAT, the LCAT. The largest proportion of ADR causality classifications were '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 rechallenge 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 to 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,[60] 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,[61] no definitive evidence exists regarding the routine prophylactic use of granulocyte colony-stimulating factors to prevent ADRs due to myelosuppression.[62]

Steroids, along with other immunosuppressant drugs, increase the risk of infection.[63] Immunosuppressant drugs 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.[64–66]

Another frequently recorded ADR in our study was postoperative bleeding, in particular secondary haemorrhage following elective tonsillectomy. The majority (23 out of 28 admissions) of these occurred in patients exposed to intravenous dexamethasone (as prophylaxis for postoperative nausea and vomiting) and NSAIDs, with ibuprofen being used commonly in the postoperative period. A few patients received either dexamethasone or NSAIDs. Dexamethasone has been linked to post-tonsillectomy bleeding[67] but its role, and the role of NSAIDs, in causing secondary haemorrhage in these children needs further study.[68,69] However, intraoperative steroid has played a major role in improving outcomes for postoperative nausea and vomiting (PONV) in children undergoing operations[68,70] and has enabled day-case surgery for many conditions, thereby reducing the LOS in hospital.

Respiratory depression following treatment of seizures with benzodiazepines – a well-recognised and potentially serious event[71] – 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.[72,73] There may be drugs, other than diazepam, which have an improved benefit–risk ratio when used to treat seizures in children.[74] Further research is therefore warranted to optimise strategies for treating seizures, for both in-hospital and out-of-hospital care.

In terms of OLUL medicine use, the results described here cannot be compared easily with those of other studies, as this is the first large admissions study of this type. Previous inpatient studies report 27–45% of prescriptions being OLUL,[3,75,76] and two previous community-based studies report 7% and 43% of prescriptions being off-label;[77,78] compare this to 28% of prescriptions in this study. With the exception of Neubert *et al.*[75] these studies all found an increased ADR risk associated with OLUL medicine use. In this study, OLUL medicines were more likely to be implicated in an ADR than medicines used within the terms of their MA; however, it is important to highlight that 87.2% of ADRs that involved at least one OLUL also involved at least one other medicine; in some cases the OLUL medicine may not have caused the ADR in the absence of an approved medicine. Previous studies have examined exposure to OLUL medicines as an explanatory variable in their multivariate analysis.[3,75,76] Unlike our analysis, this approach to analysis does not take into account the relative contribution of authorised medicines. We have been able to demonstrate that, although the number of OLUL medicines contributes to ADR risk, it does so to a similar extent as the number of authorised medicines. Different OLUL medicines have different propensities to

cause ADRs, it is not appropriate to consider them to be a homogeneous group. There are various types of OLUL medicines used, some of which may carry a greater risk of being implicated in an ADR than others. A key consideration is whether these medicines would be any less likely to be implicated in an ADR if they were used within the terms of their MA or if licensed preparations were used. A more detailed examination of the characteristics of the OLUL medicines that are implicated in ADRs may improve our understanding of why these medicines increase ADR risk and inform potential interventions to reduce that risk.

The design of the cohort study had limitations. The detection of suspected ADRs by the study team relied on two things: (1) signs and symptoms associated with the ADR being recorded by the clinical team looking after the patient and (2) the study team suspecting a link between signs and symptoms recorded and the medicines administered before admission. When signs and symptoms were not recorded or the study team missed the link, the ADR will not have been highlighted or evaluated. Although this was a single-centre study, it was carried out in a large centre providing a comprehensive range of paediatric services to a diverse population. 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 (e.g. immunosuppressant drugs) 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 cost of ADRs 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 annual admissions 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 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). We have shown that OLUL prescribing is a risk factor for ADRs and identified some drugs/classes for which further work is needed. This finding must be put in context of the fact that the number of medicines per se, irrespective of the licensing status, is also a risk factor for ADRs. Better dosing schedules for medicines, particularly those with a narrow therapeutic index, are likely to be key in reducing the burden of ADRs in children. Other ADRs that are currently unavoidable may be ameliorated by comedication, for example concomitant use of laxatives to prevent constipation. As 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. Clinicians prescribing for children should be vigilant for the occurrence of ADRs, and should prescribe the minimum number of drugs at the lowest possible dose and shortest duration of time, with continual monitoring to stop drugs when relevant and to ensure that ADRs are detected as early as possible.

Chapter 3 Adverse drug reactions in hospitalised children

This chapter contains information reproduced from Thiesen S, Conroy EJ, Bellis JR, Bracken LE, Mannix HL, Bird KA, *et al.* Incidence, characteristics and risk factors of Adverse Drug Reactions (ADRs) in hospitalised children: a prospective observational cohort study of 6601 admissions. *BMC Med* 2013;**11**:237,[22] © 2013 Thiesen *et al.*; licensee BioMed Central Ltd, an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided that the original work is properly cited; from Bellis J, Kirkham J, Thiesen S, Conroy E, Bracken L, Mannix H, *et al.* Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. *BMC Med* 2013;**11**:238,[79] © 2013 Bellis *et al.*, licensee BioMed Central Ltd, an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided that the original work is properly cited; and reproduced with permission from Bellis JR. *Adverse Drug Reactions in Children – The Contribution of Off-label and Unlicenced Prescribing*. PhD thesis. Liverpool: University of Liverpool; 2013.[31]

Abstract

Background

Adverse drug reactions are an important cause of iatrogenic harm in children. We aimed to determine the incidence of ADRs, identify risk factors for ADRs in hospitalised children, and characterise these ADRs in terms of type, drug aetiology, causality and severity.

Methods

We undertook a prospective observational cohort study in admissions to a single UK paediatric hospital. A nested case–control study within the cohort examined the impact of OLUL drug use on ADR risk. Participants were aged between 0 and 16 years 11 months, who were admitted for > 48 hours between 1 October 2009 and 30 September 2010.

Results

In total, 5118 children participated and 17.7% of all children experienced at least one ADR. Opiate analgesic drugs and drugs used in general anaesthesia (GA) accounted for > 50% of all drugs implicated in ADRs. Our nested case–control study included 1388 patients. The OR of an OLUL drug being implicated in an ADR compared with an authorised drug was 2.25 (95% CI 1.95 to 2.59; $p < 0.001$). Risk factors identified were exposure to a GA, age, oncology treatment and number of medicines.

Conclusions

The incidence of ADRs is higher in hospitalised children than in hospitalised adults, with GA agents and opiate analgesic drugs being the chief causes. OLUL drugs are more likely to be implicated in an ADR than approved drugs. It is important to develop strategies to reduce the burden of ADRs occurring in hospitalised children.

Introduction

Adverse drug reactions are an important cause of iatrogenic morbidity and mortality in patients of all ages.[59,80–83] ADRs in children may differ from those in adults owing to age-dependent physiological characteristics that affect the pharmacokinetics and pharmacodynamics of drugs.[80,81,84,85]

Off-label and/or unlicensed drug use has been identified in previous studies as an ADR risk factor. However, this has not been demonstrated consistently by all studies, many of which were small, used different methodologies and used inexact and varying definitions.[86] Off-label drug use is the use of a drug outside of the terms of its MA, and unlicensed drugs are those without a MA in the country in which they are prescribed. The reported incidences of OLUL use of medicines in children ranges from 36% to 100%.[87] OLUL prescribing has been prevalent in paediatric practice because of the lack of assessment of the use of drugs in children during the drug development process.[88] Although the recently introduced paediatric regulation in Europe[13] and the updated regulation[89] in the USA are likely to improve the situation, it is going to take time.

The aim of this study was to determine the incidence of ADRs in paediatric medical and surgical inpatients; characterise those ADRs identified in terms of type, drugs implicated, involvement of OLUL drugs, causality and severity; and also identify factors that increase the risk of ADRs. Reducing the impact of paediatric ADRs needs precise estimates of the incidence and nature of ADRs. Given the discordances in the extant literature, we designed a study that was large enough and of robust design to overcome the problems identified in the previous literature.

Methods

Study design and setting

The study was a prospective observational cohort study conducted over 1 year in a single paediatric referral centre providing a local and also specialist regional and national services in the north-west of England (Alder Hey).

The study population comprised children aged between 0 and 16 years and 11 months, who were inpatients between 1 October 2009 and 30 September 2010. Extensive pilot work was conducted prior to the beginning of the study. This pilot work established that the study team did not have the resources to carry out a detailed review of every inpatient every day. Three alternative inclusion criteria were considered: all inpatients, children admitted for > 24 hours and children admitted for > 48 hours. 'Patients admitted for > 48 hours' was the inclusion criterion selected, as this allowed study procedures to be optimised for the full observational study (frequency of follow-up visits, amount of prescription and clinical data to be recorded, source data to be considered, use of electronic database). Admissions included elective and emergency admissions to all paediatric medical and paediatric surgical specialties. Observations were carried out on 17 wards, including oncology wards and the high-dependency unit (HDU). Patients were not observed while admitted to PICU, transitional care unit (TCU), theatre, recovery or the department of radiology. Patients who spent their entire admission on PICU were excluded. The study methodology did not cover all aspects of the clinical complexity and the study team did not have the tools or expertise required to identify and assess ADRs in an intensive care environment. Patients who spent their entire admission on TCU were excluded. These patients have complex medical and nursing needs but are clinically stable. In general, they are awaiting transfer home or to a placement in the community. If they became acutely unwell during the study, they would have been admitted to the hospital and become eligible for inclusion. Children meeting the inclusion criteria were identified twice daily by means of an automated computer download. Each child was followed up every 48 hours or 72 hours on weekdays and weekends, respectively, by one member of a multidisciplinary team (MDT) of researchers comprising two research pharmacists, one research nurse and a paediatrician (LEB, JRB, KB, HM, ST). For each child, details were recorded of all drugs administered on the wards, occurrence of new symptoms or those that had worsened, and abnormal results that may indicate the occurrence of an ADR, taking into account the case history, the ADR profiles of medication and the temporal relationship between drug exposure and reaction. We aimed to include all potential reactions to any medication administered in hospital (including those started prior to admission) and present after admission to a ward; each suspected reaction was followed up with a detailed assessment by one research team member.

As highlighted by the pilot study, it was not practical to follow all admissions in the prospective cohort study in sufficient detail; therefore, a subset study of nested case–control design was undertaken to assess the involvement of OLUL drugs that were implicated in observed ADRs. Cases were those who had experienced at least one probable or definite ADR on their first admission and were matched 1 : 1 to control subjects who had not experienced any probable or definite ADRs. Matching was based on the closest date and time of admission.

Adverse drug reaction definition

In our study we used the ADR definition of Edwards and Aronson:[49] 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a drug product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dose regimen, or withdrawal of the product'. Prescribing errors, administration errors and accidental overdoses were thus not considered ADRs in this study. ADR cases were defined as suspected reactions to any systemic or topical drug product administered in hospital and presenting after admission to the ward or in A&E prior to admission to the ward. This included reactions to drug products administered in PICU, theatre, recovery, the department of radiology or TCU, providing that the reaction became apparent after transfer to a ward. Reactions to a drug product started prior to admission were included if it was continued in hospital and the reaction was not apparent on admission. Suspected reactions to certain drug products (including some blood products, total parenteral nutrition and intravenous hydration fluids) were excluded from this study. For details of included/excluded drug products see *Table 11*.

TABLE 11 Off-label and unlicensed categories

		Category	Definition
Off-label drugs	Drugs licensed for use in children	1	Authorised – drug used within the terms of its marketing authorisation
		2	Contraindication exists
		3	Dose greater than recommended
		4	Dose greater than recommended and contraindication exists
		5	Not licensed in child of this age (or child below minimum weight stated)
		6	Not licensed in child of this age and contraindication exists
		7	Not licensed by this route
		8	Not licensed by this route and contraindication exists
		9	Not licensed by this route or in a child of this age
		10	Not licensed by this route or in a child of this age and contraindication exists
		11	Not licensed for this indication
		12	Not licensed for this indication and contraindication exists
		13	Not licensed for this indication or at this dose
		14	Not licensed for this indication or at this dose and contraindication exists
		15	Not licensed for this indication or at this age
		16	Not licensed for this indication or at this age and a contraindication exists
		17	Not licensed for this indication or by this route

continued

TABLE 11 Off-label and unlicensed categories (*continued*)

		Category	Definition
		18	Not licensed for this indication or by this route and a contraindication exists
		19	Not licensed for this indication or by this route or at this age
		20	Not licensed for this indication or by this route or at this age and a contraindication exists
	Drugs not licensed for use in children	21	Not licensed for use in children
		22	Not licensed for use in children and a contraindication exists
		23	Not licensed for use in children or in adults by this route
		24	Not licensed for use in children or in adults by this route and a contraindication exists
		25	Not licensed for use in children or in adults for this indication
		26	Not licensed for use in children or in adults for this indication and a contraindication exists
		27	Not licensed for use in children or in adults for this indication or in adults by this route
		28	Not licensed for use in children or in adults for this indication or in adults by this route and a contraindication exists
Medicines excluded from analysis		29	Category cannot be assigned
		30	Theatre drug
Unlicensed drugs		31	Prepared extemporaneously
		32	Manufactured under a specials manufacturing licence
		33	Chemical
		34	Import
		35	Awaiting a MA (e.g. previous trial drug)

Drug categories

For each patient in the nested case–control study, the record of drugs administered was updated to include a detailed OLUL category for every drug. There were 30 off-label drug categories and five unlicensed drug categories (see *Table 11*). Off-label categories were defined according to the reason(s) why their use was deemed off-label when compared with the terms of the MA. The terms of the MA were found in the SmPC available online from the EMC.[50] With regard to age, if the SmPC mentioned children, the definition of this was assumed to be 28 days to 18 years. If no specific information pertaining to use in neonates was provided, the use of that drug in neonates was considered to be off-label. Although it was certainly not the case, it was assumed that all neonates were born at term because gestational age was not recorded in this study. Owing to the complex nature of the regimens used to treat malignant disease, the classification of cytotoxic drugs was simplified by consulting the BNF-C[90] for cytotoxic drugs with a UK MA. If the BNF-C monograph stated the relevant indication, it was assumed that the use was authorised. If the BNF-C monograph stated 'not licensed in children' then the use was considered to be off-label. The implications of dosage from manipulation by parents or nursing staff, such as the crushing of tablets or the addition of licensed drugs to food or drinks for ease of administration, was considered to be outside the scope of this study.

Causality and severity assessment of adverse drug reactions

Each suspected ADR was followed up with a detailed assessment by one research team member. The ADR case report was then assessed independently by a research nurse, a research pharmacist and a paediatrician using the LCAT[53] as unlikely, possible, probable or definite. Outcome reporting was based on consensus agreement between the three assessors; if agreement could not be achieved the case was referred to a panel of two senior investigators (MAT, RLS, AJN and MPir); each panel reached consensus about causality. For ADRs with a high or uncertain probability that the reaction is due to an underlying disease, the causality outcome is 'possible' unless objective evidence of the causal ADR mechanism is available.[53] Our estimate for the overall incidence was based on the sum of probable and definite ADRs only, as these ADRs are deemed to have a low probability of the underlying disease being responsible for the reaction. Severity of ADRs was assessed by the researcher compiling the case report using the Hartwig scale.[56] In addition, all ADRs that occurred prior to a patient's admission to PICU or HDU were also assessed by a paediatrician and, if required, reviewed by a panel of two senior investigators in order to evaluate their contribution to the patient being transferred to a higher level of care (Hartwig scale level 4). Reactions classified as level 4 and above were considered severe.

Incidence

Incidence was calculated in two ways: (1) the number of admissions in which at least one ADR occurred divided by the total number of admissions regardless of drug exposure and (2) the number of children with at least one ADR divided by the total number of children regardless of drug exposure.

Odds ratios

For analysis of the nested case–control study, the OR with 95% CI of a drug being implicated in a probable or definite ADR was calculated for each category of OLUL drugs administered compared with a baseline risk for authorised drugs.

Risk factor analysis

Time from admission to first ADR was calculated in days. For patients admitted to PICU, this was time to first ADR prior to PICU admission. If no ADR occurred prior to PICU admission, time from admission to first ADR was censored at the time of admission to PICU. ADRs occurring after PICU were included in the overall incidence calculation. For the analysis of risk factors, data collected for each patient during only their first admission were included.

Within the main study, we assessed age, gender, number of drugs, receipt of a GA and oncology patient status as risk factors. Oncology patients were those requiring ongoing medical treatment for a malignancy of solid organ or haematopoietic system. The number of drugs refers to the daily number of drugs administered to the patient on the ward. This risk factor was treated as a continuous, time-varying covariate in the multivariate model.

The factor 'received a GA' was considered to be present from the first day the patient received a GA until discharge from hospital. This risk factor was treated, as a binary, time-varying variable in the multivariate model that takes the value '0' on days up to the GA and '1' thereafter for the remaining days of a patient's admission.

The same risk factors were assessed in our nested case–control study. However, to avoid issues caused by including dependent variables, we replaced the 'daily number of drugs' variable in the model with the two variables 'daily number of OLUL drugs' and 'daily number of authorised drugs'. These were treated as continuous, time-varying covariates in the model.

Statistical methods

Time to first ADR was compared between groups using a log-rank test (extending to a log-rank test for trend when appropriate) and Kaplan–Meier curves estimated.

A Cox proportional hazards regression model for an ADR was fitted to the data. Results are given in terms of the hazard ratio (HR) and associated 95% CI. Owing to their clinical importance, all of the risk factor variables were included in the multivariate models fit in both the main analysis and the subset analysis.

The assumptions of the model were assessed as follows. The proportional hazards assumption for each covariate was investigated using log-cumulative hazard plots and Schoenfeld residual plots. The assumption was also tested by including a time-dependent covariate effect. Deviance residuals were plotted against the linear predictor to look for mismodelling of the data and empirical validation for the model was carried out using a data-splitting technique to assess model accuracy. Patients with missing prescription details for the entire duration of the admission were excluded from the analysis. The inclusion of patients with partially missing prescription details (e.g. prescription details for day of discharge) was assessed on a case-by-case basis.

All statistical analysis was carried out using the statistical software package R version 2.13.2 (The R Foundation for Statistical Computing, Vienna, Austria) using a two-sided significance level of 0.05 (5%) throughout.

Reporting

This study was reported according to Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) guidelines.[91]

Ethics

This study used routinely collected clinical data in an anonymised format. The chairperson of Liverpool Paediatric Local Research Ethics Committee informed us that this study did not require individual patient consent or review by an ethics committee.

Results

Participants and descriptive data

Prospective cohort study – 6825 eligible admissions were identified. A total of 181 (2.7%) admissions could not be included owing to missing data. Forty-three patients spent their entire admission on PICU and were thus excluded. The median length of follow-up time across admission was 5 days (IQR 3–8 days, range 2–280 days). The median age on admission was 3.4 years (IQR 0.6–10.7). Overall, 2297 (44.8%) were female, 4284 (83.7%) of children had one admission, 834 children had more than one admission, 2856 children (55.8%) underwent at least one GA during 3265 admissions, and 114 children (2.2%) were oncology patients.

In total, 2934 suspected ADRs were assessed. After causality assessment, 213 (7.3%) of suspected ADRs were deemed definite, 1233 (42.0%) probable, 896 (30.5%) possible and 592 (20.2%) unlikely. Consensus was reached by independent agreement in 1805 cases (61.5%) and by panel decision in 1128 cases (38.5%). All definite and probable ADRs were included in the further analysis (total number 1446; *Figure 5*).

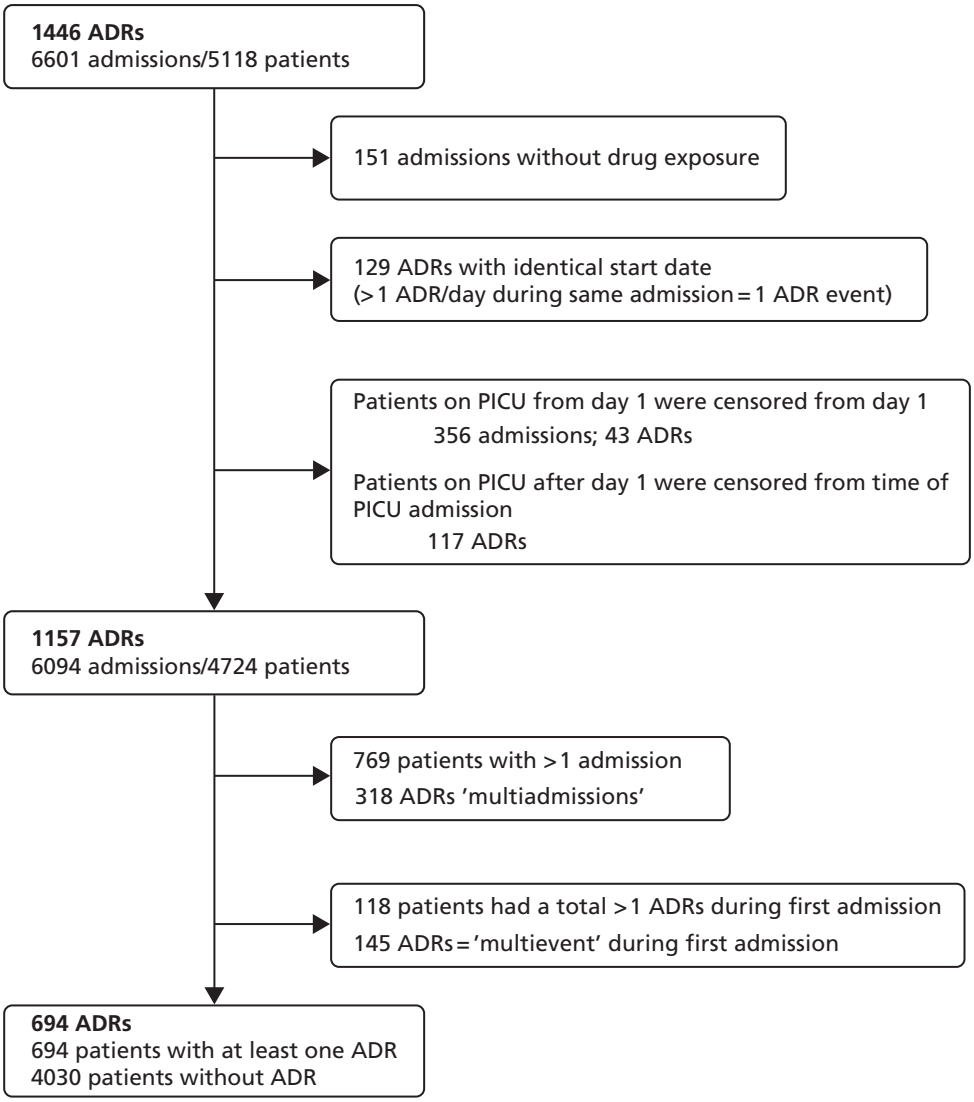


FIGURE 5 Flow chart outlining number of first admissions included in the cohort study univariate and multivariate analysis.

The overall incidence of definite and probable ADRs based on all admissions was 15.9% (95% CI 15.0% to 16.8%) and 17.7% per patient (95% CI 16.7% to 18.8%). The ADR incidence for patients with only one admission was 14.8% (95% CI 13.8% to 15.9%). For patients with more than one admission, the incidence per admission was 18.0% (95% CI 13.8% to 15.9%) and 32.7% per patient (95% CI 29.6% to 35.9%). Of the ADRs 0.9% were severe and required patient transfer to a higher level of care. One patient sustained permanent harm (peripheral neuropathy due to vincristine). No ADR resulted in patient death (see *Table 12*). Details of all severe reactions by reaction type and associated drugs are listed (*Tables 12* and *13*).

TABLE 12 Hartwig severity scale

Severity level	Description	No. of ADRs at each severity level[a]	
		n	%
1	Required no change in treatment	322	22.3
2	Drug dosing or frequency changed	66	4.6
3	Required treatment, or drug administration discontinued	1046	72.3
4	Result in patient transfer to higher level of care	12	0.8
5	Caused permanent harm to patient or significant haemodynamic instability	1	0.1
6	Directly or indirectly resulted in patient death	0	0

a Denominator was the total number of probable or definite ADRs.

TABLE 13 Severe reactions (Hartwig severity scale level of ≥ 4) by reaction type and drug implicated

Severity level	ADR type (count)	Medication implicated (count)	Admission to PICU/HDU (if more than once)
4	Cardiac failure (1)	Bisoprolol (1), carvedilol (1)	HDU
	Sedation withdrawal (1)	Fentanyl (1), midazolam (1), promethazine (1), chloral hydrate (1)	PICU
	Raised international normalised ratio and haemorrhage (1)	Warfarin (1)	HDU
	Pulmonary oedema (1)	Diazoxide (1)	HDU
	Respiratory depression (5)	Fentanyl (4), ketamine (2), midazolam (1)	PICU (3[a]), HDU (2)
	Respiratory arrest (2)	Fentanyl (2), sevoflurane (1), isoflurane (1), ketamine (1)	PICU, HDU
5	Peripheral neuropathy (1)	Vincristine (1)	N/A

N/A, not applicable.
a Adverse drug reaction was not the only factor leading to PICU admission; other, clinical factors may also have contributed.

Nested case–control study

A total of 1388 patients were analysed throughout their first admission: 694 (50%) were cases; 634 (45.6%) were female; 294 (21.2%) were < 1 year old; 341 (24.6%) were aged 1–4 years; 384 (27.7%) were 5–11 years and 369 (26.6%) were teenagers (> 12 years). The median age was 5.9 years (IQR 1.4–12.4 years). A total of 10,699 drug courses were administered in this study.

Within this nested cohort, there were 785 suspected ADRs deemed definite or probable in 694 patients during the first admission. Of the suspected ADRs, 62 (7.9%) were deemed definite and 723 (92.1%) probable. Of these, 505 (64.3%) involved one drug course, 172 (21.9%) involved two drug courses, 77 (9.8%) three and 31 (3.9%) four or more. Of the total drug courses, 10,145 (94.8%) could be categorised using *Table 11*. The remaining 554 (5.2%) courses could not be categorised, as the prescription record did not provide the required information, for example, missing dose information or insufficient detail about the exact preparation used. Of the 785 definite and probable ADRs, 301 (38%) involved only OLUL medicines, 290 (37%) involved only authorised medicines, 160 (20.4%) involved a combination of OLUL and authorised medicines, and the remaining 4.3% involved at least one medicine that could not be categorised.

Reaction types, drug classes and 'off-label and/or unlicensed' categories implicated in adverse drug reactions

Prospective cohort study

The 10 most common reaction types were vomiting and/or nausea, pruritus, constipation, diarrhoea, somnolence without cardiorespiratory symptoms, respiratory depression or arrest, candidiasis, urinary retention, rash and hypokalaemia, which, together, accounted for 76.6% of all ADRs. Pruritus, respiratory depression and urinary retention occurred almost exclusively in the post-anaesthetic setting. In over two-thirds of patients with nausea/vomiting, constipation or somnolence, drugs given during the anaesthetic and/or used in postoperative pain management were implicated (*Table 14*).

Drugs implicated in ADRs and associated reactions are listed in *Table 15*. Opioid analgesic drugs and anaesthetic agents were the most commonly implicated drug groups and accounted for 54% of all drugs associated with ADRs. Cytotoxic drugs accounted for 13% and antibiotics for 11% of medication implicated. Drugs used in postoperative pain management accounted for 6%. Each other drug group accounted for ≤ 2%.

Nested case–control study – of the 10,145 categorised drug courses, 6980 (68.8%) were authorised, 2407 (23.7%) off-label and 758 (7.5%) unlicensed; 435 (6.2%) of authorised, 298 (12.4%) of off-label, and 113 (14.9%) of unlicensed drug courses were implicated in at least one probable or definite ADR. The OR of an OLUL drug being implicated in an ADR when compared with an authorised drug course was 2.25 (95% CI 1.95 to 2.59; $p < 0.001$). In total, 19 (54.3%) of the OLUL categories (see *Table 11*) were utilised. *Table 16* shows the number of drug courses in each of these categories. Category 11 ('drug licensed for children but given for a different indication') is the most common category of off-label drug use ($n = 764$; 31.7%). Categories 3, 5 and 11 together represented 2050 (85.2%) of off-label drug courses. Category 32 ('manufactured under a specials manufacturing licence') is the most common category of unlicensed drug use ($n = 577$; 76%). *Table 16* shows the proportion of drug courses from each category implicated in at least one probable or definite ADR in comparison with the proportion of authorised drug courses implicated ($n = 6980$; 6.2%). Further analysis was undertaken on six of these categories, which contained > 100 drug courses. Results showed that category 3 ('drugs licensed for use in children but given at a dose greater than recommended') had a lower risk of being implicated in an ADR than category 1 – authorised drugs (OR 0.42, 95% CI 0.26 to 0.67). Category 5 ('drugs licensed in children but given to a child below the minimum age or weight') had the greatest risk of being implicated in an ADR (OR 3.54, 95% CI 2.82 to 4.44).

TABLE 14 Common ADR types observed

Reaction type	All reactions		Following GA[a]	
	n	% of all reactions[b]	*n*	% of reaction type where reaction followed GA
Nausea and/or vomiting	400	27.5	295	73.8
Pruritus	243	16.7	232	95.5
Constipation	155	10.6	107	69.0
Diarrhoea (nine with vomiting)	88	6.0	0	0.0
Somnolence (without cardiorespiratory symptoms)	50	3.4	34	68.0
Respiratory depression/arrest (41/3)	44	3.0	43	97.7
Candidiasis	41	2.8	0	0.0
Urinary retention	40	2.7	37	92.5
Rash	31	2.1	3	9.7
Hypokalaemia	25	1.7	0	0.0
Hypotension	22	1.5	9	40.9
Hepatotoxicity (12 transaminases increased only)	18	1.2	1	5.6
Stomatitis	16	1.1	0	0.0
Myoclonus	15	1.0	14	93.3
Pancytopenia	13	< 1	0	0.0
Hyperglycaemia	12	< 1	0	0.0
Hypertension	11	< 1	2	18.2
Allergic reactions	10	< 1	3	30.0
Pain (four with pain in jaw, two with back pain)	10	< 1	0	0.0
Other reactions (occurred < 10 times)	213	14.6	65	30.5
Total	1457		845	58.0

a Reaction occurred post theatre *and* drugs given in theatre and/or used in postoperative pain management were implicated.
b If the same patient experienced two types of reactions to the same medication(s) at the same time this would have been reported as one ADR case but will be listed here as two reaction types, for example a patient with respiratory depression and bradycardia = one ADR case, but listed as two reactions.

TABLE 15 Drug groups implicated in ADRs by frequency with associated reaction types

Drug group (*n* of ADR cases)	Total no. of drugs (% of total)	Drugs (*n*)	ADR type[a] (*n*)
Opioid analgesic drugs (688)	844 (27.9)	Morphine (426), fentanyl (267), codeine (144), dihydrocodeine (4), diamorphine (2), tramadol (1)	Pruritus (198), nausea or vomiting (186), constipation (143), respiratory arrest/ depression (3/37), somnolence without cardiorespiratory symptoms (37), urinary retention (28), myoclonus (13), hallucination (8), rash (4), bradycardia (3), dizziness (3), drug withdrawal syndrome (3), ileus (3), agitation (2), delayed recovery from anaesthesia (2), flushing (2), visual disturbance (2), other[b] (11)
Drugs used in GA (excluding opiate analgesic drugs other than remifentanil) (322)	779 (25.8)	Sevoflurane (253), propofol (200), nitrous oxide (131), remifentanil (83), desflurane (54), isoflurane (38), ketamine (6), atracurium (4), rocuronium (4), thiopental (4), atropine (1), vecuronium (1)	Nausea or vomiting (266), urinary retention (21), respiratory arrest or depression (2/6), delayed recovery from anaesthesia (5), flushing (4), bradycardia (3), allergic reaction (3), hypotension (3), pruritus (2), other[b] (7)
Cytotoxic drugs and drugs used for cytotoxic-induced side effects (179)	405 (13.4)	Vincristine (70), etoposide (56), cyclophosphamide (46), cytarabine (41), methotrexate (31), doxorubicin (22), ifosfamide (21), mesna (15), daunorubicin (13), carboplatin (12), cisplatin (12), melphalan (11), busulfan (7), asparaginase (6), fludarabine (6), clofarabine (5), actinomycin d (5), allopurinol (4), mitoxantrone (4), rasburicase (4), idarubicin (3), thiotepa (3), amsacrine (2), temozolomide (2), cladribine (1), gemcitabine (1), irinotecan (1), tretinoin (1)	Nausea or vomiting (81), stomatitis (16), pancytopenia (13), diarrhoea and vomiting (9), diarrhoea without vomiting (9), hepatotoxicity (11; 8 increased transaminases only), febrile neutropenia (6), rash (6), pain in jaw (3), constipation (3), pain other than jaw (2), headache (2), hyperglycaemia (3), oral candidiasis (3), other[b] (14)
Antibiotic drugs (162)	319 (10.6)	Cefotaxime (56), metronidazole (29), gentamicin (29), piperacillin and tazobactam (28), cefuroxime (18), teicoplanin (19), cefalexin (17), ciprofloxacin (16), flucloxacillin (15), co-amoxiclav (16), ceftazidime (13), rifampicin (10), amoxicillin (8), clarithromycin (7), vancomycin (7), penicillin V (5), benzylpenicillin (4), meropenem (4), amikacin (3),	Diarrhoea (66), candidiasis (38), rash (16), nausea or vomiting (8), *Clostridium difficile* colitis (7), colonisation with candida (4), transaminases increased (4), anaphylactic reaction (2), angioedema (2), flushing (2), hepatotoxicity (3), pruritus (2), other[b] (8)

continued

TABLE 15 Drug groups implicated in ADRs by frequency with associated reaction types (*continued*)

Drug group (*n* of ADR cases)	Total no. of drugs (% of total)	Drugs (*n*)	ADR type[a] (*n*)
		co-trimoxazole (3), tobramycin (3), trimethoprim (3), clindamycin (2), cefradine (1), ceftriaxone (1)	
Drugs used in epidurals, regional anaesthetics and intravenous drugs used in postoperative pain management other than opioid drugs (188)	195 (6.4)	Fentanyl and levobupivacaine (116), ketamine (36), clonidine and levobupivacaine (25), levobupivacaine (11), clonidine (7)	Pruritus (52), nausea and/or vomiting (35), constipation (24), urinary retention (15), somnolence without cardiorespiratory symptoms (11), respiratory depression/arrest (8/1), hypotension (7), paraesthesia (6), bradycardia (4), myoclonus (3), hypoaesthesia (2), visual disturbance (2), hallucination (2), hypertension (2), urinary incontinence (2), other[b] (12)
Corticosteroids (51)	62 (2.05)	Dexamethasone (24), methylprednisolone (14), prednisolone (14), hydrocortisone (8), beclomethasone (1), fludrocortisone (1)	Hyperglycaemia (13), hypertension (8), candidiasis (9), fluid retention (2), gastritis (2), other[b] (17)
Bronchodilators (31)	58 (1.92)	Salbutamol (35), aminophylline (21), ipratropium (2)	Hypokalaemia (15), nausea and/or vomiting (7), tremor (4), tachycardia (2), other[b] (3)
Antiemetic drugs (50)	55 (1.82)	Ondansetron (51), levomepromazine (3), cyclizine (1)	Constipation (45), disorientation (2), other[b] (4)
Antiepileptic drugs (45)	49 (1.62)	Midazolam (35), pregabalin (4), carbamazepine (3), diazepam (3), gabapentin (2), lorazepam (1), valproate (1)	Nausea and/or vomiting (24), somnolence without cardiorespiratory symptoms (6), abnormal behaviour (2), constipation (2), delayed recovery from anaesthesia (2), respiratory depression (2), other[b] (7)
Diuretic drugs (28)	41 (1.36)	Furosemide (30), spironolactone (8), metolazone (2), chlorothiazide (1)	Hyponatraemia (9), hypokalaemia (8), hypotension (3), hypomagnesaemia (4), other[b] (5)
Drugs affecting the immune responses (suppression and modulation) + cytokine modulators (31)	34 (1.12)	Alemtuzumab (11), ciclosporin (7), aldesleukin (5), rabbit antihuman thymocyte immunoglobulin (3), tacrolimus (3), rituximab (2), azathioprine (1), mycophenolate (1), tocilizumab (1)	Pyrexia (4), candidiasis (4), infusion associated reaction (3), stomatitis (3), oedema (2), pruritus (2), vomiting (2), other[b] (11)

TABLE 15 Drug groups implicated in ADRs by frequency with associated reaction types (*continued*)

Drug group (*n* of ADR cases)	Total no. of drugs (% of total)	Drugs (*n*)	ADR type[a] (*n*)
Drugs affecting the cardiovascular system (23)	27 (0.89)	Captopril (10), lisinopril (4), amlodipine (4), milrinone (3), bisoprolol (1), dinoprostone (1), enalapril (1), hydralazine (1), isoprenaline (1), carvedilol (1)	Hypotension (11), hyperglycaemia and glycosuria (3), other[b] (9)
NSAIDS (+ aspirin) (24)	24 (0.79)	Diclofenac (15), ibuprofen (5), naproxen (2), aspirin (2)	Nausea and/or vomiting (11), haematemesis (3), other gastrointestinal bleed (2), constipation (2), other[b] (5)
Laxatives (20)	22 (0.73)	Lactulose (12), macrogol (6), docusate (3), sennoside (1)	Diarrhoea (17), abdominal pain (2), vomiting (1)
Antifungal and antiviral drugs (20)	21 (0.69)	Amphotericin (7), aciclovir (5), fluconazole (4), voriconazole (2), itraconazole (1), miconazole (1), ribivarin (1)	Diarrhoea (8), hepatotoxicity (3), hypokalaemia (3), other[b] (5)
Drugs used in diabetes and hypoglycaemia (13)	16 (0.53)	Insulin (4), insulin aspart (4), insulin detemir (4), diazoxide (3), glucagon (1)	Hypoglycaemia (7), fluid overload (2), hypokalaemia (2), other[b] (2)
Other (69)	73 (2.41)	–	–

a If the same patient experienced two types of reactions to the same medication at the same time then this would have been reported as one ADR case but will be listed here as two ADR types, for example patient with respiratory depression and bradycardia = one ADR case but listed as two types.
b Reactions that occurred once are listed as other.

TABLE 16 Number of drug courses in each authorised, OLUL category and number implicated in at least one possible and definite ADR ($n = 10,145$)

		Category[a]	No. of drug courses	% of courses implicated in at least one possible and definite ADR	OR of ADR vs. authorised	95% CI
Off-label drugs	Drugs licensed for use in children	1	6980	6.2	1.00	–
		2	1	0	–	–
		3	698	2.7	0.42	0.26 to 0.67
		5	588	19.0	3.54	2.82 to 4.44
		6	1	0	–	–
		7	61	9.8	1.64	0.70 to 3.83
		11	764	14.3	2.50	2.00 to 3.13
		13	8	0	–	–
		15	35	25.7	5.21	2.43 to 11.18
		17	21	0	–	–
		19	2	0	–	–
	Drugs not licensed for use in children	21	215	18.6	3.44	2.41 to 4.91
		22	1	100.0	–	–
		23	1	0	–	–
		25	11	18.2	3.34	0.72 to 15.52
Unlicensed drugs		31	143	14.7	2.59	1.61 to 4.16
		32	577	14.9	2.64	2.05 to 3.38
		33	1	0	–	–
		34	37	16.2	2.91	1.21 to 7.02

a See *Table 11* for category definitions.

Table 17 shows the proportion of drug courses implicated in a probable or definite ADR specifically for drugs, with > 100 courses administered, and the proportion of courses that were categorised as OLUL. Fentanyl via any route excluding epidural had the greatest proportion of courses implicated in an ADR, 48.0% of courses were implicated with 99.3% of courses categorised as off-label. Fentanyl via the epidural route had 44.3% of courses implicated with 100% of courses categorised as unlicensed. Morphine via any route had 35.0% of courses implicated, of which 39.6% were OLUL. *Table 18* shows the four most frequently implicated drugs by OLUL category. The majority of fentanyl courses were category 11 – given for a different indication; 91.7% of implicated fentanyl courses fell into this category. A total of 60.4% of morphine courses were authorised and 49.1% of implicated morphine courses fell into this category. Over one-third of morphine courses were category 5 ('not licensed in child of this age or child below minimum weight stated') and 50.3% of implicated morphine courses fell into this category.

TABLE 17 Drugs course frequency administered, implicated and off-label, unlicensed or unknown (only drugs with > 100 courses shown, $n = 7007$)

Category of drug use	Drug (no. of courses)	% of courses off-label or unlicensed[a]	% of courses implicated in at least one ADR	No. of courses unknown
Drugs with only authorised courses	Cefuroxime (245)	0	4.5	1
	Cefotaxime (388)	0	9.0	0
Drugs with off-label courses	Chlorphenamine (339)	0.3	0.3	1
	Diazepam (107)	1.9	1.9	0
	Ibuprofen (545)	4.8	0.7	0
	Lactulose (272)	4.8	2.2	0
	Cefalexin (148)	6.1	7.4	0
	Metronidazole (257)	8.2	7.8	0
	Furosemide (123)	11.8	9.8	0
	Paracetamol (1786)	33.4	0.1	2
	Ondansetron (550)	52.7	5.8	48
	Salbutamol (146)	56.8	8.9	0
	Ranitidine (109)	59.6	0.9	0
	Dexamethasone (166)	64.5	6.6	7
	Fentanyl (150)	99.3	48.0	0
Drugs with unlicensed courses	Fentanyl and levobupivicaine epidural (106)	100	44.3	0
Drugs with off-label and unlicensed courses	Codeine phosphate (752)	1.6	13.2	257
	Morphine (500)	39.6	35.0	0
	Diclofenac (331)	45.0	1.5	159

a Drugs within each category listed in ascending order.

TABLE 18 Off-label and/or unlicensed category proportions for drugs with > 10% of courses implicated

Category[a]	Fentanyl (implicated)	Fentanyl + levobupivicaine epidural (implicated)	Morphine (implicated)	Codeine (implicated)
1	1 (0)	–	302 (86)	483 (67)
3	–	–	2 (0)	–
5	1 (0)	–	189 (88)	9 (0)
11	136 (66)	–	6 (1)	–
15	12 (6)	–	–	–
29	–	–	–	257 (32)
32	–	106 (47)	1 (0)	3 (0)
Total	150 (72)	106 (47)	500 (175)	752 (99)

a See *Table 11* for category definitions.

Risk factor analysis

Prospective cohort study

In the univariate analysis, age was a significant predictor of ADR risk and oncology patients were more likely to experience an ADR than non-oncology patients (*Table 19* and *Figure 6*). Multivariate risk factor analysis of first admissions ($n = 4724$, see *Figure 5*) showed that at any time, the hazard of an ADR in a child following a GA was six times greater than the hazard of an ADR in a child who had not had a GA; the hazard of an ADR increased by 25% with each additional drug given (median daily number of drugs administered 3, IQR 1–5); the hazard of an ADR in oncology patients is nearly twice that of non-oncology patients; and the hazard of an ADR in children increased by 6% for each year of age.

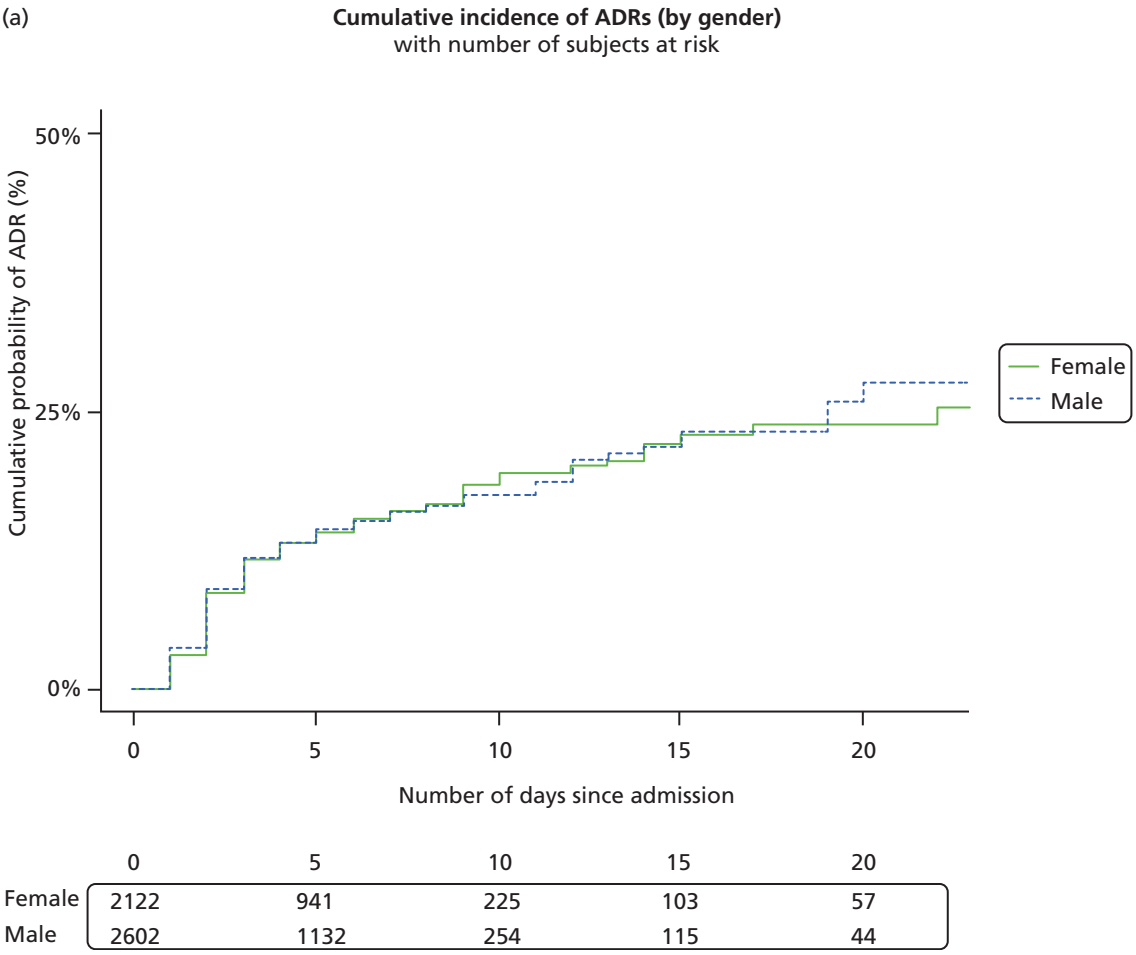
Nested case–control study

Multivariate risk factor analysis of the nested cohort showed that age on admission and receipt of a GA both had a significant effect on ADR risk. Gender and oncology patient status did not have a significant effect on the hazard of an ADR. The hazard of an ADR increased by 30% with each additional OLUL drug given (median daily number of OLUL drugs administered 1, IQR 0–2). Similarly, the hazard of an ADR increased by 20% with each additional authorised drug (median daily number of authorised drugs administered 2, IQR 1–3) (*Table 20*).

TABLE 19 Prospective cohort study univariate analysis by categorical time invariant risk factor

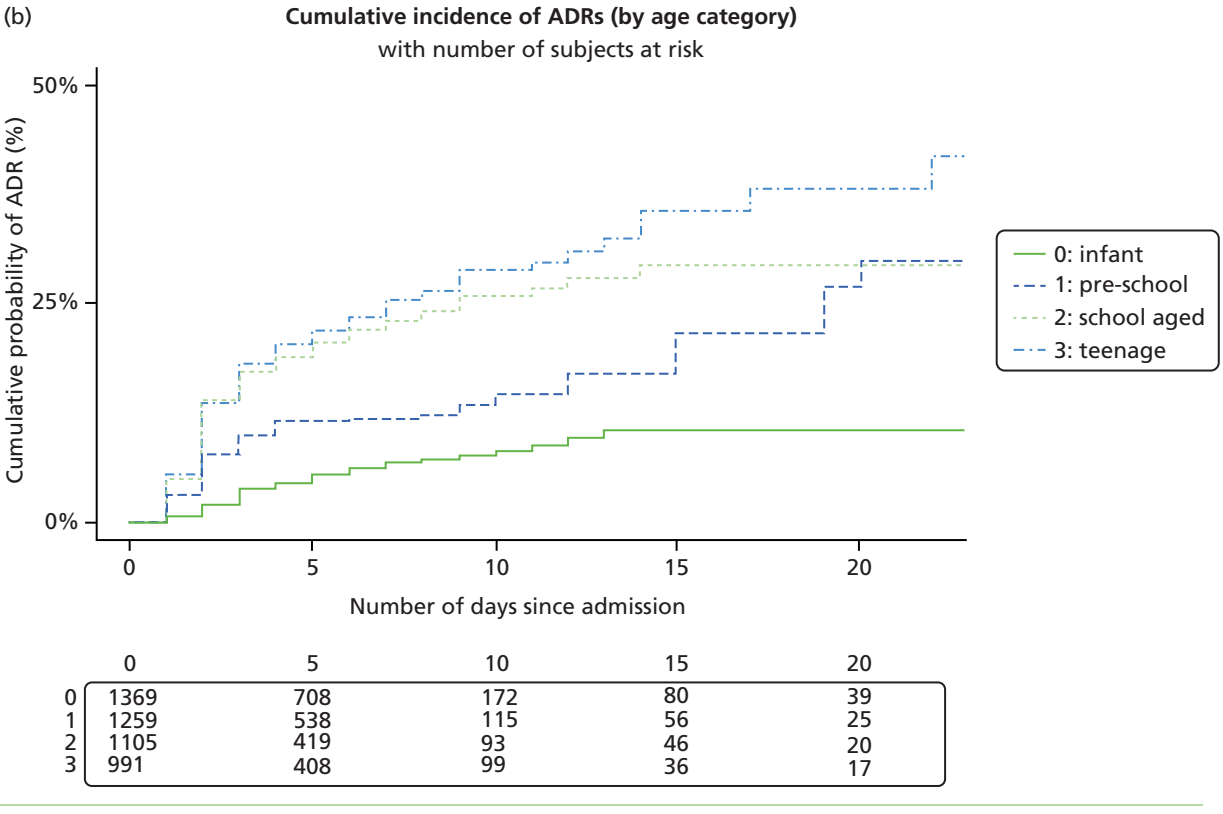
Covariate		Total patients	No. of patients with ADR	Log-rank statistic (*p*-value)
Gender	Male	2602	382	0.900
	Female	2122	312	
Age	Infant (< 1 year)	1369	78	< 0.001
	Pre-school (1–5 years)	1259	155	
	School aged (5–11 years)	1105	231	
	Teenage (> 11 years)	991	230	
Oncology	Yes	106	45	< 0.001
	No	4625	649	

(a)



	0	5	10	15	20
Female	2122	941	225	103	57
Male	2602	1132	254	115	44

(b)



	0	5	10	15	20
0	1369	708	172	80	39
1	1259	538	115	56	25
2	1105	419	93	46	20
3	991	408	99	36	17

FIGURE 6 Cumulative incidence curves by categorical time invariant risk factor. (a) Gender; (b) age (by category); and (c) oncology status. (*continued*)

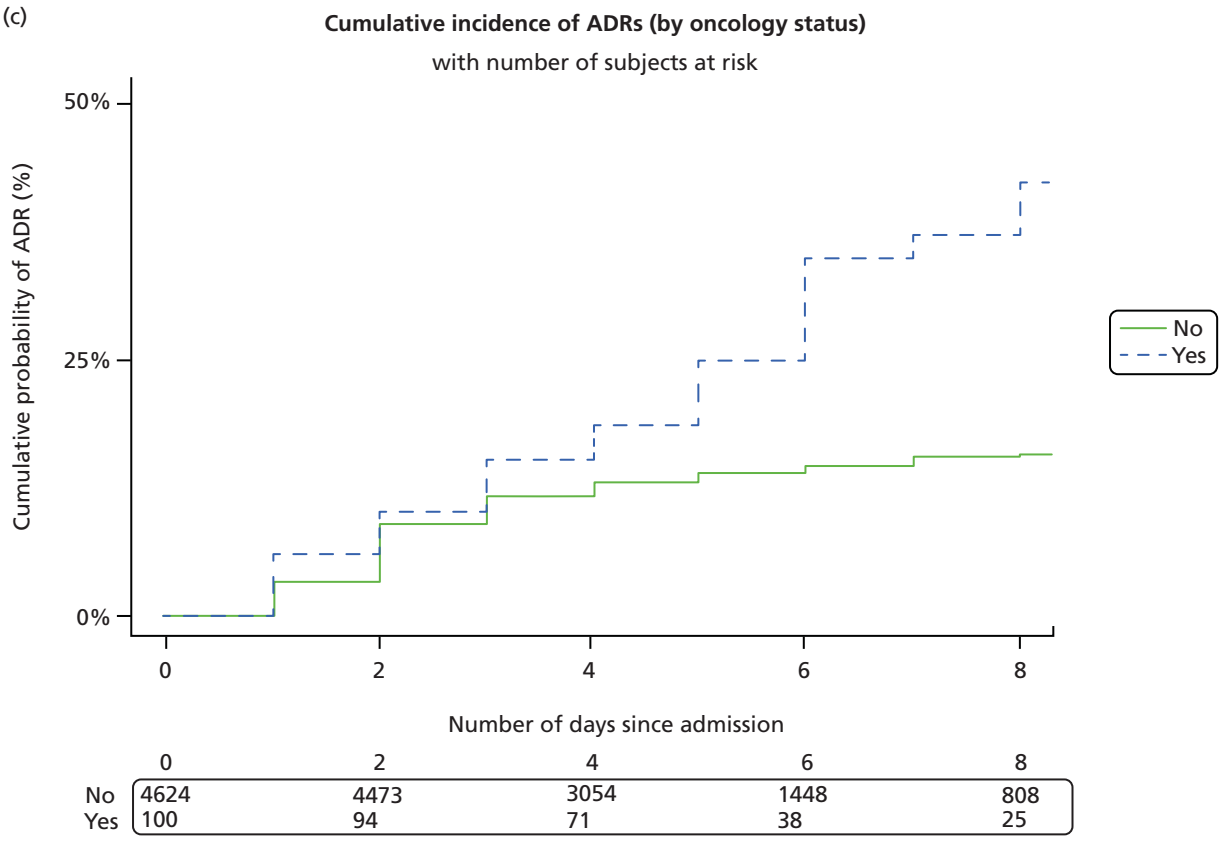


FIGURE 6 Cumulative incidence curves by categorical time invariant risk factor. (a) Gender; (b) age (by category); and (c) oncology status.

TABLE 20 Risk factors for ADRs assessed by multivariate analysis

Covariate		Prospective cohort study		Nested case–control study	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age on admission (in years)		1.06 (1.04 to 1.07)	< 0.001	1.04 (1.02 to 1.05)	< 0.001
Gender	Female	1	0.301	1	0.152
	Male	0.93 (0.80 to 1.08)		0.90 (0.77 to 1.04)	
No. of drugs		1.25 (1.22 to 1.28)	< 0.001	N/A	
No. of authorised drugs		N/A		1.22 (1.17 to 1.26)	< 0.001
No. of OLUL drugs		N/A		1.27 (1.20 to 1.34)	< 0.001
Received a GA	No	1		1	
	Yes	6.38 (5.30 to 7.68)	< 0.001	5.30 (4.42 to 6.35)	< 0.001
Oncology	No	1		1	
	Yes	1.89 (1.36 to 2.63)	< 0.001	0.93 (0.66 to 1.30)	0.655

N/A, not applicable.

Discussion

Our data show that 17.7% of all children who spent > 48 hours as an inpatient experienced at least one ADR, 58% of which occurred after a GA. Opiate analgesic drugs and drugs used in GA were the most commonly implicated drugs. The risk of experiencing an ADR in patients undergoing a procedure under GA has not been assessed previously, including age, oncology treatment and the use of multiple drugs. OLUL medicines were significantly more likely to be implicated in an ADR than medicines used within the terms of their MA (OR 2.25, 95% CI 1.95 to 2.59). Multivariate analysis in our case–control study indicated that risk factors for ADRs were the administration of a GA and the number of medicines administered per day, consistent with the findings of the cohort study.

Strengths and weaknesses of the study

This is the largest paediatric in-hospital study investigating ADRs. Although this was a single-centre study, the study population represents a wide range of paediatric medical and surgical specialties, as the hospital serves as a paediatric centre for the local catchment area, and is the regional paediatric referral centre. Our methodology included causality and severity assessments using validated tools. Denominator data are available for all medication administered on the wards, whereas details on medication given during GA were recorded only in patients if there was a suspected ADR to those drugs. As a result, the effect that increasing the number of drugs given during GA has on the risk of an ADR remains unknown.

The observational approach depends on documentation by the clinical team regarding signs and symptoms. Despite this intense surveillance, it is possible that some ADRs will be missed. Most symptoms that are dependent on patient communication (e.g. nausea, pain, hallucinations) are under-represented in younger or mentally disabled children. This could explain why the risk of developing an ADR increased with age. In addition, some of the most common reaction types observed in our study, such as vomiting and diarrhoea, are perhaps more likely to be manifestations of underlying illness among hospitalised infants and toddlers. The possibility that an underlying illness is an alternative cause may mean that these events are less likely to be assessed as probable or definite ADRs.

We recorded ADRs observed between 1 October 2009 and 30 September 2010. Patients who experienced an ADR before 1 October 2009 or after 30 September 2010, respectively, were counted as admissions without an ADR in the analysis. Consequently, there are 180 admissions that lie outside the observation period where an ADR may have occurred that has not been recorded.

In terms of assigning drug courses an OLUL category, our nested case–control study also had its limitations. First, we required a minimum amount of information to be available about the use of a drug before it could be categorised as off-label. The absence of this information was a result of how drugs were recorded on prescription charts; in general they were prescribed by the name of the active ingredient, and details such as the exact preparation administered were not recorded. Hence the prescription chart records were adequate for their primary purpose but not for our study. Second, there were assumptions outlined in our methodology pertaining to the SmPC definitions of age, gestational age and the classification of cytotoxic drugs.

Strengths and weaknesses in relation to other studies

Our study confirmed risk factors previously identified: increasing age, oncology treatment and multiple drug therapy. The risk of experiencing an ADR in patients undergoing a procedure under GA has not been assessed previously. In our study it increased the risk by more than six times. Most previous paediatric inpatient studies were carried out in general paediatric settings in which only a small number of patients will have undergone GAs. Rashed *et al.*[81] conducted a paediatric study on general medical wards and reported that anaesthetic drugs, which accounted for only 1% of all prescriptions, were among the drugs most commonly implicated in ADRs.[81] In the two previous inpatient studies investigating paediatric surgical patients and providing medication details, opiate analgesic drugs were among the two most commonly implicated drugs. However, GAs were not included, perhaps because they were not specifically

investigated.[3,92] The differences of our study population are also reflected in the spectrum and severity of common reaction types observed. Some reaction types, such as urinary retention and respiratory depression/arrest, occurred almost exclusively in the postoperative period. In addition to the differences in study populations, it is likely that reactions to drugs used in postoperative pain management were well documented in our study population, as patients on these medications are specifically monitored for side effects and are followed up by a specialist pain management team.

A recent review of preventability assessment (called avoidability assessment by some authors) of ADRs by Ferner and Aronson[25] concluded that no universal definition of preventability exists and that the reliability of existing definitions is imperfect. The most frequently used avoidability assessment tools (AATs) were Schumock and Thornton[44] and Hallas,[54] which are based on appropriateness of prescribing or treatment choice. Although these tools might be used successfully to improve prescribing practice in specific clinical circumstances, they become problematic wherever treatment is guided by tertiary paediatric specialist advice, as it would be desirable to use the same expert input when assessing the prescribed treatment. The same applies to areas outside paediatric specialties in which expert input would be required, for example to assess the choice of GA drugs used. It is noticeable that studies that previously reported avoidability of ADRs in hospitalised children had much smaller event numbers compared with 1446 ADRs in our study (0–41 ADRs/study);[19] one multicentre study detected only 408 ADRs between five centres,[81] which would make literature searches and gathering expert advice more feasible.

The prevalence of OLUL prescriptions in paediatric inpatients ranges from 18% to 60%, and 3.4% to 36%, respectively.[87] The corresponding figures in our case–control study were 23.7% and 7.5%, respectively. These figures collectively are similar to a previous study from our centre[3] in 1999, which showed that 35% of prescriptions were OLUL. Our data show that OLUL were significantly more likely to be implicated in an ADR than drugs used within the terms of their MA (OR 2.25, 95% CI 1.95 to 2.59). The risk estimate is higher than that found previously,[3,75] which may be a reflection of the fact that the previous studies were smaller (OR 1.5 and OR 1.08),[3,75] looked at different ward types (e.g. included paediatric intensive care)[3] and used different definitions of OLUL drugs.[75] We also categorised ADR risk according to the type of OLUL use. By focusing on six categories that all had > 100 drug courses, we found that (1) drugs licensed for use in children, but given at a dose greater than recommended, had a lower risk of being implicated in an ADR than authorised drugs and (2) drugs licensed in children, but given to a child below the minimum age or weight, had the greatest risk of being implicated in an ADR. These two findings seem counterintuitive but can be explained by the fact that 69% of the drug courses given at a higher dose than recommended were paracetamol. This reflects the widespread use of 15–20-mg/kg doses for 'severe symptoms', as recommended in the BNF-C.[90] Paracetamol at these doses is relatively safe particularly in inpatient settings, and indeed, paracetamol was rarely implicated in ADRs throughout the entire study (see *Table 17*). We removed all paracetamol courses from our data set and reanalysed; 15.4% of OLUL courses were implicated in at least one ADR and the OR of an OLUL medicine being implicated in an ADR was 2.24 (95% CI 1.94 to 2.59). Category 5 ('drugs licensed in children but given to a child below the minimum age or weight') had a diminished RR of being implicated in an ADR (OR 2.97, 95% CI 2.36 to 3.73) but were still the most likely category to be implicated in an ADR. Category 3 ('drugs licensed for use in children, but given at a dose greater than recommended') had an increased (rather than a reduced) risk of being implicated in an ADR compared with category 1 ('authorised medicines') (OR 1.20, 95% CI 0.74 to 1.94).

Multivariate analysis of both the full cohort data and the nested case–control data indicates that risk factors for ADRs are the administration of a GA and the number of drugs administered per day. Furthermore, these findings are consistent with those of Santos *et al.*[76] who found that off-label drug use was significantly associated with ADR risk (RR 2.44, 95% CI 2.12 to 2.89). However, in our study, we have dissected drug use, and show that the number of OLUL drugs administered per day had a similar influence on ADR risk to the number of authorised drugs administered per day. Most studies, including those in adults, have shown that ADR risk increases with the number of drugs used by patients,[3,59,75,93,94] which reflects the complex interaction that occurs between drugs targeting different biological systems within the

body, the interaction with disease (i.e. sicker patients are more likely to require a higher number of drugs) and the occurrence of drug–drug interactions.

Implications of study findings

Our study used the same incidence calculations as a comparable prospective adult study by Davies *et al.*,[59] who reported incidence figures of 14.7% on episode (admission) level and 15.8% on patient level. This compares to our incidence figures of 15.9% and 17.7%, respectively. However, Davies *et al.*[59] used the Naranjo CAT and included definite, probable and possible ADRs, whereas we excluded 'possible' and 'unlikely' ADRs. It is therefore likely that our figures underestimate the true incidence of untoward events that should be attributed to drugs. The assessment of symptoms due to the underlying condition and differentiating these from those caused by drugs (e.g. tachycardia in patient treatment for acute asthma) remains a challenge.

Although < 1% of reactions in our study were classified as severe, this does not take into account what impact an ADR might have on the child and/or parent. The most common reaction in our study was vomiting, which was mainly observed in postoperative patients. Vomiting is a common and non-specific symptom in children. Such episodes are unlikely to be regarded as particularly significant by clinicians. However, parents and children often have very different views. For instance, Diez[95] reported that parents placed a very high value on the distress caused by PONV. A teenage patient is likely to feel very distressed about having to be catheterised because of urinary retention or having to receive an enema to treat constipation. Parents of children included in this study reported that suspected ADRs cause them concern, irrespective of the 'medical' severity of the suspected reaction. Parents valued the proactive explanations of ADRs given by oncologists and we suggest that a detailed discussion of ADRs should form part of the preoperative assessment.[96]

In terms of OLUL drug use, our findings highlight the impact of the use of multiple drugs (whether OLUL or authorised) and thus the need for good prescribing practice in reducing ADRs. The minimum number of drugs should be given for the treatment of a disease process, at the lowest possible dose for the shortest possible time. Our data implicate OLUL drugs as risk factors for ADRs in paediatric inpatients. Off-label use is complicated and in some cases can be justified by the fact that evidence which may not necessarily have led to a change in the SmPC is available in the scientific literature as a result of academic investigations.[97] For instance, some of the most commonly implicated drugs in our study were frequently used off-label (e.g. dexamethasone). However, we have no evidence that if these products were used in accordance with a MA, they would be implicated in any fewer ADRs. An area of concern identified in our data is the use of fentanyl, commonly OLUL, where 48% of courses were implicated in ADRs. A key issue with fentanyl may be the dose used in children, suggesting a need for further evaluation of dosing strategies.

With all drugs, irrespective of their licensing status, the dose administered and thus the systemic exposure to that drug, is an important determinant of the likelihood of an ADR. The importance of this is highlighted by our finding that drugs licensed in children, but given to a child below the minimum age or weight had the greatest risk of being implicated in an ADR, reflecting the lack of pharmacokinetic data in children of different ages and/or weights. Advances in the development, and application, of paediatric pharmacokinetic models will be important in the defining, and implementation, of age- and weight (or body surface area)-specific dosing regimens.[98] Although such approaches are now being incorporated in paediatric investigation plans for new drugs, the challenge for all stakeholders will be how to improve this knowledge for drugs already on the market, most of which are not only generic off-patent compounds but are also the most widely used.

In conclusion, our data show that ADRs in hospitalised children are as common as those observed in hospitalised adults.[59] The high proportion of ADRs occurring in the postoperative period and the indication that OLUL drugs are more likely to be implicated in ADRs are of particular concern.

Chapter 4 Systematic review of paediatric adverse drug reactions

Abstract

Background

Adverse drug reactions in children are an important public health problem. We have undertaken a systematic review of observational studies in children in three settings: causing admission to hospital, occurring during hospital stay, and occurring in the community. We were particularly interested in understanding how ADRs might be better detected, assessed and avoided.

Methods

We searched 19 electronic databases using a comprehensive search strategy. In total, 102 studies were included. The primary outcome was any clinical event described as an ADR to one or more drugs. Additional information relating to the ADR was collected: associated drug classification; clinical presentation; associated risk factors; and methods used for assessing causality, severity and avoidability.

Results

Seventy-one per cent (72/102) of studies assessed causality and 33% (34/102) performed a severity assessment. Only 19 studies (19%) assessed avoidability. Incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children [pooled estimate of 2.9% (95% CI 2.6% to 3.1%)] and from 0.6% to 16.8% of all children exposed to a drug during hospital stay. Anti-infective drugs and antiepileptic drugs were the most frequently reported therapeutic class associated with ADRs in children admitted to hospital (17 studies and 12 studies, respectively) and children in hospital (24 studies and 14 studies, respectively), whereas anti-infective drugs and NSAIDs were frequently reported as associated with ADRs in outpatient children (13 studies and six studies, respectively). Fourteen studies reported rates ranging from 7% to 98% of ADRs being either definitely or possibly avoidable.

Conclusions

There is extensive literature that investigates ADRs in children. Although these studies provide estimates of incidence in different settings and some indication of the therapeutic classes most frequently associated with ADRs, further work is needed to address how such ADRs may be prevented.

Introduction

Adverse drug reactions are a major health problem to the individual as well as for society.[99] The WHO's definition of an ADR is 'a response to a drug which is noxious, and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function'.[100] The high incidence of ADRs in children has been reported in three previous systematic reviews of observational studies covering the period from 1966 to 2010.[34,35,101] The reviews provided estimates of ADR rates causing hospital admission, in hospitalised children and in outpatient children, and demonstrated that ADRs in hospitalised children are a considerable problem. Two of the

reviews[35,101] provide data on the clinical presentation of the ADR and the drugs involved. In addition, the more recent review[101] provides information on the methods and persons involved in identifying ADRs.

However, there are a number of limitations to the previous reviews. Each review[34,35,101] applied a search strategy, using a limited number of keywords to just two electronic bibliographic databases – MEDLINE and EMBASE. Importantly, as a consequence, relevant studies may have been excluded. In addition, the reviews excluded studies that included adults as well as children, thus reducing the number of eligible studies, and the more recent reviews excluded studies that evaluated adverse drug events (ADEs).

These reviews do not provide information about the drugs involved in ADRs or about which methods were used for detecting, or assessing, the causality of an ADR.[23] Establishing the relationship between the drug and suspected reaction is fundamental to drug safety and being able to determine the avoidability[44] of an ADR in order to try to prevent its future occurrence is crucial to reducing the burden of ADRs.

We therefore undertook this systematic review to provide a more comprehensive assessment of all relevant studies and to understanding how ADRs might be better detected, assessed and avoided.

Methods

Study selection

Criteria for considering studies for this review

Included studies Observational studies that estimate the incidence of ADRs including retrospective and prospective cohort studies of children.

Excluded studies Studies that focus on ADRs in relation to a specific drug (e.g. antibiotic drugs or carbamazepine), clinical condition (e.g. epilepsy, asthma) or specific clinical presentations of ADRs (anaphylaxis); case–control studies; those carried out exclusively on a neonatal intensive care unit; and studies reporting medication errors, therapeutic failures, non-compliance, accidental and intentional poisoning, and drug abuse.

Participants

Children as defined by the researchers. Studies included three defined populations:

1. children admitted to hospital
2. children in hospital
3. children within the community.

Interventions

Exposure to any systemic or topical medicinal product, including herbals and aromatherapy, as defined by researchers.

Types of outcome measure

Any clinical event described as an ADR or non-avoidable ADE to an individual or group of drugs.

Search methods for identification of studies

A range of electronic bibliographic databases were searched (see *Appendix 1*) using a search strategy of text words and medical subject headings (MeSH) terms (see *Appendix 2*). In addition, we examined references in relevant studies and those cited by previous systematic reviews. Contact with experts was made to identify other potentially relevant published and unpublished studies. We did not apply language restrictions to the search.

Selection of studies

Screening on title, abstract and full publication stage

Duplicate citations were removed. A study eligibility screening pro forma based on prespecified inclusion criteria was used. Two reviewers (RMDS, EG) independently screened each title and categorised as 'include', 'exclude' or 'unsure'. The two independent categorisations for all titles were compared and the title was categorised again following discussion if two reviewers disagreed. When there was agreement to exclude, the citation was excluded at this stage. All other citations were reviewed at abstract level. This process was repeated and when there was disagreement, discussion took place between reviewers and citations were recategorised. Those with agreement to include or considered 'unsure' were reviewed at full publication level. The process was repeated at full publication stage. Studies considered as unsure or included at full publication stage were reviewed by a third reviewer (JJK). Reasons for exclusion were documented at the abstract and full paper stage of the screening process.

Checking for correct exclusion at each stage

Two reviewers (RMDS, EG) independently viewed the abstracts for a proportion (2%) of studies excluded at title screening stage. Independent categorisations were compared (as above). This process was repeated at abstract stage where a third reviewer (JJK) reviewed 10% of full papers for studies excluded based on abstract. This was repeated at full publication stage, when the same reviewer (JJK) reviewed 20% of excluded full papers. If any studies were excluded incorrectly at any stage then additional checking was performed.

Data extraction

We extracted the following data from each study:

1. *Study characteristics* Country; year completed; duration; number of sites; design (prospective or retrospective); clinical setting; number of children.
2. *Identification of ADR* Definition of ADR, including definition of drug exposure; incidence definition and calculation (numerator and denominator, either at patient or episode level); assessment of causal relationship to drug; person who assessed and categorised ADRs; any method (e.g. case record review) or reporting system used (e.g. Yellow Card scheme).
3. *Information relating to the ADR* Clinical presentation; associated drug(s)/drug classification; associated risk factors (including age, gender, polypharmacy); ADR considered avoidable.

Assessment of methodological quality of included studies

As we were unable to find a validated assessment tool for critically appraising observational studies of ADRs, we developed a quality assessment form specifically for the review. The following aspects were deemed important when assessing study quality: study design; methods for identifying ADRs; methods used to establish the causal relationship between drug and effect; tools for assessing avoidability of the ADR; and tools for assessing severity of the ADR. Criteria were graded as 'yes', 'no', 'unclear' or 'not reported'. Two reviewers (RMDS, EG) independently assessed methodological quality of each study (*Table 21*).

Statistical analysis and data synthesis

For each of the three defined populations; children admitted to hospital, children in hospital and children within the community, a forest plot was produced to present the ADR incidence rate and 95% CI for each relevant study. Studies were subgrouped according to whether the incidence rate was reported at the patient and/or episode level, and whether or not all patients had been exposed to a drug. Further, for rates reported at the patient level a distinction was made between studies that had included one admission per patient and those that had included multiple admissions per patient. All results provided per study were included. Pooled estimates were calculated if the variability in incidence rates was not considered too large.

TABLE 21 Assessment of methodological quality

Aspect of study	Criteria	Grade
Study design	Was the study design clear (prospective, retrospective or combined)?	Yes/no/unclear/not reported
Methods for identifying ADRs	Were the methods used to identify ADRs described in sufficient detail?	Yes/no/unclear/not reported
	Were data collection methods (case record review, drug chart review and laboratory data) clearly described?	Yes/no/unclear/not reported
	Were the individuals (clinicians, self-reported, researchers) who identified ADRs clearly described?	Yes/no/unclear/not reported
Methods for determining causality	Was the process of establishing the causal relationship described in detail?	Yes/no/unclear/not reported
	Were standard methods (validated tool) used in the assessment?	Yes/no/unclear/not reported
Methods for determining avoidability	Was the assessment process of establishing avoidability described in detail?	Yes/no/unclear/not reported
	Were standard methods (validated tool) used in the assessment?	Yes/no/unclear/not reported
Methods for determining predictability	Was the assessment process of establishing predictability described in detail?	Yes/no/unclear/not reported
	Were standard methods (validated tool) used in the assessment?	Yes/no/unclear/not reported

Univariate meta-regression was used to determine if study level characteristics (setting, gender, age, oncology and number of drugs used) are associated with ADR incidence. Incidence rates for ADRs causing admission and occurring in hospital, calculated at the patient level for a single episode were included. Multivariate meta-regression was not undertaken owing to the paucity of covariate data. Risk factor analyses reported by any study were collated.

Results

The search was originally undertaken in November 2009 and retrieved 20,906 potentially relevant citations. An update search was subsequently performed in October 2010 and retrieved an additional 3234 citations. Combining both searches we identified 24,140 potentially relevant citations, of which 5039 duplicate citations were removed. Screening at title and abstract stage excluded a further 18,592 and 251 citations, respectively. Full papers were reviewed and 95 citations met the inclusion criteria. Agreement between reviewers at each stage of the review is described in *Figure 7*. Additional citations were identified through checking for correct exclusion at each stage ($n = 3$), reference checking ($n = 13$) and personal communication with authors ($n = 5$). In total, 116 citations relating to 101 studies were included in the review (see *Figure 7*).

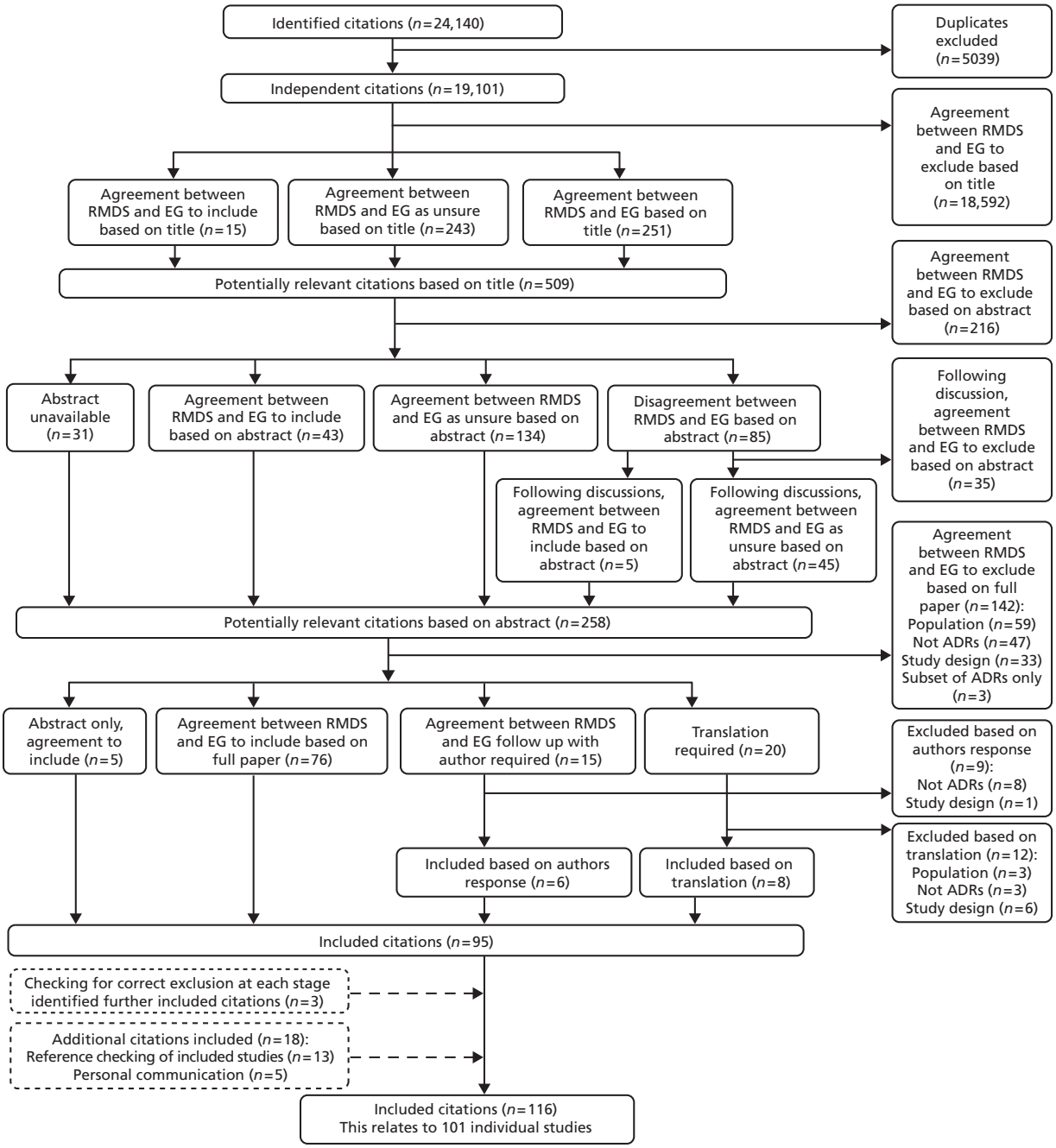


FIGURE 7 Agreement of reviewers.

Included studies

A total of 101 studies (116 citations), were included in the review. Eighty (80/101) studies described the clinical event as an ADR. In 10 of these studies, ADR was a category within 'drug-related' problems/admissions; three studies described ADRs as drug-induced disease/illness. Sixteen studies described an ADE, in which the non-preventable ADE was the same as our definition, and two studies used the term 'iatrogenic disease' to describe an ADR. Some studies included multiple settings: 42 studies investigated ADRs as the cause of admission to hospital, 53 studies investigated ADRs in the hospital setting, and 35 studies investigated ADRs in the community setting. Characteristics for each individual study are provided in *Appendix 3*.

Assessment of methodological quality of included studies

All studies, including those that evaluated ADEs, explicitly stated that they had used either the WHO ADR definition[1] or a similar one, and that they excluded drug errors. Methodological features of each individual study are provided in *Tables 22–27*.

TABLE 22 Drug class and clinical presentation of ADRs: causing admission studies

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Anti-infective drugs ($n = 17$)	Easton (1998)[41]	1682 admissions	10	1 (10)	Colitis, ileus
	Impicciatore (2002)[48]	116 children	12	4 (33.3)	Urticaria, periorbital oedema, neutropenia
	Lamababusuriya (2003)[47]	39,625 admissions	63	38 (60.3)	Erythema multiforme, Stevens–Johnson syndrome, rash, raised intracranial pressure
	Oshikoya (2007)[46]	3821 children	17	7 (41.1)	Provided for deaths only × 1
	Easton (2004)[102]	2933 admissions	29	Not reported	Not reported
	Mitchell (1988)[33]	7271 children	288	10 (3.5)	Diarrhoea, fever, erythema multiforme death × 2
	Major (1998)[103]	457 children	26	6 (23)	Not reported
	Santos (2000)[104]	624 children	14	6 (42.8)	Not reported
	Gallagher (2011)[20]	462 children	18	3 (16.6)	Diarrhoea
	Duczmal (2006)[105]	4996 admissions	58	Not reported	Not reported
	Ganeva (2007)[106]	73 children	6	4 (66.6)	Not reported
	Fattahi (2005)[107]	404 children	9	4 (44.4)	Not reported
	Martinez-Mir (1996)[42]	490 children	21	10 (47.6)	Not reported
	Yosselson-Superstine (1982)[43]	906 children	29	Not reported	Not reported
	McKenzie (1976)[32]	3556 admissions	72	Not reported	Provided for deaths only × 2
	ADRIC 1	6821 children	249	16 (6.4)	Diarrhoea, rash, vomiting, lip swelling, deranged LFTs, thrush

TABLE 22 Drug class and clinical presentation of ADRs: causing admission studies (*continued*)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Antiepileptic drugs ($n = 12$)	Easton (1998)[41]	1682 admissions	10	3 (30)	Increased fitting, rash, aphasia/motor regression
	Impicciatore (2002)[48]	116 children	12	2 (16.6)	Coma
	Lamababusuriya (2003)[47]	39,625 admissions	63	4 (6.3)	Ataxia and cerebellar signs, liver failure, Stevens–Johnson syndrome
	Oshikoya (2007)[46]	3821 children	17	1 (5.8)	Not reported
	Mitchell (1988)[33]	7271 children	288	23 (7.9)	Lethargy, ataxia, rash, erythema
	Le (2006)[36]	64,403 admissions	35	Not reported	Not reported
	Santos (2000)[104]	624 children	14	1 (7.1)	Not reported
	Yosselson-Superstine (1982)[43]	906 children	29	Not reported	Not reported
	McKenzie (1976)[32]	3556 admissions	72	Not reported	Not reported
	Fattahi (2005)[106]	404 children	9	1 (11.1)	Not reported
	Jonville-Bera (2002)[37]	260 children	4	1 (25)	Convulsion
	ADRIC 1	6821 children	249	2 (0.8)	Constipation, respiratory depression
NSAIDS ($n = 9$)	Duczmal (2006)[105]	4996 admissions	58	Not reported	Not reported
	Impicciatore (2002)[48]	116 children	12	1 (8.3)	Coma
	Lamababusuriya (2003)[47]	39,625 admissions	63	3 (4.7)	Rectal bleeding, aspirin – Reye's syndrome
	Major (1998)[103]	457 children	26	2 (7.6)	Not reported
	Gill (1995)[108]	909 admissions	10	1 (10)	Not reported
	ADRIC 1	6821 children	249	31 (12.4)	Postoperative bleeding, haematemesis, constipation, abdominal pain
	Gallagher (2011)[20]	462 children	18	1 (5.5)	Haematemesis
	Mitchell (1988)[33]	7271 children	288	12 (4.1)	Gastritis
	Jonville-Bera (2002)[37]	260 children	4	1 (25%)	Melaena
Cytotoxic drugs ($n = 8$)	Mitchell (1988)[33]	7271 children	288	Not reported	Deaths × 2
	Major (1998)[103]	457 children	26	10 (38.4)	Not reported
	Santos (2000)[104]	624 children	14	2 (14.2)	Not reported
	Yosselson-Superstine (1982)[43]	906 children	29	Not reported	Death × 1
	McKenzie (1976)[32]	3556 admissions	72	Not reported	Provided for deaths only × 3

continued

TABLE 22 Drug class and clinical presentation of ADRs: causing admission studies (*continued*)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
	Fattahi (2005)[107]	404 children	9	2 (22.2)	Not reported
	ADRIC 1	6821 children	249	110 (44.2)	Thrombocytopenia, anaemia, vomiting, mucositis, deranged liver function tests, immunosuppression, diarrhoea, nausea, constipation, headache, abdominal pain, back pain, haematuria, leukoencephalopathy, deranged renal function
	Gallagher (2011)[20]	462 children	18	9 (50%)	Pyrexia, neutropenia, lethargy, decreased responsiveness, vomiting
Corticosteroids (*n* = 7)	Easton (1998)[41]	1682 admissions	10	1 (10%)	Unstable diabetes
	Santos (2000)[104]	624 children	14	1 (7.1%)	Upper gastrointestinal bleed
	Yosselson-Superstine (1982)[43]	906 children	29	Not reported	Not reported
	McKenzie (1976)[32]	3556 admissions	72	Not reported	Not reported
	Ganeva (2007)[106]	73 children	6	2 (33.3%)	Not reported
	ADRIC 1	6821 children	249	102 (41.0%)	Immunosuppression, postoperative bleeding, hyperglycaemia, hypertension, gastritis, increased appetite, impaired healing, adrenal suppression
	Gallagher (2011)[20]	462 children	18	1 (5.5%)	Vomiting
Vaccines (*n* = 7)	Easton (1998)[41]	1682 admissions	10	1 (10%)	Hypotonic–hyporesponsive episode
	Lamababusuriya (2003)[47]	39,625 admissions	63	9 (14.2%)	Rash, encephalopathy, fits, head lag
	Easton (2004)[102]	2933 admissions	29	Not reported	Not reported
	Mitchell (1988)[33]	7271 children	288	5 (1.7%)	Not reported
	Santos (2000)[104]	624 children	14	1 (7.1%)	Not reported
	Gill (1995)[108]	909 admissions	10	2 (20%)	Seizures, fever
	ADRIC 1	6821 children	142		Fever, rash, irritability, seizure, vomiting, pallor, apnoea, limb swelling, lethargy, thrombocytopenia, diarrhoea, abdominal pain, respiratory distress, Kawasaki's disease

LFT, liver function test.

TABLE 23 Drug class and clinical presentation of ADRs: in-hospital studies

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Anti-infective drugs ($n = 24$)	Al-Tajir (2005)[109]	2351 episodes	2	2 (100)	Not reported
	Baniasadi (2008)[110]	693 children	27	Not reported	Not reported
	Choonara (1984)[111]	268 children	15	5 (33.3)	Vomiting, oral monilia, diarrhoea
	Dharnidharka (1993)[112]	703 children	7	1 (14.2)	Skin rash
	dos Santos (2006)[113]	265 children	47	18 (38.2)	Not reported
	dos Santos (2009)[114]	3726 episodes	302	57 (18.8)	Not reported
	Easton-Carter (2003)[115]	17,432 episodes	41	Not reported	Not reported
	Farrokhi (2006)[92]	81 children	3	1(33.3)	Not reported
	Fattahi (2005)[107]	380 children	40	35 (87.5)	Not reported
	Gill (1995)[108]	899 episodes	76	15 (19.7)	Not reported
	Gonzalez-Martin (1998)[116]	219 children	46	4 (8.6)	Not reported
	Jha (2007)[117]	943 children	13	12 (92.3)	Macupapular rashes, vomiting, diarrhoea, drug fever
	Jonville-Bera (2002)[37]	227 children	6	2 (33.3)	Diarrhoea, rash
	Impicciatore (2002)[48]	1619 children	29	9 (31.0)	Urticaria, increased transaminase levels, vomiting, diarrhoea
	Le (2006)[36]	64,403 admissions	1060	Not reported	Not reported
	Leach (1998)[118]	499 episodes	58	23 (39.6)	Vomiting, rash, diarrhoea, arthropathy, neutropenia, nausea, fits
	Mitchell (1979)[119]	1669 children	280	Not reported	Not reported
	Maistrello (1999)[120]	1103 children	59	24 (40.6)	Gastointestinal disorders
	Martinez-Mir (1999)[121]	490 children	68	Not reported	Not reported
	Neubert (2004)[75]	156 children	31	Not reported	Not reported
	Oshikoya (2007)[46]	3821 children	27	12 (44.4)	Red man syndrome, pustular rash, Stevens–Johnson syndrome, erythema, jaundice, anaphylaxis, urticaria, fever
	Shockrollah (2009)[122]	230 children	5	2 (40)	Not reported
	Turner (1999)[3]	936 episodes	157	34 (21.6)	Not reported
	Vazquez de la Villa (1989)[123]	597 children	26	9 (34.6)	Diarrhoea, vomiting, rash

continued

TABLE 23 Drug class and clinical presentation of ADRs: in-hospital studies (*continued*)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Antiepileptic drugs ($n = 14$)	Choonara (1984)[111]	268 children	15	7 (46.6)	Drowsiness, hyperactivity, ataxia
	Dharnidharka (1993)[112]	703 children	7	1 (14.2)	Skin rash
	dos Santos (2009)[114]	3726 episodes	302	26 (8.6)	Not reported
	Easton-Carter (2003)[115]	17432 episodes	41	Not reported	Not reported
	Gill (1995)[108]	899 episodes	76	3 (3.9)	Not reported
	Gonzalez-Martin (1998)[116]	219 children	46	5 (10.8)	Not reported
	Le (2006)[36]	64,403 admissions	1060	Not reported	Not reported
	Leach (1998)[118]	499 episodes	58	1	Apnoea
	Mitchell (1979)[119]	1669 children	280	Not reported	Not reported
	Martinez-Mir (1999)[121]	490 children	68	Not reported	Not reported
	Neubert (2004)[75]	156 children	31	Not reported	Not reported
	Oshikoya (2007)[46]	3821 children	27	2 (7.4)	Erythema
	Telechea (2010)[a]	123 children	46	15 (32.6)	Not reported
	Vazquez de la Villa (1989)[123]	597 children	26	4 (15.3)	Sedation, paradoxical reaction
Corticosteroids ($n = 10$)	dos Santos (2006)[113]	265 children	47	11 (23.4)	Not reported
	Gill (1995)[108]	899 episodes	76	6 (7.8)	Not reported
	Gonzalez-Martin (1998)[116]	219 children	46	3 (6.5)	Not reported
	Impicciatore (2002)[48]	1619 children	29	1 (3.4)	Rash
	Leach (1998)[118]	499 episodes	58	1 (1.7)	Gastric irritation
	Mitchell (1979)[119]	1669 children	280	Not reported	Not reported
	Neubert (2004)[75]	156 children	31	Not reported	Not reported
	Telechea (2010)[a]	123 children	46	4 (8.6)	Not reported
	Turner (1999)[3]	936 episodes	157	10 (6.3)	Not reported
	Vazquez de la Villa (1989)[123]	597 children	26	1 (3.8)	Cushing syndrome
Bronchodilators ($n = 9$)	Choonara (1984)[111]	268 children	15	3 (20)	Tachycardia
	Easton-Carter (2003)[115]	17,432 episodes	41	Not reported	Not reported
	Gill (1995)[108]	899 episodes	76	8 (10.5)	Not reported
	Gonzalez-Martin (1998)[116]	219 children	46	8 (17.3)	Not reported
	Impicciatore (2002)[48]	1619 children	29	5 (17.2)	Tremor, tachycardia
	Neubert (2004)[75]	156 children	31	Not reported	Not reported
	Telechea (2010)[a]	123 children	46	8 (17.3)	Not reported
	Turner (1999)[3]	936 episodes	157	8 (5.0)	Not reported
	Vazquez de la Villa (1989)[123]	597 children	26	11 (42.3)	Tachycardia, nervousness, vomiting

TABLE 23 Drug class and clinical presentation of ADRs: in-hospital studies (*continued*)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Cytotoxic drugs ($n = 7$)	dos Santos (2009)[114]	3726 episodes	302	10 (3.3)	Not reported
	Gonzalez-Martin (1998)[116]	219 children	46	7 (15.2)	Not reported
	Jonville-Bera (2002)[37]	227 children	6	4 (66.6)	Vomiting
	Le (2006)[36]	64,403 admissions	1060	Not reported	Not reported
	Leach (1998)[118]	499 episodes	58	1 (1.7)	Thrombocytopenia
	Mitchell (1979)[119]	1669 children	280	Not reported	Not reported
	Telechea (2010)[a]	123 children	46	1 (2.1)	Not reported
Diuretic drugs ($n = 6$)	Easton-Carter (2003)[115]	17,432 episodes	41	Not reported	Not reported
	Leach (1998)[118]	499 episodes	58	1 (1.7)	Overdiuresis
	Mitchell (1979)[119]	1669 children	280	Not reported	Not reported
	Neubert (2004)[75]	156 children	31	Not reported	Not reported
	Telechea (2010)[a]	123 children	46	9 (19.5)	Not reported
	Turner (1999)[3]	936 episodes	157	31 (19.7)	Not reported

a Telechea M, Lucas N, Giachetto L, Nanni G, Menchaca A. Importance of drug-induced pathology in an intensive care unit of children. 2010, unpublished data.

TABLE 24 Drug class and clinical presentation of ADRs: community

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Anti-infective drugs ($n = 13$)	Cirko-Begovic (1989)[124]	2459 children	63	49 (78)	Not reported
	Easton-Carter (2003)[125]	8601 consultations	118	Not reported	Not reported
	Horen (2002)[77]	1419 consultations	20	9 (45)	Not reported
	Juntti-Patinen (2006)[126]	Not reported for children only	4	Not reported for children only	Not reported for children only
	Kaushal (2007)[127]	1689 children	226	158 (70)	Nausea, vomiting and diarrhoea
	Kramer (1985)[78]	4244 courses of therapy	200	Not reported	Diarrhoea, other gastrointestinal complaints and skin rashes
	Menniti-Ippolito (2000)[128]	7890 children	119	79 (66)	Cutaneous, gastrointestinal, eosinophilia, neurological, angioedema, fever
	Planchamp (2009)[129]	12,995 consultations	43	Not reported	Not reported
	Sanz and Boada (1987)[130]	1327 children	10	4 (40)	Cutaneous reaction and diarrhoea
	Munoz (1998)[131]	47,107 consultations	447	49.5%	Included skin reactions
	Jonville-Bera (2002)[37]	A&E, 428 children; private paediatricians, 1192 children	A&E, 4; private paediatricians, 8	A&E, 2 (50); private paediatricians, 6 (75)	Diarrhoea, rash, vomiting
	Woods (1987)[132]	1590 children	235	40 (17)	Diarrhoea, drowsiness, rash, headache, hyperactivity, anorexia, abdominal pain, vomiting, sleep disturbance
	Zahraoui (2010)[133]	Not reported	24	Not reported	Not reported
NSAIDs ($n = 6$)	Kaushal (2007)[127]	1689 children	226	2 (1)	Not reported
	Menniti-Ippolito (2000)[128]	7890 children	119	3 (3)	Cutaneous, haematuria, hypertranspiration
	Munoz (1998)[131]	47107 consultations	447	Not reported	Not reported
	Planchamp (2009)[129]	12,995 consultations	43	Not reported	Not reported
	Sanz and Boada (1987)[130]	1327 children	10	1 (10)	Not reported
	Woods (1987)[132]	1590 children	235	9 (4)	Drowsiness, abdominal pain, aggressiveness, vomiting

TABLE 24 Drug class and clinical presentation of ADRs: community (*continued*)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Analgesic drugs ($n = 5$)	Kaushal (2007)[127]	1689 children	226	1 (0.4)	Not reported
	Munoz (1998)[131]	47,107 consultations	447	Not reported	Not reported
	Planchamp (2009)[129]	12,995 consultations	43	Not reported	Not reported
	Woods (1987)[132]	1590 children	235	11 (5)	Drowsiness, irritability, aggressiveness
	Zahraoui (2010)[133]	Not reported	24	Not reported	Not reported
Vaccines ($n = 5$)	Horen (2002)[77]	1419 consultations	20	5 (25)	Not reported
	Jonville-Bera (2002)[37]	A&E, 428; private, 1192 (children)	A&E, 4; private 8	A&E, 1 (25); private, 2 (25)	A&E rash; private, fever
	Menniti-Ippolito (2000)[128]	7890 children	119	14 (12)	Not reported
	Munoz (1998)[131]	47,107 consultations	447	? 9.2%	Not reported
	Planchamp (2009)[129]	12,995 consultations	43	Not reported	Not reported
Antihistamine drugs ($n = 4$)	Cirko-Begovic (1989)[124]	2459 children	63	2 (3)	Not reported
	Kaushal (2007)[127]	1689 children	226	2 (1)	Not reported
	Menniti-Ippolito (2000)[128]	7890 children	119	2 (2)	Not reported
	Woods (1987)[132]	1590 children	235	46 (20)	Drowsiness, aggressiveness, dry mouth, headache, irritability, diarrhoea
Bronchodilators ($n = 3$)	Kaushal (2007)[127]	1689 children	226	16 (7)	Not reported
	Kramer (1985)[78]	4244 courses of therapy	200	Not reported	Various manifestations of central nervous stimulation
	Woods (1987)[132]	1590 children	235	6 (3)	Hyperactivity, shakiness, dizziness, irritability, sleep disturbance
Steroids ($n = 3$)	Horen (2002)[77]	1419 consultations	20	1 (0.05)	Not reported
	Kaushal (2007)[127]	1689 children	226	12 (5)	Not reported
	Woods (1987)[132]	1590 children	235	5 (2)	Abdominal pain, diarrhoea

TABLE 25 Drug class and clinical presentation of ADRs: combined settings (causing admission and in hospital)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Anti-infective drugs ($n = 2$)	Haffner (2005)[134]	703 admissions	101	Not reported	Not reported
	Speranza (2008)[135]	173 children	24	10 (41.6)	Not reported
Bronchodilators ($n = 1$)	Haffner (2005)[134]	703 admissions	101	Not reported	Not reported
Antiepileptic drugs ($n = 2$)	Haffner (2005)[134]	703 admissions	101	Not reported	Not reported
	Speranza (2008)[135]	173 children	24	4 (16.6)	Not reported
Cardiovascular drugs ($n = 1$)	Haffner (2005)[134]	703 admissions	101	Not reported	Not reported
Analgesic drugs ($n = 1$)	Speranza (2008)[135]	173 children	24	2 (8.3)	Not reported
Antiulcer drugs ($n = 1$)	Speranza (2008)[135]	173 children	24	2 (8.3)	Not reported
Psychotropic drugs ($n = 1$)	Speranza (2008)[135]	173 children	24	2 (8.3)	Not reported

TABLE 26 Drug class and clinical presentation of ADRs: combined settings (in hospital and community)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Anti-infective drugs ($n = 1$)	Kushwaha (1994)[136]	20,310 admissions	267	Not reported	Erythematous maculopapular rash, thrombophlebitis, erythema multiforme, fixed drug reaction, urticaria, jaundice, aplastic anaemia, thrombocytopenia purpura
Vaccines ($n = 1$)	Kushwaha (1994)[136]	20,310 admissions	267	Not reported	Nodular cyst in gluteal region, injection abscess
NSAIDs ($n = 1$)	Kushwaha (1994)[136]	20,310 admissions	267	Not reported	Erythematous maculopapular rash
Analgesic drugs ($n = 1$)	Kushwaha (1994)[136]	20,310 admissions	267	Not reported	Erythematous maculopapular rash, urticaria
Steroids ($n = 1$)	Kushwaha (1994)[136]	20,310 admissions	267	Not reported	Injection abscess

TABLE 27 Drug class and clinical presentation of ADRs: combined settings (admission, in hospital and community)

Drug class	Study	Population of study	No. of ADRs	No. of ADRs due to drug class (%)	Clinical presentation
Steroid ($n = 1$)	McKenzie (1973)[137]	658 children	175	Not reported	Psychotic reaction, Cushing syndrome, cataracts, hypertension
Anti-infective drugs ($n = 1$)	McKenzie (1973)[137]	658 children	175	Not reported	Rash, diarrhoea, facial flush, monilia, pain in injection site
Cytotoxics ($n = 1$)	McKenzie (1973)[137]	658 children	175	Not reported	Alopecia, peripheral neuritis, mouth ulcer, injection site inflammation, leukopenia, secondary infection

Notes
One patient in the Zahraoui (2010)[133] study died (gastrointestinal bleeding and severe thrombocytopenia after prolonged anticonvulsant treatment).
Mitchell (1988):[33] five deaths (fever, vomiting, arrhythmia and cardiopulmonary arrest attributed to theophylline and erythromycin; cardiac arrest and hypernatraemia attributed to halothane, and nitrous oxide pneumonia attributed to chemotherapy-induced immunosuppression; cardiotoxicity attributed to doxorubicin; candida sepsis and meningitis attributed to chemotherapy-induced immunosuppression).
Yosselson-Superstine (1982):[43] one death (no details provided).

Meta-regression

Study design

The majority of studies were carried out prospectively ($n = 84$; 83%), which included 13 in those causing admission, 26 studies with the ADR occurring in hospital, 23 in the community, 16 in hospital and causing admission, and six in mixed hospital and community settings. Fourteen studies were carried out retrospectively, which included six causing hospital admission, two in hospital studies, and four in the community, one causing admission and in the hospital setting, and one the study that considered ADRs that resulted in any medical care contact. Two studies (one in hospital and one in hospital and causing admission) used both study designs. For the remaining study we were unable to determine the study design (see *Tables 22–27*).

Persons involved in identifying adverse drug reactions

Sixty-three studies reported that a clinician – medical doctor, nurse or pharmacist – was involved in the identification of ADRs. Thirty studies reported also involving either the child or parent. Eight studies did not provide information about who identified the ADRs.

Methods for identifying adverse drug reactions

Several methods were used to detect ADRs. Multiple ADR detection methods were used in 58/101 studies; these consisted of a combination of case record review, drug chart review, laboratory data, computerised ADR reporting system, attendance at ward rounds, and interviewing patients/parents or clinicians. In 31 studies, case record review alone was undertaken. The remaining 11 studies used parental interviews/questionnaires (five studies), clinical assessments (three studies), clinician questionnaires (one study), ward round (one study) and a nationwide computer database (one study). The remaining study report did not refer to the methods used.

Studies estimating the proportion of paediatric hospital admissions related to adverse drug reactions

Description of studies

There were 42 studies in which ADRs had been investigated as the cause of admission to hospital. The period under study varied widely, and ranged from 1 week to 11 years. The majority of studies were described as being performed in a general paediatric unit or ward ($n = 22$).[20,21,32,33,43,45,46,48,102,104,105,109,135,137–145] Four studies[41,47,103,117,146] included general medicine, one study[147] in a hospital emergency department. Two studies[37,148] covered general medicine and a hospital emergency department, and one study[149] an integrated primary care information database. Two studies were performed in the PICU,[108] one[134] in combination with general paediatrics. Seven studies[110,150–155] covered a combination of clinical settings. The three remaining studies were performed in dermatology and venereology,[106] infectious diseases[107] and an isolation ward.[42]

Adverse drug reaction incidence

We do not have ADR incidence rates for 12 out of 42 of these studies, as the child-only data were not available ($n = 4$), data were not split by clinical setting ($n = 5$), data were provided for ADRs in hospital but not causing admission ($n = 2$), and data were provided for the total number of ADRs but not the ADR frequency at the patient or episode level ($n = 1$). *Figure 8* presents data from all of the studies that provide incidence rates for ADRs causing admission to hospital ($n = 30$). These rates range from 0.4% to 10.3% of children (single admission). One study was an extreme outlier[48] and if this was excluded we found a reduction in the upper limit of this range to 4%, and a pooled incidence estimate of 2.9% (95% CI 2.6% to 3.1%).

Studies estimating the proportion of children experiencing an adverse drug reaction during their admission

Description of studies

We have included 51 studies in which ADRs have been investigated in the hospital setting. The period under study varied widely and ranged from 1 day to 10 years. The majority of studies were described as being performed in a general paediatric unit or ward ($n = 24$),[32,37,45,46,48,109,111–117,123,135,137,142,144,145,156–160] two[134,161] of which included intensive care also. Six studies[108,122,124,162–164] were performed solely in the intensive care setting, one[118] of which included general medicine. Three studies[75,165,166] included children on an isolation ward. One study was performed using an integrated primary care information database.[149] The remaining 13 studies covered a combination of clinical settings.[3,92,107,110,119,120,150,152–155,167,168]

Adverse drug reaction incidence

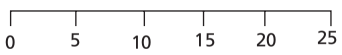
We do not have ADR incidence rates for 18 out of 54 of these studies, as the child-only data were not available ($n = 3$), the data were not split by clinical setting ($n = 7$), data were provided for the total number of ADRs but not the ADR frequency at the patient or episode level ($n = 5$), data were provided for ADRs and ADEs combined ($n = 2$), and data provided for ADRs causing admission but not in hospital ($n = 1$). *Figure 9* presents data from all of the studies that provide incidence rates for ADRs in hospital ($n = 36$). These estimates range from 0.6% to 16.8% of patients (at a single episode and with prior drug exposure). A pooled estimate has not been calculated, as the rates are considered too varied.

Studies estimating the incidence of adverse drug reactions in outpatient children

Description of studies

We have included 36 studies, where ADRs have been investigated in the community setting. The period under study varied widely and ranged from 1 week to 11 years. The majority of studies were described as being performed in a hospital outpatient or A&E department ($n = 21$).[109,124–126,129,131,133,155,168–180] Nine studies were performed in general practice.[77,78,127,128,130,181–184] The remaining six studies were performed in

Study	Setting	Events	Total	Proportion (in %)	95% CI
All patients (single admission)					
Gallagher 2012[21]	1	142	6821	2.08	1.76 to 2.45
Jonville-Bera 2002[37]	1	4	260	1.54	0.42 to 3.89
Mitchell 1988[33]	1	288	7271	3.96	3.52 to 4.43
Pouyanne 2000[146]	1	10	525	1.90	0.92 to 3.47
Santos 2000[104]	1	14	800	1.75	0.96 to 2.92
Yosselson-Superstine 1982[43]	1	28	906	3.09	2.06 to 4.44
Impicciatore 2002[48]	2	12	116	10.34	5.46 to 17.37
Oshikoya 2007[46] (retrospective)	2	13	3139	0.41	0.22 to 0.71
Oshikoya 2007[46] (prospective)	2	4	682	0.59	0.16 to 1.49
Speranza 2008[135]	2	3	173	1.73	0.36 to 4.98
Fattahi 2005[107]	3	9	404	2.23	1.02 to 4.19
All patients (some multiple admissions)					
Buajordet 2002[45]	1	35	665	5.26	3.69 to 7.24
Gallagher 2011[20]	1	16	462	3.46	1.99 to 5.56
Whyte 1977[145]	1	12	844	1.42	0.74 to 2.47
Baniasadi 2008[110]	2	1	740	0.14	0.00 to 0.75
Kunac 2009[143]	2	3	135	2.22	0.46 to 6.36
Martinez-Mir 1996[42]	2	21	490	4.29	2.67 to 6.48
Only patients with prior drug exposure (single admission)					
Gallagher 2012[21]	1	142	4656	3.05	2.57 to 3.58
Jonville-Bera 2002[37]	1	4	119	3.36	0.92 to 8.38
Major 1998[103]	1	24	457	5.25	3.39 to 7.71
Santos 2000[104]	1	14	624	2.24	1.23 to 3.74
Ives 1987[139]	2	0	24	0.00	0.00 to 14.25
Only patients with prior drug exposure (some multiple admissions)					
Martinez-Mir 1996[42]	2	21	256	8.20	5.15 to 12.27
Ganeva 2007[106]	4	6	73	8.22	3.08 to 17.04
All admissions					
Gallagher 2012[21]	1	240	8345	2.88	2.53 to 3.26
Al-Tajir 2005[109]	1	0	2351	0.00	0.00 to 0.16
Buajordet 2002[45]	1	49	919	5.33	3.97 to 6.99
Gallagher 2011[20]	1	18	473	3.81	2.27 to 5.95
Haffner 2005[134]	1	13	703	1.85	0.99 to 3.14
Lamabadusuriya 2003[47]	1	63	39625	0.16	0.12 to 0.20
McDonnell 2002[140]	1	6	2046	0.29	0.11 to 0.64
McKenzie 1976[32]	1	72	3556	2.02	1.59 to 2.54
van der Hooft 2006[141]	1	871	109047	0.80	0.75 to 0.85
van der Hooft 2008[149]	1	1	301	0.33	0.01 to 1.84
Whyte 1977[145]	1	12	932	1.29	0.67 to 2.24
Easton 1998[41]	2	10	1682	0.59	0.29 to 1.09
Easton 2004[102]	2	29	2933	0.99	0.66 to 1.42
Martinez-Mir 1996[42]	2	21	512	4.10	2.56 to 6.20
Gill 1995[108]	5	10	909	1.10	0.53 to 2.01
Only admissions with prior drug exposure					
Gallagher 2012[21]	1	240	6020	3.99	3.51 to 4.51
Duczmal 2006[105]	1	58	4996	1.16	0.88 to 1.50
Gallagher 2011[20]	1	18	277	6.50	3.90 to 10.08
Martinez-Mir 1996[42]	2	21	259	8.11	5.09 to 12.13
Ganeva 2007[106]	4	7	77	9.09	3.73 to 17.84

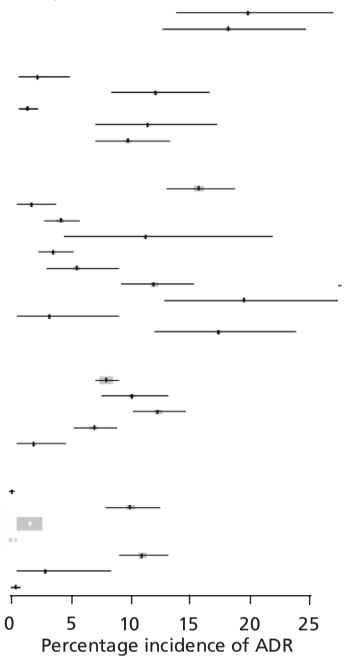


Setting key

1 All wards including oncology
2 Excluding oncology
3 Infectious diseases department
4 Dermatology department
5 ICU

FIGURE 8 What proportion of all paediatric hospital admissions are ADR related? ICU, intensive care unit.

Study	Setting	Events	Total	Proportion (in %)	95% CI
Only patients with prior drug exposure (single episode)					
Gonzalez-Martin 1998[116]	1	30	219	13.70	9.44 to 18.97
Jonville-Bera 2002[37]	1	6	227	2.64	0.98 to 5.66
Mitchell 1979[119]	1	280	1669	16.78	15.01 to 18.66
Classen 1991[151]	2	17	2078	0.82	0.48 to 1.31
dos Santos 2006[113]	2	33	265	12.45	8.73 to 17.04
Impicciatore 2002[48]	2	29	1619	1.79	1.20 to 2.56
Oshikoya 2007[46] (prospective)	2	9	682	1.32	0.61 to 2.49
Oshikoya 2007[46] (retrospective)	2	18	3139	0.57	0.34 to 0.90
Benkirane 2009[163]	3	5	155	3.23	1.06 to 7.37
Fattahi 2005[107]	5	40	380	10.53	7.63 to 14.06
Neubert 2006[165]	6	46	371	12.40	9.22 to 16.19
Only patients with prior drug exposure (some may have had multiple episodes)					
Buajordet 2002[45]	1	105	579	18.13	15.08 to 21.52
Dharnidharka 1993[112] (IHS)	1	6	340	1.76	0.65 to 3.80
Dharnidharka 1993[112] (VHS)	1	1	363	0.28	0.01 to 1.53
Uppal 2000[160]	1	36	16652	0.22	0.15 to 0.30
Whyte 1977[145]	1	39	595	6.55	4.70 to 8.85
Baniasadi 2008[110]	2	27	693	3.90	2.58 to 5.62
Kunac 2009[143]	2	15	135	11.11	6.35 to 17.66
Martinez-Mir 1996[42]	2	59	409	14.43	11.17 to 18.21
Vazquez de la Villa 1989[123]	2	26	597	4.36	2.86 to 6.32
Shockrollah 2009[122]	6	5	230	2.17	0.71 to 5.00
Farrokhi 2006[92]	6	3	81	3.70	0.77 to 10.44
Neubert 2004[75]	3	31	156	19.87	13.92 to 27.00
Weiss 2002[166]	4	33	181	18.23	12.89 to 24.64
All patients (single episode)					
Jonville-Bera 2002[37]	1	6	260	2.31	0.85 to 4.95
dos Santos 2006[113]	2	33	272	12.13	8.50 to 16.61
Jha 2007[117]	2	13	934	1.38	0.74 to 2.35
Speranza 2008[135]	2	20	173	11.56	7.21 to 17.29
Fattahi 2005[107]	5	40	404	9.90	7.17 to 13.24
All patients (some may have had multiple episodes)					
Buajordet 2002[45]	1	105	665	15.79	13.10 to 18.79
Dharnidharka 1993[112] (IHS)	1	6	347	1.73	0.64 to 3.73
Whyte 1977[145]	1	39	932	4.18	2.99 to 5.68
Seidi 1966[150]	1	7	62	11.29	4.66 to 21.89
Baniasadi 2008[110]	2	27	740	3.65	2.42 to 5.26
Choonara 1984[111]	2	15	268	5.60	3.17 to 9.06
Martinez-Mir 1996[42]	2	59	490	12.04	9.29 to 15.26
Telechea 2010 (unpublished data)	3	24	123	19.51	12.92 to 27.63
Farrokhi 2006[92]	6	3	94	3.19	0.66 to 9.04
Neubert 2004[75]	4	31	178	17.42	12.15 to 23.80
Only episodes with prior drug exposure					
dos Santos 2009[114]	1	302	3726	8.11	7.25 to 9.03
Leach 1998[118]	1	51	499	10.22	7.70 to 13.22
Turner 1999[3]	2	116	936	12.39	10.35 to 14.68
Gill 1995[108]	3	63	899	7.01	5.43 to 8.88
Shockrollah 2009[122]	3	5	252	1.98	0.65 to 4.57
All episodes					
Al-Tajir 2005[109]	1	2	2351	0.09	0.01 to 0.31
Haffner 2005[134]	1	71	703	10.10	7.97 to 12.57
Le 2006[36]	1	1060	64403	1.65	1.55 to 1.75
Easton-Carter 2003[115]	2	41	17432	0.24	0.17 to 0.32
Turner 1999[3]	2	116	1046	11.09	9.25 to 13.15
Farrokhi 2006[92]	4	3	102	2.94	0.61 to 8.36
Phan 2010[169]	7	9	2191	0.41	0.19 to 0.78



Setting key

1 All wards including oncology
2 Excluding oncology
3 ICU
4 Surgery
5 Infectious diseases department
6 Isolation ward
7 Pediatric emergency department

FIGURE 9 What proportion of children in hospital experience an ADR during their admission? ICU, intensive care unit; IHS, intensive hospital surveillance; IVS, voluntary hospital surveillance.

an infant care and educational establishment,[133] local community setting,[185,186] general practice and emergency department,[37] outpatient population seeking medical care[187] and after discharge from hospital.[45]

Adverse drug reaction incidence

We do not have ADR incidence rates for 18 (18/35) of these studies, as the child-only data were not available ($n = 10$), the data were not split by clinical setting ($n = 3$), data were not available for the total number of children/visits ($n = 3$), data were provided for the total number of ADRs but not the ADR frequency at the patient or visit level ($n = 1$), and data were provided for errors only ($n = 1$). *Figure 10* presents data from studies that provide incidence rates for ADRs in the community ($n = 15$). Two studies were not included in this figure owing to their method of ADR ascertainment.

All settings

Drugs and clinical presentation associated with adverse drug reaction

We do not have information on the drugs involved in ADRs for 49 out of 101 studies, as the child-only data were not available (37 studies), ADRs were a subset of events looked at and ADR-specific data were not reported (10 studies), and drug data were not available in the publication (two studies). For studies that provided data (52/101); anti-infective drugs were the drug class most commonly reported across the three settings. Proportions ranged from 3.5% to 66.6% for causing admission studies (17 studies); 8.6% to 100% for in-hospital studies (24 studies); and 17% to 78% for community studies (13 studies). The most common associated clinical presentations reported were nausea, vomiting, diarrhoea and skin rash. Antiepileptic drugs were the second most common reported drug class in both the causing admission and in-hospital studies; proportions ranging from 0.8% to 30% (12 studies) and 3.9% to 46.6% (14 studies), respectively. Reported clinical presentations were ataxia, skin rash, increased fitting and drowsiness. NSAIDs were frequently reported as being associated with ADRs in studies in children in outpatients, with proportions ranging from 1% to 10% (six studies). Reported clinical presentations were cutaneous reactions, haematuria, hypertranspiration, drowsiness, abdominal pain, aggressiveness and vomiting.

In addition, corticosteroids were commonly reported across the three settings. Proportions ranging from 5.5% to 41.0% for causing admission studies (seven studies); 1.7% to 23.4% for in-hospital studies (10 studies); and 0.05% to 5% for community studies (three studies). The most common associated clinical presentations reported were immunosuppression, postoperative bleeding, gastric irritation and diarrhoea.

The distribution of drugs implicated in ADRs reflect the prescribing practices for the individual settings. For example, vaccines were commonly reported in causing admission studies (seven studies) and community studies (five studies). Proportions ranged from 1.7% to 41.0% and 9.2% to 25% respectively, with rash and fever being the most commonly associated clinical presentations. Cytotoxic drugs were reported in both causing admission (eight studies) and in hospital studies (seven studies), and proportions ranged from 14.2% to 50% and 1.7% to 66.6%, respectively. The remaining studies reported a variety of drugs implicated in ADRs, and for some more than one drug was the cause of a single ADR (see *Tables 22–27*).

Univariate meta-regression results (*Table 28*) suggest that the incidence rate for ADRs occurring in hospital is higher than for ADRs causing admission (OR = 2.73, 95% CI 0.93 to 8.03). In addition, the results suggest that the incidence rate is higher for studies with a relatively high mean/median number of drugs per patient (OR = 1.49, 95% CI 1.14 to 1.94), a high percentage of females (OR = 1.13, 95% CI 0.91 to 1.40), a high percentage of oncology patients (OR = 1.15, 95% CI 0.89 to 1.50) and low mean age of patients (OR = 0.71, 95% CI 0.39 to 1.27). However, only the variable representing the mean/median number of drugs per patient achieves statistical significance.

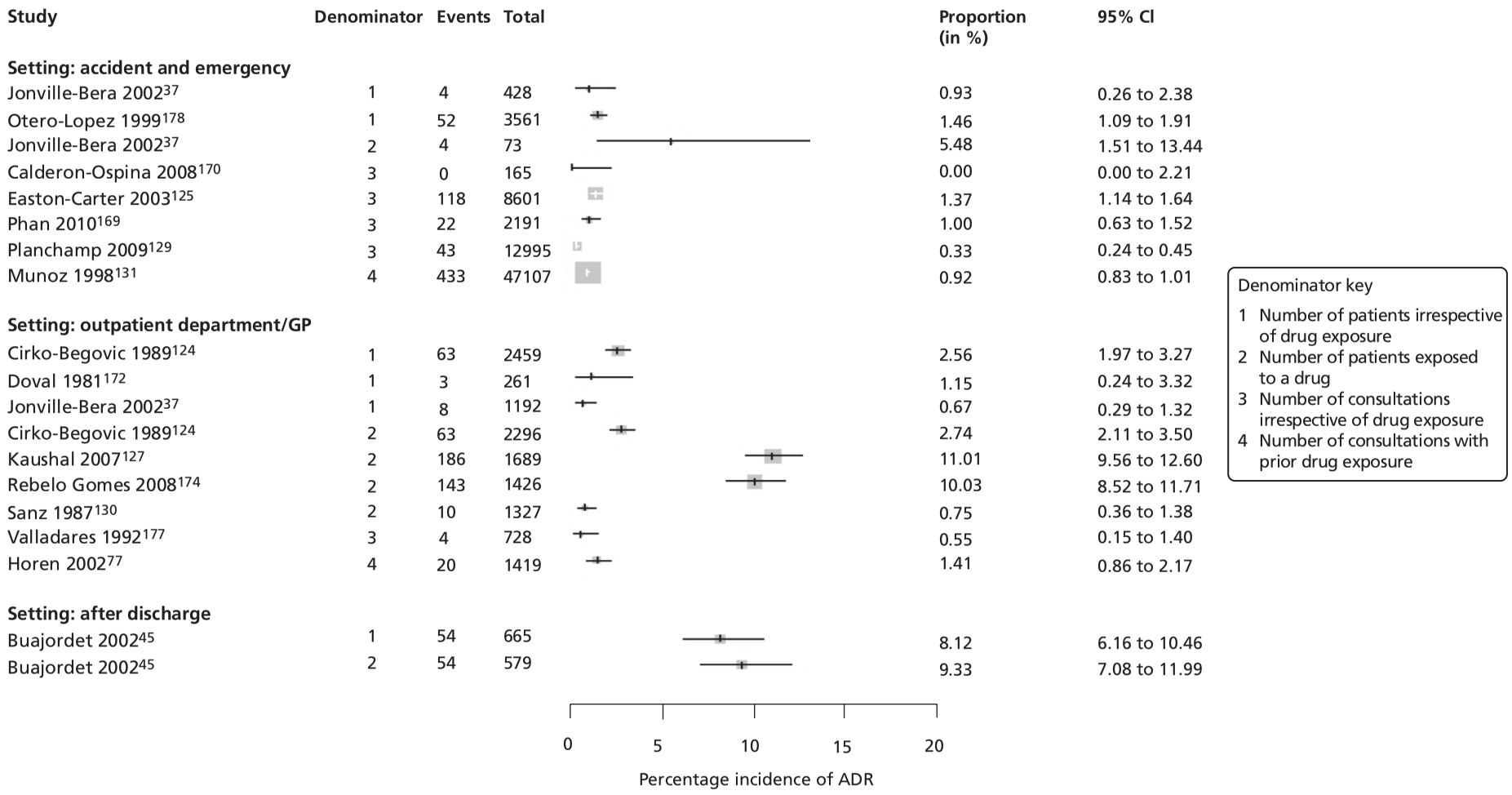


FIGURE 10 What proportion of outpatient children experience ADRs? GP, general practice.

TABLE 28 Univariate meta-regression results for causing admission and in hospital incidence rates

Covariate		OR (95% CI)	*p*-value
Setting	Admission	1 (0.93 to 8.03)	0.07
	Hospital	2.73 (0.93 to 8.03)	
% female patients		1.13 (0.91 to 1.40)	0.23
Mean age (years)		0.71 (0.39 to 1.27)	0.21
Mean/median number of drugs		1.49 (1.14 to 1.94)	0.01
% oncology patients		1.15 (0.89 to 1.50)	0.25

Risk factors

Risk factor analyses reported by all studies were collated. Consistent with the meta-regression results, evidence is provided – from 10 out of 19 studies that consider gender as a risk factor – that boys are less likely to have an ADR and, from 16/17 studies, that risk increases with the number of drugs taken. In addition, three out of three studies suggest that the risk of ADRs is greater with off-label use. Only two studies considered oncology as a risk factor. The results for the age analyses do not follow a clear pattern and are difficult to interpret owing to the variety of age categorisations used.

Tools for assessing causality

Nearly three-quarters of the studies (71/101) mentioned a causality assessment, of which the Naranjo algorithm was the most frequently used tool (29/71). Of the 71 studies, six used a self-assessment method rather than a published CAT. Despite the majority of studies mentioning a causality assessment, only half of these studies (36/71) reported causality data that were complete for all identified ADRs, specific to the paediatric population and did not include errors as part of the assessment.

Tools for assessing severity

Thirty-four (34/101) studies performed an ADR severity assessment. Rates ranged from 0% to 66.7% of reported ADRs considered to be severe. By setting, the proportion of ADRs occurring in hospital assessed as severe ranged from 0% to 66.7%, compared with 0–45.5% of ADRs causing admission, and 0–32.6% of ADRs occurring in the community. Twenty studies provided a reference to indicate the severity tools used; however, tools differed widely. Examples of ADRs assessed as severe were those that caused death or were directly life-threatening, caused hospital admission, prolonged hospitalisation or caused transfer to higher level of clinical care.

Assessment of avoidability

Nineteen (19/101) studies performed an avoidability assessment; however, data were available for only 14 out of 19 studies, as child-only data were not available in 4 out of 19 and ADR-specific data were not provided in 1 out of 19 studies. For these 14 studies, 7–98% of ADRs were designated as either definitely or possibly avoidable. Three studies provided the rationale for 62 avoidable ADRS: inappropriate selection or indication for use of drug ($n = 14$), inadequate patient education ($n = 14$), prescribing not rational ($n = 11$), lack of appropriate prophylaxis for known ADR ($n = 9$), lack of appropriate monitoring of drugs ($n = 5$), previous known ADR to medication ($n = 3$), dose prescribed was too high ($n = 3$), inappropriate duration of treatment ($n = 1$), drug was not prescribed per treatment protocol ($n = 1$), inappropriate duration of drug and monitoring of treatment ($n = 1$). Ten studies used a recognised AAT, of which half used that of Schumock and Thornton.[44]

Discussion

This is the largest systematic review of ADRs in children to date and shows clearly that ADRs are an important clinical problem for children and have been the subject of a large number of studies. Unlike other systematic reviews,[34,35,101] our review searched for studies using a comprehensive search strategy of a large number of databases, including those specific to toxicology and pharmacology. We included studies in which ADEs had been evaluated, and that included both adults and children. When compared with the previous reviews this resulted in an additional 69 studies being included in our review, of which we were able to extract data from 24. In addition, we contacted authors of studies to obtain unpublished information. As a result, we were able to obtain unreported ADR incidence data for an additional 24 out of 101 studies. This allowed us to make a more informed judgement regarding ADR incidence estimates.

In agreement with previous studies, this review found that ADR incidence rates were generally higher in hospitalised children than ADR rates causing hospital admission or in an outpatient setting. One of the main difficulties with comparing ADR incidence rates, particularly from observational studies, is the different numbers and denominators used, leading to high levels of variability between studies in the calculation and reporting of incidence rates. Owing to this, a pooled estimate has been provided for ADRs causing admission only.

Concerning risk factors associated with ADRs, we found evidence – from both univariate meta-regression and the collation of risk factor analyses from individual studies – that the use of multiple drugs is an important predictor of ADRs. This may be due to the additive risk of an ADR when receiving several drugs or drug–drug interactions.

We examined the methods used for detecting, and assessing, the causality, severity and avoidability of an ADR. The assessment of causality in individual cases of ADRs is required to establish whether or not there is an association between the untoward clinical event and the suspected drug.[23] The detection of ADRs depends on the validity and reliability of the tests used and if sensitive methods are performed, in theory, all ADRs should be detected. We found that one-third (30/101) of studies did not report which CAT they used, with an additional six not using a recognised algorithm. As a consequence there may be either an underestimation or overestimation of ADRs in these studies. Over one-third of studies (34/101) assessed ADRs for the severity of the reactions, just eight of which did not report any severe ADRs. The ability to classify ADRs by severity provides a mechanism for clinicians to identify problem areas and implement interventions to inform paediatric pharmacovigilance practice.

The absence of avoidability data was most noticeable in this review, with only 14 studies (14/101; 14%) providing avoidability data. Therefore, it is not possible to consider this important aspect of drug safety in order to prevent future ADRs.[44] Further studies are clearly required to determine which ADRs are potentially avoidable. These studies could provide the necessary data in order to enable clinicians to administer medications in the safest and appropriate way.

The reporting quality of some of the included studies was poor, which may have affected the results. Not all provided a clear definition of the term ‘ADR’, and often insufficient information was given in the publication in order to determine whether ADRs included medication or prescribing errors. ADR incidence data were not always clearly described in the publications; in many studies ($n = 48/101$) reporting was unclear regarding whether the incidence rate was reported at the patient and/or episode level, and whether or not all children had been exposed to a drug.

It is disappointing, given the large number of studies that we identified that addressed this problem, that most did not include these important methodological aspects, which means that few lessons have been learnt about how to prevent ADRs in children.

Conclusions

This review confirms previous studies that have shown ADRs to be an important problem in children and has highlighted therapeutic classes of drugs most commonly associated with them. Further work to address prescribing practices in different settings and avoidability of ADRs is needed to indicate how such ADRs may be prevented.

Chapter 5 Causality assessment of adverse drug reactions

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Abstract

Aim
To develop and test a new ADR CAT.

Methods
A comparison between seven assessors of a new CAT (formulated by an expert focus group) 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 LCAT, using 40 cases from an observational study, showed causality categories of one unlikely, 62 possible, 92 probable and 125 definite (1, 62, 92, 125) and 'moderate' IRR [kappa (κ) = 0.48] compared with Naranjo (0, 100, 172, 8) with 'moderate' IRR ($\kappa = 0.45$). In a further 40 cases, the LCAT (0, 66, 81, 133) showed 'good' IRR ($\kappa = 0.6$), whereas Naranjo (1, 90, 185, 4) remained 'moderate'.

Conclusions
The LCAT 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.

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, the pharmaceutical industry and regulators, and in different settings, including clinical trials.[188–191] At an individual level, health-care providers assess causality informally when dealing with ADRs in patients to make decisions regarding future therapy. Many regulatory authorities assess spontaneous ADR reports,[189,191] where causality assessment can help in signal detection and risk–benefit decisions regarding medicines,[192,193] using formal CATs to aid in this process.

An early paper by Sir Austin Bradford Hill[194] describing minimum criteria for establishing causality of AEs, pre-dates the earliest attempts to formulate ADR CATs. 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 elements of assessing strength of relationship

between exposure (drugs) and outcome (adverse reaction) are used widely in ADR CATs. Attempts to formalise causality assessment of ADRs into structured CATs have been ongoing for > 30 years.[23,195] It is known that assessing ADR likelihood without structure can lead to wide disagreements between assessors.[196] 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 CATs 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.[197]

One of the most widely used CATs is the Naranjo ADR probability scale.[23] 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 rechallenge/previous exposure. Each element of the questionnaire is weighted and the total score is 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.[59,198] However, the reliability and validity of the Naranjo scale has been questioned by a number of investigators.[24,188,193,199,200]

While undertaking a prospective observational pilot study of ADRs in children, we found several difficulties with using the Naranjo scale, and aimed to address those difficulties. Our original aim was to use the Naranjo ADR Probability Scale for the larger 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 with the Naranjo scale, the investigators found that 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 recognising 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 that 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 (1) making it as easy, or easier, to use than the Naranjo scale (a feature that holds a distinct advantage for large observational studies of ADRs among other situations) and (2) ensuring that the basic principles of assessing causality were maintained. The specific aim of this study was to develop a CAT with good face validity and acceptable inter-rater reproducibility.

Methods

The pilot study team (RG, JB, KB) noted concerns with using the Naranjo scale. This triggered a process in which each of seven investigators (RG, JB, KB, MPir, TN, RS, MT) independently assessed the first 40 consecutive case reports from an observational study of suspected ADRs causing hospital admission using the Naranjo scale. In summary, there were eight cases in which problems with assessments were

found. There was one case in which major discrepancies occurred between at least two out of seven raters, i.e. where the range of causality probability differed by more than one category (e.g. possible and definite), and seven cases in which close to half of the raters differed from the others by one causality category. The questions (within the Naranjo scale) that caused the discrepancies in these cases were identified and reviewed. This exercise led to the recognition that a new CAT was required.

The team made several choices at the start of the development of the new CAT. 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, 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: first, use the extensive clinical and pharmacovigilance expertise in the group to develop a tool that had face validity to the team, and, second, iteratively assess the tool to optimise interobserver 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 (1) retain it (with or without modification); (2) reject it; or (3) combine it with another question(s). The aim was to create a new, more appropriate CAT (*Table 29*).

The new LCAT 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 score of 0.51 (95% CI 0.19 to 0.82). The team considered that there was an inappropriate bias towards the category of definite. Accordingly, the CAT 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 major discrepancies were then modified. The new CAT was then tested on a further 20 case reports: 10 from the ADRIC study and 10 from an observational study of inpatient ADRs in an adult hospital. Collated causality categories for the 10 ADRIC 1 cases showed 0 (0%) unlikely, 24 (34%) possible, 39 (56%) probable and 7 (10%) definite with a kappa score of 0.27 (95% CI 0.11 to 0.44). Collated causality categories for the 10 adult cases showed 0 (0%) unlikely, 13 (19%) possible, 48 (69%) probable and 9 (13%) definite, with a kappa score of 0.13 (95% CI –0.14 to 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 11*).

After the third iteration, the investigators were satisfied with the final version of the new tool (*Figure 12*) 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 IRR within the study team for the LCAT followed a stepwise procedure:

- The original 40 case reports (case reports of raw clinical data from an observational study) initially assessed using the Naranjo scale were assessed by each of the seven investigators using the new CAT to compare the outcomes of the methods and the IRR 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* and independently evaluated by the seven assessors using only the new tool.
- As 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 was then used to assess IRR using both the Naranjo scale and the LCAT.

TABLE 29 Decisions made about questions within the Naranjo scale

No.	Naranjo scale questions	Yes	No	Do not know	Outcome for LCAT
Q1	Are there previous *conclusive* reports on this reaction?	+1	0	0	*Retained* Knowledge of previous reports can be important when assessing if an AE is due to drug or disease
Q2	Did the AE 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 re-administered?	+2	–1	0	*Combined* Knowledge of rechallenge, 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 AE
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 rechallenge. This may provide evidence of susceptibility, and likelihood, of the event being related to a drug
Q10	Was the AE confirmed by any objective evidence?	+1	0	0	*Modified* See Q7

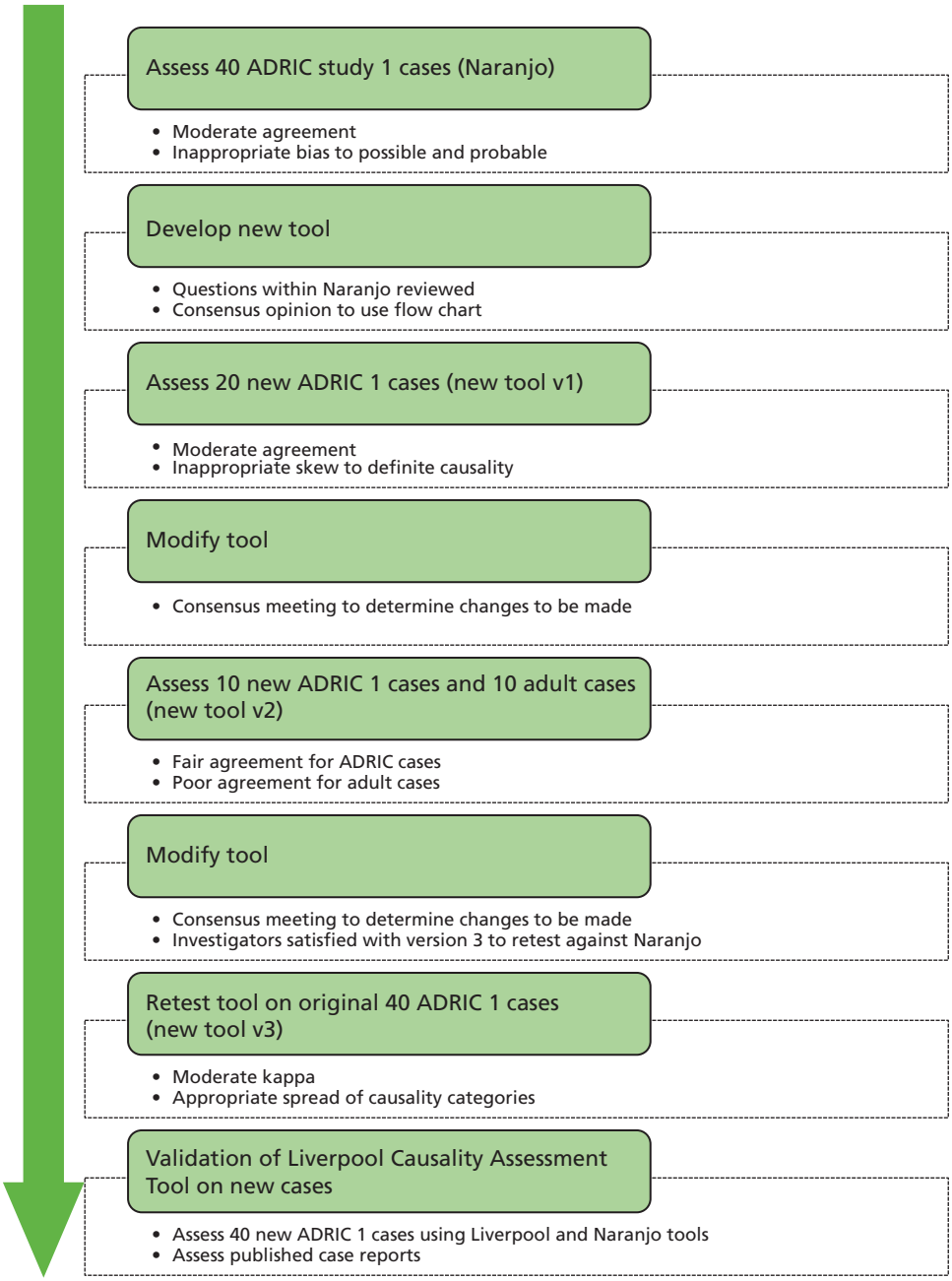

FIGURE 11 Flow chart of the development of the Liverpool ADR Causality Assessment Tool.

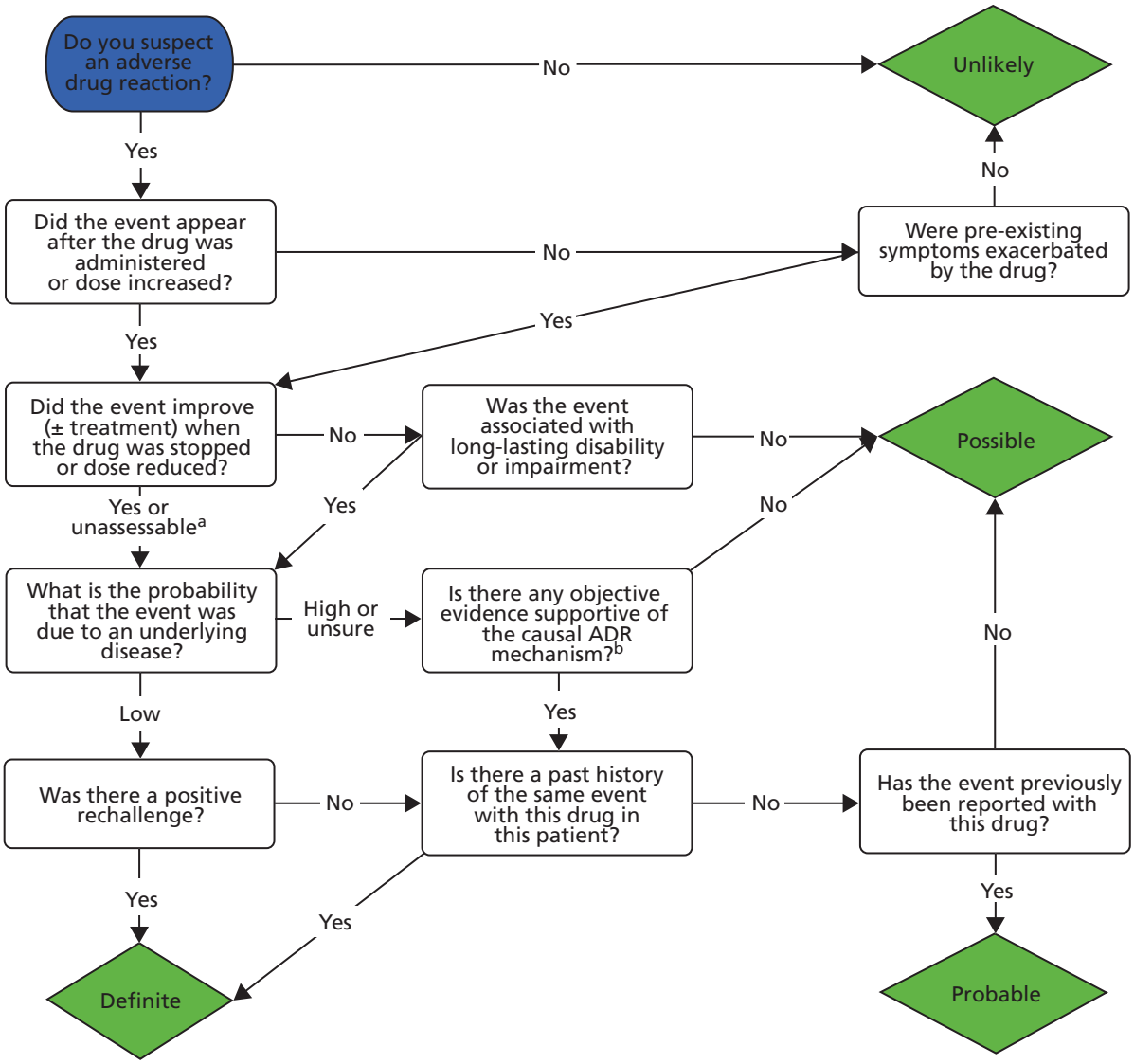

FIGURE 12 Liverpool Causality Assessment Tool (LCAT). a, unassessable refers to situations where the medicine is administered on one occasion (e.g. vaccine), the patient receives intermittent therapy (e.g. chemotherapy), or is on medication which cannot be stopped (e.g. immunosuppressant drugs); and b, examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supratherapeutic drug levels and good evidence of a dose-dependent relationship with toxicity in the patient. An independent panel with extensive expertise in pharmacovigilance and statistics (the ADRIC Steering Group) was asked to review the tool upon completion of the internal evaluation.

Analysis

The inter-rater agreements at each stage of the assessment process were assessed using a linear weighted kappa with 95% CI 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 one rater and possible for the other), were also computed to measure extreme disagreements between pairwise rater assessments. To supplement the pairwise kappa scores, a global kappa score measuring nominal scale agreement across multiple assessors was calculated with 95% CI.[201] 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:[202] poor agreement < 0.2; fair 0.21–0.40; moderate 0.41–0.60; good 0.61–0.80; and very good 0.81–1.00.

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 30*). %EA for the pairwise comparisons between raters ranged from 43% to 93%. The %ED was 2.5% for four of the 21 pairwise comparisons. There were no extreme disagreements in 17 out of 21 pairwise comparisons. Pairwise kappa scores ranged from 0.27 to 0.86 and the assessors achieved moderate IRR with a global kappa score of 0.45 (95% CI 0.35 to 0.54) (*Table 31*). The same cases assessed using the new LCAT showed collated causality categories of 1 (0.4%) unlikely, 62 (22%) possible, 92 (33%) probable and 125 (45%) definite. %EA ranged from 43% to 93%. All 21 pairwise comparisons displayed with %ED ranging from 5–20%. Pairwise kappa scores ranged from 0.27 to 0.84, and the assessors achieved moderate IRR with a global kappa score of 0.48 (95% CI 0.42 to 0.54) (see *Table 31*).

TABLE 30 Causality category assignments of investigators for the original 40 cases assessed using the Naranjo tool and the LCAT

		ADRIC original ($N = 40$)			
Assessor	Tool	Unlikely: *n* (%)	Possible: *n* (%)	Probable: *n* (%)	Definite: *n* (%)
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)
JB	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)
MPir	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 31 Naranjo tool and LCAT assessment of 40 original ADR cases from an observational study

			Assessor 2						
			RG	JB	KB	MT	TN	MPir	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 to 0.77)	0.47 (0.21 to 0.73)	0.44 (0.19 to 0.69)	0.45 (0.21 to 0.69)	0.36 (0.09 to 0.62)	0.29 (0.04 to 0.54)
	JB	%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 to 0.67)		**0.86 (0.71 to 1.00)**	0.46 (0.22 to 0.69)	0.56 (0.34 to 0.78)	0.47 (0.19 to 0.75)	0.40 (0.15 to 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 to 0.49)	**0.69 (0.52 to 0.87)**		**0.60 (0.39 to 0.81)**	0.43 (0.19 to 0.66)	0.43 (0.15 to 0.71)	0.55 (0.32 to 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 to 0.56)	**0.62 (0.45 to 0.80)**	0.49 (0.31 to 0.67)		0.45 (0.20 to 0.70)	0.37 (0.11 to 0.62)	0.48 (0.23 to 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 to 0.46)	0.42 (0.21 to 0.62)	0.30 (0.10 to 0.50)	0.49 (0.26 to 0.72)		0.33 (0.05 to 0.62)	0.35 (0.06 to 0.63)
	MPir	%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 to 0.69)	**0.68 (0.49 to 0.86)**	0.54 (0.33 to 0.74)	**0.69 (0.49 to 0.89)**	**0.62 (0.39 to 0.84)**		0.38 (0.11 to 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 to 0.55)	0.54 (0.32 to 0.76)	0.46 (0.24 to 0.67)	**0.66 (0.44 to 0.87)**	0.52 (0.27 to 0.76)	**0.84 (0.66 to 1.00)**	

The %EA/ED and kappa scores: white boxes represent Naranjo scale analyses and shaded boxes represent Liverpool ADR causality tool analyses.
Kappa scores in bold text 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 LCAT 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 32*). %EA ranged from 57% to 97%. Pairwise comparisons between raters showed some extreme disagreement (18/21), with the %ED ranging from 5% to 11%, whereas three showed no extreme disagreements. Pairwise kappa scores ranged from 0.31 to 0.96 and the assessors achieved moderate IRR with a global kappa of 0.43 (95% CI 0.34 to 0.51) (*Table 33*).

These case reports were not assessed by the investigators using the Naranjo scale. The *Annals of Pharmacotherapy* require authors to apply a Naranjo assessment prior to publication of each case report in the journal. The collated categorisation of the case report author assessments for the 37 cases showed 0 unlikely, 5 (14%) possible, 29 (78%) probable and 3 (8%) definite (see *Table 32*).

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 34*). %EA ranged from 63% to 90%. %ED was 2.5% for four pairwise comparisons. There were no extreme disagreements in 17 out of 21 comparisons. The pairwise kappa scores ranged from 0.19 to 0.81, with moderate IRR and a global kappa score of 0.44 (95% CI 0.33 to 0.55) (*Table 35*). The same cases assessed using the LCAT showed collated causality categories of 0 (0%) unlikely, 66 (24%) possible, 81 (29%) probable and 133 (48%) definite. %EA ranged from 65% to 88%. %ED ranged from 2.5% to 7.5% for 14 pairwise comparisons. There were no extreme disagreements in 7 out of 21 comparisons. Pairwise kappa scores ranged from 0.51 to 0.85 and the assessors achieved good IRR with a global kappa of 0.60 (95% CI 0.54 to 0.67) (see *Table 35*).

TABLE 32 Causality category assignments of investigators for the 37 case reports published by the *Annals of Pharmacotherapy*

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

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

TABLE 33 Liverpool Causality Assessment Tool assessment of 37 randomly selected published ADR case reports

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

%EA and kappa scores in shaded boxes represent Liverpool ADR causality tool analyses.
Kappa scores outlined in bold demarcate either a good or very good level of agreement.

TABLE 34 Causality category assignments of investigators for the 40 new ADR cases assessed using the Naranjo tool and the LCAT

		ADRIC new (*N* = 40)			
Assessor	Tool	Unlikely: *n* (%)	Possible: *n* (%)	Probable: *n* (%)	Definite: *n* (%)
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)
JB	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)
MPir	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 35 Naranjo tool and LCAT assessment of 40 new ADR cases from an observational study

			Assessor 2						
			RG	JB	KB	MT	TN	MPir	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 to 0.98)**	**0.61 (0.38 to 0.84)**	0.46 (0.25 to 0.66)	0.51 (0.26 to 0.75)	0.46 (0.20 to 0.71)	0.23 (0.03 to 0.42)
	JB	%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 to 0.81)**		0.49 (0.23 to 0.76)	0.45 (0.25 to 0.64)	0.59 (0.35 to 0.83)	0.54 (0.29 to 0.79)	0.22 (0.02 to 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 to 0.79)**	**0.73 (0.57 to 0.90)**		0.40 (0.16 to 0.63)	0.56 (0.29 to 0.83)	0.50 (0.22 to 0.78)	0.19 (–0.06 to 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 to 0.81)**	**0.70 (0.52 to 0.88)**	**0.64 (0.45 to 0.84)**		0.367 (0.12 to 0.62)	0.40 (0.15 to 0.65)	0.25 (0.003 to 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 to 0.93)**	**0.73 (0.57 to 0.88)**	**0.61 (0.43 to 0.79)**	**0.79 (0.64 to 0.93)**		0.48 (0.18 to 0.77)	0.38 (0.09 to 0.66)
	MPir	%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 to 0.81)**	**0.75 (0.59 to 0.91)**	**0.64 (0.46 to 0.82)**	**0.76 (0.61 to 0.91)**	**0.85 (0.73 to 0.97)**		0.41 (0.12 to 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 to 0.78)**	0.57 (0.40 to 0.74)	0.50 (0.31 to 0.69)	**0.73 (0.58 to 0.88)**	**0.77 (0.62 to 0.91)**	**0.67 (0.51 to 0.84)**	

%EA/ED and kappa scores: white boxes represent Naranjo scale analyses and shaded boxes represent LCAT analyses.
Kappa scores in bold text demarcate either a good or very good level of agreement.

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'.[188] 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 LCAT.

In assessing the original 40 possible ADR cases with the Naranjo tool, several difficulties were found with some of the questions in the tool. Some of the questions were frequently, or always, answered as 'unknown'. There were two questions that caused discrepancies between raters in eight cases when scoring with the Naranjo tool. The first question that caused difficulty was *question 5* (see *Table 30*) ['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', whereas 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 10* ('Was the AE confirmed by any objective evidence?') was the second that caused discrepancies in Naranjo scoring. This caused problems for assessors in two very different ways: first, assessors had difficulty in deciding, on an individual case basis, what constitutes objective evidence and, second, 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 5* and whether or not 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 10*. Some raters may suggest that a physical examination 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 10* positively because of the evidence, in effect scoring positively for the same information twice. It seems counterintuitive to take account of positive evidence and score it twice when assessing a possible ADR report. Even so, there were still very few discrepancies between the scores overall with most assessments resulting in a 'possible' or 'probable' causality being assigned.

We designed a new method, the LCAT, using an algorithm in the form of a flow chart. This new tool was assessed to have face validity by a multidisciplinary investigating group. Seven assessors used both the LCAT and Naranjo tool to initially assess 40 possible ADR cases from the large observational study. The LCAT performed just as well as Naranjo in terms of IRR 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 LCAT outperformed Naranjo, showing a 'good' IRR.

We believe that the LCAT 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 IRR improved over time with the new tool, whereas the IRR when using Naranjo remained similar, despite the fact that there was as much exposure to this tool within the assessing group. The improved IRR with the new tool may be explained by increasing experience of its use. The proportion of exact agreements between assessors was similar between the two tools for both sets of cases despite the improvement in the global kappa score 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 with the kappa scores that adjust for chance agreement. This paradox has been discussed previously in the literature.[203–205] The percentage of extreme disagreement between raters was higher for the LCAT than the Naranjo tool. Owing to the difficulty in achieving a 'definite' score with the Naranjo tool, the chances of

finding extreme disagreement, when comparing pairwise assessments, is likely to be falsely low. The observed %ED decreased when using the LCAT, 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 LCAT. An e-learning package is under evaluation.

Second, the IRR 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 rechallenge. 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 flow diagram rather than scoring system was used in the new CAT 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, as we need to compare different settings when assessing causality of ADRs.

In summary, we present a new CAT, developed by a MDT, which we believe to be at least equivalent to, if not better than, the Naranjo scale. We believe the new tool to be practicable and likely to be acceptable for use by health-care 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 ADRIC. Although this validation is equivalent to, if not better than, that undertaken for many other tools,[23,206,207] one limitation is that the increase in IRR 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.

Chapter 6 Development of the Liverpool Adverse Drug Reaction Avoidability Tool

Abstract

Background

A recent systematic review of ADRs in children[19] highlighted that few studies performed an avoidability assessment (19/102). There was wide variation in the results with rates ranging from 7% to 98% of ADRs being classed as either possibly or definitely avoidable.[19] There is currently no standardised method for determining avoidability and many of the established tools are not suitable for use in paediatrics. We have used an adapted version of the Hallas scale[54] as a basis for the development of a new AAT.

Objectives

1. To develop and test a new AAT that is more suitable for use in paediatrics but which is also generalisable and applicable to a variety of other settings.
2. To compare individual to group assessments of avoidability.

Setting

A large children's hospital providing a local and also specialist regional and national services: Alder Hey.

Main outcome measures

Inter-rater reliability, measure of disagreement, utilisation of avoidability categories.

Methods

The study involved multiple phases. Phase 1 consisted of three parts (defining the tool, modifying the tool and refining the tool), all of which involved a MDT approach. Phase 2 involved the independent assessment of 50 ADR cases from the ADRIC inpatient study by six reviewers and a comparison of the results. Phase 3 will involve consensus meetings and group testing.

Results

Phase 1 The assessment of 20 ADR cases was undertaken by two different MDT groups. Group members commented that a mixture of professions was needed to give a full assessment of avoidability. Changes to the tool were made as a result of the findings with two of the questions being amended to include 'known preventative strategies'.

Phase 2 The assessment of 50 ADR case reports by six individual reviewers, where pairwise kappa scores ranged from poor to good. Stronger agreement was found within professions than between professions.

Discussion

To date, the ADRIC avoidability work stream has defined a tool to assess avoidability of suspected ADRs. We have conducted preliminary testing. Following the completion of phase 2, further discussion of the tool and methodology suggested that additional testing was needed and that this should be carried out in a group setting using consensus methods.

Conclusion

Avoidability assessment is feasible but needs careful attention to methods. Further testing in a group setting is required to develop and validate the tool. The next step in the development process will be to investigate how to optimise group assessment.

Introduction

Preventability, or avoidability as it is sometimes referred to, is an important concept in the study of ADRs.[25] Preventing avoidable harm due to ADRs is a prime clinical motivation for studying drug safety. According to the WHO, ADRs rank among the top 10 leading causes of mortality in some countries. ADRs are common yet often preventable.[208] Patient and medication safety is high on the agenda of the EMA,[209] the Council of Europe[210] and the WHO.[208] The WHO has identified some key areas including measuring harm, understanding causes, identifying solutions, evaluating impact and translating evidence into safer care. Hakkarainen *et al.*[211] conducted a meta-analysis of preventable ADR studies and they concluded that preventable ADRs are a significant burden to the health-care system and a cause of morbidity among outpatients, and that roughly half of all ADRs in adults both inpatients (45%) and outpatients (52%) may be preventable.

The importance of examining avoidability of ADRs became clear from two sources: the ADRIC systematic review indicated the few previous studies that had examined avoidability and those that had used inconsistent methods;[19] difficulties were encountered during the assessment of avoidability using existing tools (see *Chapter 3*).

The study of avoidability is complex. A key factor causing this complexity is that there is no universally accepted definition for preventability.[25] Ferner and Aronson[25] stated that there are two aspects to preventability: whether or not in principle an event is preventable, in the absence of error and, if it is, whether or not we can, in fact, prevent it. They gave the example of penicillin hypersensitivity reactions, which, in principle, can be avoided in patients who are known to be susceptible, by not giving the drug; however, in practice these reactions can still occur owing to lack of information available to the prescriber.[25] They also stated that harm is never absolutely preventable, but any intervention that reduces the probability of harm can be said to have made a contribution to prevention.[25] Ferner and Aronson[25] concluded in their systematic review that several definitions exist and none fits all circumstances. In a follow-up paper, they outlined a novel method for determining preventability.[212] This novel method involves classifying ADRs by mechanism and clinical manifestation to inform judgement about theoretical preventability.[212] According to Ferner and Aronson,[25] complete analysis requires consideration of pharmacodynamic and pharmacokinetic mechanisms of the ADR, its time course, its dose-responsiveness and individual susceptibility factors.[212]

Despite the importance of avoiding ADRs, this area remains under-researched. This may be attributable to the methodological problems in the area, which Hakkarainen *et al.*[26] have summarised in a systematic review on methods for assessing the preventability of ADEs.[26] They listed inconsistent terminology as one of the problems; there is wide variation in the terms and definitions used (ADRs, ADEs, etc.) and this hinders the interpretation and comparison of studies.[26] In their review they used the term ADE, which included ADRs and other AEs related to medications. The definition of an ADR used in this study is that of Edwards and Aronson:[49] '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'.

The need for developing a new AAT arose during the ADRIC inpatient study when we tried to use the Hallas scale[54] to determine avoidability but had difficulties with some of the language used particularly 'present-day knowledge of good medical practice' and that the event could have been avoided by 'an effort exceeding obligatory demands'. In the ADRIC admissions study Gallagher *et al.*[21] used the Hallas scale[54] to determine avoidability and found that 78% of ADRs were unavoidable, and 22% were either possibly or definitely avoidable. Gallagher *et al.*[21] suggested some potential prevention strategies for ADRs based on their assessment of the ADRs they classed as 'definitely avoidable' – that more careful attention to practical aspects of care, such as improved monitoring, following prescribing guidelines and improved patient education, could lead to a reduction in the frequency of ADRs causing admission.[21] The Hallas scale[54] was used for the ADRIC admissions study but appeared unsuitable for the ADRIC inpatient study owing to difficulties mentioned before around the terminology used. As a result of this it was decided by

the study group that we would design a new AAT that would be more suitable for use in paediatrics but could also be used in other settings. Ideally, the newly developed AAT should be generalisable to a variety of different patient groups, reproducible and easy to use.

Aim and objectives of this work

The aim of the ADRIC avoidability work stream was to assess the avoidability of ADRs reported in ADRIC and to identify strategies for clinical practice that might reduce the incidence of ADRs. A preliminary step was to develop a new avoidability tool that met all of the criteria of a good tool as described by Hakkarainen *et al.*[26] and was also generalisable. The objectives were to develop an algorithm with dichotomous responses based on Hallas *et al.*[54] and to conduct reliability/validity testing on the new tool as per Hakkarainen *et al.*[26] recommendations.

Methods

Preliminary work

A modified version of the Hallas scale[54] was used as the starting point for the development of a new AAT but the focus was on the available information sources. We wanted to ascertain if the relevant information was available in sources that prescribers would be expected to use, and, if so, whether the recommended advice was followed. The intention was to keep the tool as generalisable as possible by asking if accessible management or treatment plans were available. These could be local, national or international. We recommended that only high-quality guidelines were considered, for example Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Care Excellence (NICE), Royal College of Paediatrics and Child Health (RCPCH) or other peer-reviewed guidelines.[213] Because guidelines are not always available, or contain no information on prevention of ADRs, we added other information sources, for example BNF-C, SmPC (*see Appendix 4*).

A pilot study was carried out in November 2011, when three reviewers independently assessed 50 cases using a modified version of the Hallas scale and 50 cases using the original Hallas scale.[54] The results were compared and IRR testing was carried out on both groups. The kappa scores for both groups were low – the modified Hallas[54] group scores were poor and it was decided that the AAT should be converted to a flow diagram in an attempt to make it easier and more consistent to use. It was also decided that some questions needed reviewing and that this should be done by a consensus approach.[25] We achieved consensus by agreement among peers without pre-set criteria and the consensus group was a MDT (research nurse, doctor and pharmacist).

Phase 1a: define the tool

It was agreed that the best way to develop a new tool was to take a consensus approach in reviewing cases. The format of the new tool was a flow diagram, with dichotomous responses to each question followed by a routing to the next relevant question; it was decided this would differ from the specific criteria Hallas[54] has for each avoidability category. Initially, 20 cases were reviewed to define the tool. This was carried out by a MDT [MAT, AJN and HLM (LEB as an observer)] working together to discuss clinical practice and avoidability outcome. Each question in the newly modified avoidability flow diagram was reviewed by the investigators during the consensus meetings and any necessary changes were made. Any cases that were classified as 'unassessable' had the rationale recorded as either lack of information about the case or of available guidance. The MDT initially looked at 20 cases (randomly selected) from the ADRIC inpatient study and carried out an avoidability assessment. It was felt that it was not appropriate to distinguish between guidelines, and, for the purpose of ADRIC inpatient study cases, we accepted any available guidance based on an acceptable body of opinion, for example SIGN, Alder Hey guidance or NICE guidance. A glossary was prepared to further explain this and other terms. Any areas of disagreement or discrepancies were reviewed by MPir, who also reviewed the iterations as they moved through the various stages of development.

Phase 1b: modify the tool

The flow diagram was modified using 20 randomly selected cases from the ADRIC inpatient study, with rephrasing of questions and adding information. Consensus of opinion was reached and this version of the tool (*Figure 13*) was carried forward to the next phase.

Phase 1c: refine the tool

Two MDT groups (the original plus a new group: nurse, pharmacist and paediatrician) reached consensus about a second set of 20 cases from the ADRIC inpatient study, which were a randomly selected stratified sample (probable and definite cases: 11 surgical, 4 oncology, 2 medical and 3 cardiology). Both groups reviewed the same 20 cases. The results were compared, kappa scores were calculated and the concordance of routes and the final avoidability categories were assigned. Both MDT meetings were observed with assumptions and approaches of the teams recorded. Changes to the tool were made as a result of the findings with two of the questions being amended to include 'known preventative strategies'.

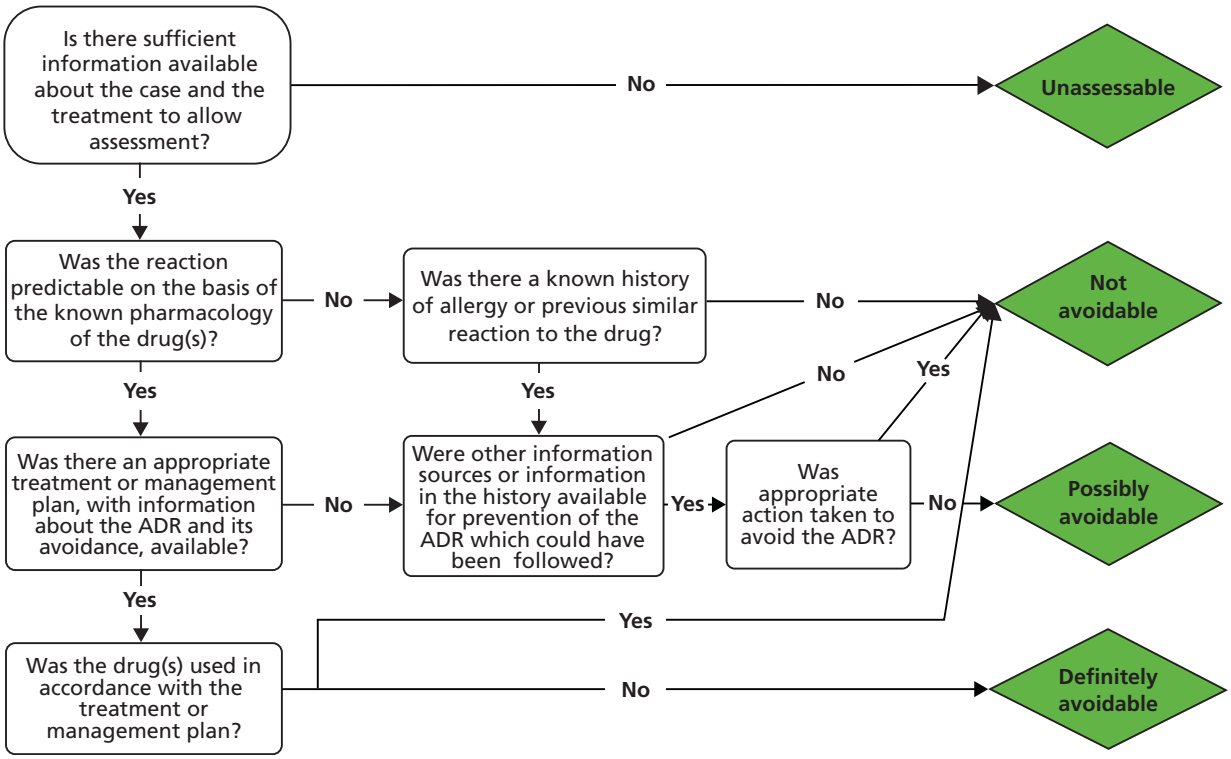

FIGURE 13 Version of the AAT used in phase 1c.

Phase 2: testing and validation of the tool

The refined tool (*Figure 14*) was then tested on a further set of ADRIC inpatient study cases with the aim being to improve IRR. This phase involved the assessment of a further 50 cases by six individual reviewers using the newly refined tool. See the accompanying glossary and guide (see *Appendix 4*) to the questions in the tool for further details on completing an avoidability assessment. These 50 cases were a stratified sample (possible, probable and definite cases: 26 surgical, nine oncology, nine medical and six cardiology). The reviewers included two nurses, two pharmacists and two doctors. These cases were assessed in terms of pairwise agreements between the investigators. Cases where extreme disagreement occurred, i.e. where the avoidability assessment differed by more than one category, for example 'not avoidable' and 'definitely avoidable', and any cases for which half of the raters differed in assigning a category were identified and the questions that caused the discrepancies were reviewed.

The results were presented as categorical scores from the newly developed tool and inter-rater agreements were calculated using kappa scores with 95% CI, and pairwise kappa scores were compared with global kappa scores. The %ED where the avoidability scores between two raters of the same case are wider than one interval apart were calculated to measure extreme disagreement between pairwise kappa scores. Pairwise kappa scores were also calculated by specialty to investigate the differences between surgical, medical, oncology and cardiology cases.

Phase 3: consensus meetings and individual testing

The next step in the development process (*Figure 15*) will be to investigate if group avoidability assessments are superior to individual avoidability assessments.

Following the completion of phase 2, it was decided that further testing was needed and that perhaps the best way to assess avoidability is in a group setting. Agreement in phase 2 ranged from poor to good; possible reasons for this may be due to lack of experience in certain specialty areas or a possible training effect. The next step in the development process will be to carry out group assessments of additional cases and compare these with assessments made by individual reviewers. This further testing in a group setting is required to develop and validate the tool.

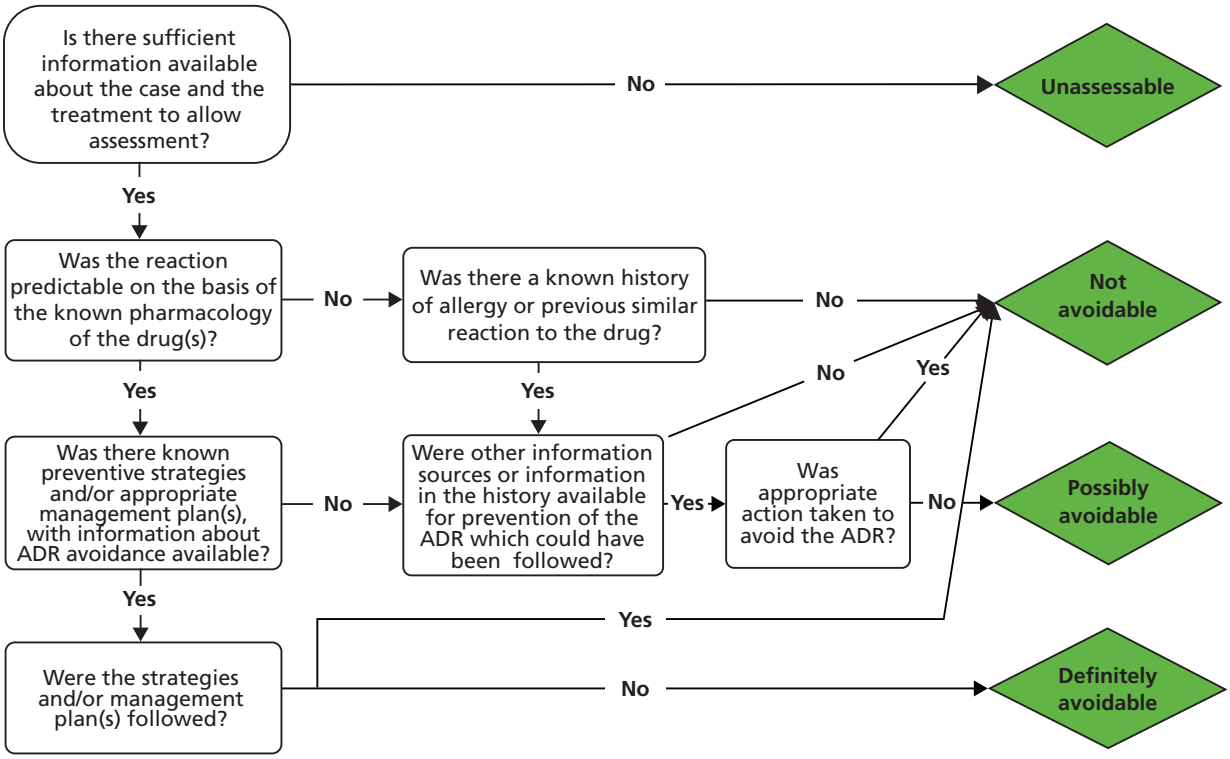

FIGURE 14 The Liverpool ADR Avoidability Assessment Tool.

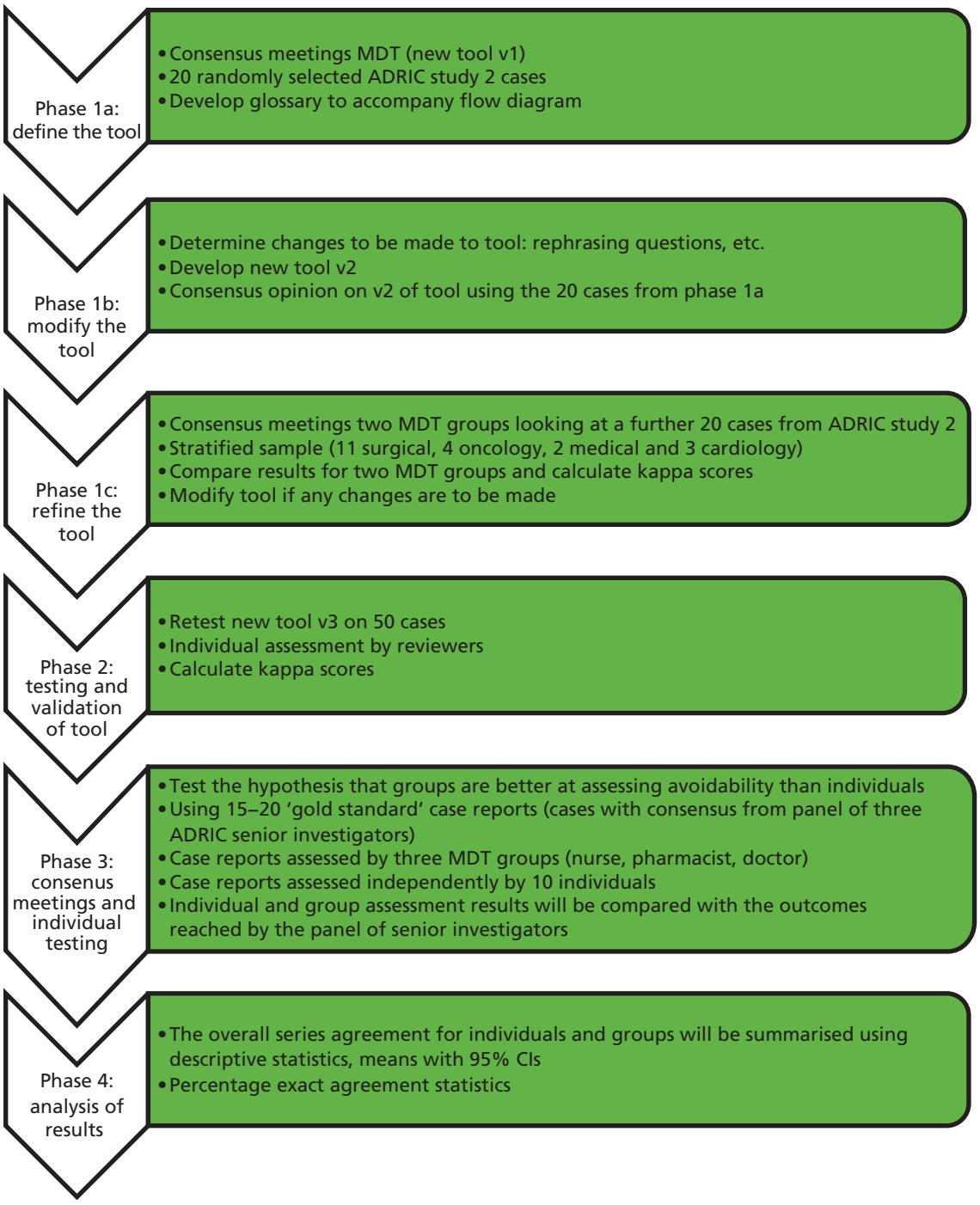

FIGURE 15 The development process.

Results

Phase 1 The assessment of 20 ADR cases was undertaken by two different MDT groups. Group members commented that a mixture of professions was needed to give a full assessment of avoidability. Changes to the tool were made as a result of the findings, with two of the questions being amended to include 'known preventative strategies'.

Phase 2 The assessment of 50 ADR case reports by six individual reviewers, where pairwise kappa scores ranged from poor to good. Stronger agreement was found within professions than between professions.

Discussion

To date, the ADRIC avoidability work stream has defined a tool to assess avoidability of suspected ADRs. We have conducted preliminary testing. The tool has face validity and is easy to use. However, a number of issues were raised. These include the dependence on guidelines and variations in clinical practice. It may not be possible to define a generalisable tool. It may be possible to define a tool that individuals can use consistently. However, the tool in itself may not be sufficient to develop consistent results between individuals or across settings. Consistent results may require a standard body of guidelines, or gold standards for acceptable care. Consistent results may require clinical experience relevant to the suspected ADR. Nevertheless, the tool may provide useful insights within an individual setting. The next step in the development process will be to investigate if group assessment improves agreement and reliability.

There have been many attempts to devise tools or scales to help determine avoidability. Commonly used scales include Hallas *et al.*,[54] Schumock and Thornton,[44] Dormann *et al.*,[214] Ducharme *et al.*[215] and Olivier *et al.*[216] The Ferner and Aronson[25] systematic review identified eight different approaches to assessing avoidability. They suggested an approach to preventability based on analysis of the mechanisms of ADRs and their clinical manifestations.[25,212] Hakkarainen *et al.*[26] identified 18 unique instruments for assessing preventability of ADEs, which ranged from implicit instruments to explicit algorithms in which criteria for preventability were clearly expressed.[26] They also reported that although there was wide variation in the methods used they all shared a common theme; the basis for defining preventability was whether an error or substandard care had resulted in an ADE.[26]

Hakkarainen *et al.*[26] have made some useful suggestions for future research. They recommend that future studies include reliability and validity testing; take action to standardise the measurement process; provide information on the assessors in terms of training and experience in assessing preventability; and describe how the assessments took place (i.e. whether cases were assessed independently or via consensus and how any disagreement is dealt with). They also stated that owing to the limitations and diversity of assessments it remains unknown if variation in preventability rates in different settings and populations is due to the methodology used or actual differences in preventability rates.[26] They suggested that there is a need for modifying previous instruments or developing new ones for use in different settings, and that a starting point for developing a new instrument could be to begin with a clear definition for the preventability of different types of ADEs.[26] They also recommended that any newly developed instruments should be compared with existing ones and that if one or more instrument gained rigorous evidence and became a gold standard it would facilitate comparisons of different studies.

Future work in adverse drug reactions in children

- The assessment of ADRIC admissions study cases using the newly developed avoidability tool, comparing the results with the Hallas (14) assessments carried out in *Chapter 2*.
- Identifying reasons for avoidable ADRs.
- Using suggestions about possible strategies to avoid ADRs from ADRIC to see if there are generalisable steps to take that will promote avoidability.

Conclusions

Avoidability assessment is feasible but needs careful attention to methods. The Liverpool ADR AAT showed mixed IRR in the individual assessment phase; therefore, further testing in a group setting is required to develop and validate the tool.

Chapter 7 Families' experiences of suspected adverse drug reactions: implications for communication and pharmacovigilance

Abstract

Background

There is little research on families' experiences of suspected ADRs in children and little evidence to guide clinicians when communicating with families about problems with medicines.

Aims

To identify any unmet information and communication needs described by families following a suspected ADR in a child.

Methods

Semistructured qualitative interviews with 20 children and young people and the parents of 44 children and young people who had experienced a suspected ADR. Interviews were conducted face to face or by telephone; most were audio recorded and transcribed. Analysis was informed by the principles of the constant comparative method.

Results

Many parents described being dissatisfied with clinicians' communication about ADRs. In contrast, the accounts of parents of children with cancer emphasised confidence in clinicians' management of ADRs and the way clinicians communicated about medicines. The accounts of children and young people largely reflected parents' accounts. Families were positive about the Yellow Card Scheme and felt that recording and reporting ADRs was important. Parents, children and young people linked symptoms to medicines using a similar reasoning as clinicians use to evaluate the possibility of an ADR.

Conclusions

Most parents felt that clinicians' communication about ADRs was poor, suggesting that improvements are needed. The accounts of parents of children with cancer indicate that prospective explanation about ADRs can be effective. Convergence between parents and clinicians in their reasoning for linking children's symptoms to medicines could be a starting point for improved communication.

Introduction

To inform communication with families about ADRs and to guide strategies for actively involving families in pharmacovigilance, we conducted qualitative interviews with children who had experienced a suspected ADR and their parents – the ADRIC-QUAL study.

Clinical communication with families about adverse drug reactions

The literature on communicating about medicines indicates the advantages of involving patients in open discussions about the benefits and risks of medicines in order to support informed consent and decision-making. However, patients have generally been found to be poorly informed about medicines.[12,27] A great deal of work on communication about medicines has been motivated by a concern to promote treatment adherence, rather than on enhancing communication about medicines as an important goal in its own right.[217] Although optimising adherence is an important objective, concern with promoting treatment adherence has, arguably, meant that little attention has been given to examining the experiences of patients following a suspected ADR.[28]

Even less attention has been given to investigating the particular experiences and needs of child patients and their parents following a suspected ADR. Their situation is likely to be complicated by the frequent prescribing of OLUL drugs in paediatrics[218–220] and by parents' distinctive role in caring for their children.[221] Evidence that members of the public are particularly concerned about the risks of medicines to children comes from a study comparing laypeople's responses to hypothetical scenarios involving medicines for child or adult patients. Respondents perceived the risks of ADRs to be more severe and reported that they would be less likely to take (or give) a medicine when the recipient was a child rather than an adult.[222]

Families' involvement in pharmacovigilance

The MHRA is responsible for monitoring medicines in the UK. One way they do this is by collecting spontaneous reports of suspected ADRs submitted via the Yellow Card Scheme.[223] Given the frequent use of OLUL medicines in paediatrics,[218] health practitioners are strongly recommended to submit Yellow Cards for suspected ADRs in children.[17] However, there is considerable concern about under-reporting of ADRs,[40,224,225] and partly in response to such concerns, the Yellow Card Scheme was extended to patients and their families in 2005.[223]

Adult patients who use the Yellow Card Scheme or its international equivalents have been found to provide more detailed reports of ADRs than clinical practitioners and to value the opportunity to contribute to pharmacovigilance.[12,226–232] These patients have spoken of having altruistic motives for reporting ADRs, as do clinicians,[226,233] and being motivated by the severity of the ADR and a concern that certain ADRs were not listed on the medicine patient information leaflet.[233] However, public awareness and participation in the Yellow Card Scheme is low[12,27,28] and studies of patients who have managed to access the Yellow Card Scheme are, therefore, likely to be of limited use in identifying strategies to promote wider participation. Research with patients who have experienced an ADR but have not used the Yellow Card Scheme is limited. A recent study of adult patients who had been hospitalised because of a suspected ADR but had not used the Yellow Card Scheme indicated that they considered the scheme to be remote and impersonal, and they felt that it was not a patient's responsibility to report ADRs to the MHRA.[28]

Exploring the particular motives of parents for using the Yellow Card Scheme and the barriers they encounter is important for several reasons. Previous research has focused primarily on adult patients, yet the need for parental confidence in pharmacovigilance is particularly pressing owing to the widespread use of OLUL medicines in children[218,234] and public concern about the safety of children's medicines.[219,235–240] Also, the perspectives of parents may differ from those of other lay users of spontaneous reporting pharmacovigilance schemes because of parents' distinctive caring and protective role.[221,241] Moreover, previous research has largely focused on the experiences of people who have used the Yellow Card Scheme, which as we note above, is likely to be of limited use in enhancing participation. It is important to test those assumptions by examining the views of parents who have witnessed ADRs in their children but

have not previously used the Yellow Card Scheme, as well as those who have used the Yellow Card Scheme.

Aims

We designed our qualitative study to explore all aspects of participants' experiences and views, from their accounts of communication at the point at which medicines were prescribed to their views about the implications of ADRs for future health, and their views and experiences of reporting ADRs using the Yellow Card Scheme.

Methods

Sampling, setting and recruitment

The methods used have been detailed elsewhere,[29,96] so only a brief outline is provided here. As recommended in qualitative research when there has been little previous research on a topic, we sampled for maximum variation[242,243] using three sampling routes to ensure participant diversity, particularly in terms of clinical specialty and the nature of the suspected ADRs. Route 1 comprised the two cohort studies (see *Chapters 2* and *3*) that were part of the ADRIC programme. 'ADRIC families' were eligible for the study if they could be approached before discharge. Treating clinicians initially introduced the study to families. The interviewers subsequently provided the parents, children and young people who expressed an interest in participating with more detailed information and then arranged the interview. We used route 2, the Yellow Card Scheme,[223] to access parents with experience of reporting ADRs to the MHRA.[242,243] The MHRA sent invitation letters to all parents who had submitted a Yellow Card on behalf of a child of < 17 years of age, outlining the study and inviting parents to return a reply slip to the study team if they wished to participate. Qualitative interviewers telephoned parents to further explain the study and arrange an interview.

As we recruited few children via route 1 and none via route 2, we used a third sampling route to extend the sample of children in the study. For this extended sample, clinical teams identified children who had experienced a suspected ADR while receiving inpatient care at Alder Hey. ADRIC researchers facilitated this process by publicising the study, regularly visiting wards and clinics to prompt staff to identify eligible participants, and checking nursing notes via the hospital computerised records system.

Sampling to all routes ran in parallel with data analysis and was discontinued when saturation on the main analytical categories was reached.[244] A UK NHS research ethics committee approved the study (Northwest 3 Research Ethics Committee 08/H1002/7). All participants gave written informed consent or assent.

Interviews

Interviewers (JA, HH and ES) explained their independence from clinical teams and the MHRA before all interviews. Face-to-face interviews were conducted with participants, with the exception of Yellow Card parents, who we interviewed by telephone as they resided across all parts of the UK. Interviews were semistructured and informed by a topic guide that contained prompts about families' experiences of children's signs and symptoms and how they linked these to a medicine; awareness of suspected ADRs; written and verbal communication with clinicians and views about the implications of ADRs for children, and views and experiences of the Yellow Card Scheme. Interviewers tailored their approach and questions to ensure that interviews were conversational and suited to the needs of both parent and child participants. Interviews were audio-recorded and transcribed. Transcripts were checked by the interviewer, who removed all identifying details before analysis.

Analysis

The analysis drew on the constant comparative approach[244–250] and was broadly interpretive. JA led the analysis reading transcripts several times to develop analytic categories. BY and MT supported this process

by reading a sample of the transcripts and by 'testing' and developing the analysis through periodic discussion with JA. All three analysts compared within and between transcripts, and iterated between developing analytical categories and new data.[245,247–253] We used a number of methods that are recommended to help ensure rigour in the analysis of qualitative data including respondent validation,[245,252] attending to exceptional or 'outlier' cases[247–250,252,253] and scrutinising the quality of the developing analysis for its coherence and potential to influence practice. The latter was also assisted by discussion among the wider ADRIC team[252,254] to support multidisciplinary investigator triangulation.[255,256] Excerpts from interviews are presented to evidence the analysis; in these omitted speech is indicated by [. . .], explanatory text by [text] and excerpts are coded 'AP' (ADRIC parents), 'AC' (ADRIC children) 'YCP' (Yellow Card parents) or 'EC' (extended child sample).

Results

Participants

We conducted audio-recorded interviews with a total of 45 parents (41 mothers, 4 fathers) and 19 children. Of these, 27 parents and 11 children were recruited via the ADRIC cohort studies (route 1), 17 parents were recruited via the Yellow Card Scheme (route 2) and eight children were recruited via route 3 (the extended children's sample).

Interviews lasted approximately 60 minutes (range 17 to 138 minutes) and were conducted between 1 and 56 weeks after the suspected ADR. Four participants were interviewed in a private setting in the hospital. The remainder were interviewed in their homes. *Appendix 5* shows the characteristics of participants, including child age range, gender, ranked Index of Multiple Deprivation (IMD), type of drug associated with the suspected ADR and the body system affected by the ADR.

The findings from the interviews are presented in two parts: Part 1 focuses on participants' perspectives on communication about ADRs; Part 2 focuses on participants' perspectives on contributing to pharmacovigilance through the UK's spontaneous reporting scheme.

Part 1: participants' perspectives on communication about adverse drug reactions

Little explanation of the risks of medicines at the time they were prescribed

Although some of the children reported receiving general advice about potential ADRs before a medicine was given, most children and parents indicated that clinicians did not explain the risks of medicines when the medicines were prescribed: 'No side-effects were made known to me' (YCP5); 'I didn't know codeine would make me constipated' (AC07); 'They didn't really tell me about anything about being sick or being itchy. They never really said anything about that' (EC13). Parents explained how clinicians focused on other issues, such as explaining their child's condition and the importance of medicines or surgery in treating the condition: 'They [the surgeons] don't discuss the drugs; they discuss the surgery itself' (AP23). If the risks of medicines were discussed, it was often at a time when parents struggled to absorb information, such as shortly before a child was due to be anaesthetised: 'On the day your child is being operated on or when the anaesthetist comes up you are not thinking of anything other than [. . .] what's going to happen in the operation' (AP16). Participants also reported difficulties with written information about medicines and potential ADRs. They either did not receive these documents or found them hard to engage with: 'I did a carefree glance [at the patient information leaflet] and chucked it' (YCP13).

A key exception to these accounts was the parents of children with cancer, who described how clinicians provided comprehensive information about the types of reactions that medicines could cause and emphasised how clinicians carefully timed and paced their explanations so that parents could absorb the

information: 'They explained things in little bits so it sinks in [. . .] they did say he would become neutropenic' (AP6).

How participants become aware of adverse drug reactions

Parents usually described an initial period in which they began to suspect something was wrong based on a wide collection of physical symptoms and changes in their child's behaviour that were 'out of the ordinary'. With the exception of patients whose suspected ADR had first been identified by clinicians or those who had cancer, participants initially tended to attribute symptoms to trivial causes, such as minor illness, injury, or changes in lifestyle or environment. It was only when symptoms worsened that participants became concerned: 'His colour dropped and his breathing went a bit funny and he started to panic, that worried me' (AP25) and they started to consider possible links to medicines.

Participants reported how they started to link symptoms to a medicine when they noticed patterns, such as temporal associations between a medicine being given and the onset of symptoms: 'It just seems strange to me that she had it [the medicine] and then straight away like she got that temperature' (AP10); 'When I went on the ketamine I wasn't being sick at all. Then when I went on the morphine I was being sick. So, it was quite obvious that it was the morphine that was making me sick' (AC09). Some also noticed how symptoms receded between doses and then returned following another dose: 'I noticed a difference [. . .] when she was having it [the medicine] and when she wasn't having it [. . .] she started on it again and then we noticed the symptoms within a few days again of having it' (YCP7). The absence of an alternative explanation for the symptoms also influenced participants' attributions: '[The medicine] is the only thing she's had and she hadn't had a cold or been ill before it' (YCP10); 'I was like, well, the only reason this would have happened would probably have been the medication' (AC08).

With few exceptions, parents were critical about adverse drug reaction management and communication

Parents indicated that clinicians' communication about suspected ADRs was often poorly matched to their needs. They described receiving contradictory information and a lack of communication that might help them understand what was happening to their child while his/her symptoms were being assessed: 'No-one actually ever said why it [the hallucination] was happening, the nurses thought it was a bit funny, they all kept coming over to see him and laughing with him sort of thing' (AP14). The way in which clinicians managed and communicated uncertainty surrounding an ADR's identification did little to reassure parents 'I was saying "well, when she goes home, can I give her paracetamol? Can she never have paracetamol or can she never have a drug that might affect her liver?" And they were going "well [. . .] it should be fine" but no-one was saying "well you can, I'll write it down and you can have it" ' (AP12). Parents also described receiving detailed information at times when they were anxious (e.g. when a child was critically unwell or immediately prior to surgery). At these times parents found it hard to absorb information. They reported receiving little or no information at times when they were less anxious and better able to absorb information. Children voiced fewer concerns in communicating with practitioners than parents, perhaps because most children relied on their parents for information about medicines 'Sometimes I can't understand them [the doctors] so I just ask my dad' (AC01); 'My mum deals, is the information box and if I have any questions I just ask her' (AC10).

Some parents were intensely critical of how practitioners communicated about ADRs. One parent was frustrated during a visit to outpatients when clinicians could not explain what was happening to his/her child and spoke of feeling that he/she was being lied to by clinicians: 'They were fobbing me off [. . .] I felt like they were lying to us' (AP5). More commonly, parents emphasized how their concerns had been ignored or dismissed by clinicians: 'Dismissive and wasn't taking me very seriously' (AP10). Yellow Card and ADRIC parents both voiced criticisms of clinicians' communication, although Yellow Card parents were particularly emphatic in their criticisms. This was prominent when they felt clinicians had ruled out the possibility that a child's symptoms could be related to a medicine with seemingly little exploration of parents' concerns or explanation of the reasons for ruling out an ADR: 'She [general practitioner] literally said word for word "what would you like me to do?" And I just felt that was really dismissive' (YCP14).

Parents who felt clinicians had ignored or dismissed their concerns described a sense of abandonment: 'I just, just felt like nobody cared, nobody was interested and they just wanted me to go away' (YCP5).

A striking exception to the highly critical accounts of these parents came from the parents of children with cancer. These parents were almost uniformly highly positive in their accounts of how clinicians communicated about ADRs.

Parents of children with cancer were positive about adverse drug reaction communication

Despite the life-threatening nature of the illness and the risks of cancer treatment, parents of children with cancer felt well supported by how clinicians communicated with them about medicines. There was a sense from these parents that clinicians took ADRs seriously, were adept in communicating about them and had well-developed systems in place for the management of ADRs: 'It's quite scary when you first go home with this big bag of drugs [. . .] they said [. . .] you can ring any time, and I rang nearly every day' (AP7). Parents pointed to how clinicians discussed possible ADR symptoms and how to respond before an ADR happened, so that parents were clear about what to look out for and what action to take in the event of a suspected ADR. Consequently, parents felt that clinicians communicated about medicines and ADRs in a way that was ordered, timely and reassuring.

Implications of poor communication about suspected adverse drug reactions

Parents who were dissatisfied with how practitioners had communicated reflected on the implications. They commented on how a lack of information about potential ADRs at the time of prescription had prevented them from being involved in decisions about their child's care. In one case, a lack of information at the time of prescription had resulted in a parent continuing to give morphine to alleviate their child's agitation, only to subsequently discover that agitation could be a result of itchiness caused by morphine: 'As she kept getting more and more agitated we kept boosting it [the morphine] [. . .] and the more we pressed the booster [. . .] the itchier she got' (AP16). A few parents remarked on how they blamed themselves for what had happened because they felt 'responsible for what goes into' their child (YCP10) and pointed to the distress this had caused: 'I was devastated [. . .] I just felt like crying all the time' (AP8). Parents also spoke of fearing a repetition of the ADR: 'Will it happen again? [. . .] could it happen to him, to the baby?' (AP8) and of their uncertainty about the implications of ADRs for their child's future health and use of medicines. Parents were also confused about whose responsibility it was to prevent a recurrence of the ADR: 'I don't know if it would be down to me to turn round and say something or whether they have actually put something in their notes' (AP14). Some assumed that the responsibility was theirs alone: 'It's something that I [. . .] have to ask to make sure he never gets given that again' (AP18). By contrast, children tended to focus on their experience of the symptoms of the suspected ADR. One child emphasised how he had not been perturbed because the hallucinations that he experienced had 'distracted' (AC04) him from the pain that he was feeling. However, most children described the experience as unpleasant or frightening: 'It was really scary. I wasn't bothered about pain [. . .] I just felt so scared' (AC10).

In the context of poor communication, the experience of a suspected ADR sometimes coloured parents' views about medicines and some expressed reluctance to give certain medicines to their child in the future. For example, one parent became convinced that her child's ADR was a reaction to morphine and that her child could never have morphine again: 'She's due for this big operation and she can't have morphine' (AP11). However, clinical review of this particular case suggested that the suspected ADR was linked to an avoidable over-dosage and that, rather than avoiding morphine altogether in future, it might be in the child's best interests to personalise the dose. Another parent refused to allow her child to have the final course of her vaccine: 'I will categorically say that [. . .] I will definitely not let her have the third [human papilloma virus] vaccine' (YCP3). One child said he would refuse a medicine again: 'I don't want to have that medicine ever again because [. . .] it just makes you go all angry' (AC09), although most children reported they would take the medicine again if it was likely to help them.

How participants thought communication about suspected adverse drug reactions should be handled

Reflecting their accounts of poor communication about ADRs and the resulting implications as described above, parents wanted clinicians to help them to understand what had happened to their child. Children similarly described a need to understand their experience 'I would have liked to have known that the floppiness wasn't just me and I would have liked to have known that I would have felt sick after' [. . .] all I want to know is what is going to happen, when is it going to happen, how is it going to happen and am I going to be in pain' (EC17). As one parent explained, the need to understand the ADR seemed to be intrinsic rather than motivated by ulterior considerations: '[It's] not necessarily the case that everyone's going to jump and say, "Right, I'm going to sue the drug company" and all of these sorts of things. I think parents genuinely, who are concerned about their child's health, want to know what it was' (YCP8). Participants wanted discussions about ADRs to be paced and timed in a way that would help them to absorb the information: 'You just don't think straight when you're there [. . .] doctors have got to understand that [. . .] and maybe spend a little more time to try and explain a little bit more than they do' (AP11); 'Because when you are in hospital and they ask have you got any questions, you can't really think of it because you are drugged up [. . .] and your mind goes blank. And when you get home and then you do a bit of revising and stuff like you think "oh, I should have asked that question" and stuff like that' (EC12).

Parents particularly wanted to understand what the suspected ADR meant for their child's future health care, to know what steps would be taken to help prevent their child suffering further ADRs and to ensure he/she would receive appropriate medicines in the future. Without exception, parents accepted that a certain level of risk came with medicines and most appreciated that clinicians faced uncertainty in identifying ADRs: 'I think it was the antibiotics. The doctors think it is that but they can never say it is that, because there is a possibility that it's not that' (AP1); 'It's just something that, you know, just happens [. . .] I'm sort of accepting about it' (YCP13). Many parents were critical of how clinicians communicated about ADRs and some of them got the impression that clinicians were unwilling to discuss ADRs. However, none of the parents blamed clinicians for their child's ADR or said they intended to formally complain. Only one parent expressed a slight 'loss of trust' (YCP8) in clinicians. However, as we note above, a few participants explained that their trust in medicines had diminished. Alongside their wish for dialogue with clinicians about ADRs, several participants also wanted accessible and reliable written information about ADRs: 'They should give you a little pamphlet or something to say [. . .] look this is what she's got' (AP12).

Part 2: participants' perspectives on pharmacovigilance

Awareness of the Yellow Card Scheme

Most Yellow Card parents remarked that they had found out about the Yellow Card Scheme through their training or work as a health practitioner: 'The only reason I knew about it was because of the course that I'd done' (YCP7), or through friends or relatives who were health practitioners. In contrast, only two ADRIC parents had heard of the Yellow Card Scheme before we interviewed them and both were nurses. None of the children had previously heard of the Yellow Card Scheme. None of the ADRIC or Yellow Card participants knew for certain whether or not the practitioners had submitted a Yellow Card reporting the suspected ADR: 'I don't know if one was filled in or not' (AP20), but some remarked that they would appreciate being informed if a practitioner had done so: 'Yeah, I think they should tell you' (AC02).

Motivations, views and experiences of parents who submitted Yellow Cards

Most Yellow Card parents emphasised how they had submitted a Yellow Card because they wanted to help prevent other children experiencing the sorts of ADRs that their child had suffered. They also hoped that their report would contribute to the review of certain medicines 'if they look into things, and [. . .] if there is too many incidents, they might have to relook at the tablet or relabel the information leaflet' (YCP7). Parents did not usually think their reports would directly help their own child: 'I didn't think it would help me at all. I didn't have any expectation for us' (YCP10) and none of them wanted a medicine

to be withdrawn from the market solely because of the difficulties their child had experienced. Linked to their altruistic motivations, Yellow Card parents also described a sense, albeit nebulous, of 'achieving something positive from that experience rather than just sort of happening' (YCP14). Those Yellow Card parents who had professional knowledge of the Yellow Card Scheme added that they were motivated to submit a report by a sense of professional obligation. Those who were not health practitioners expressed a preference for reports about suspected ADRs to come from health practitioners rather than themselves: 'I wished it [Yellow Card] had come from the doctor first' (YCP10).

Some Yellow Card parents seemed to understand that a certain number of reports would be needed in order to trigger action by the MHRA: 'if enough people say something about this then something should and probably will get done' (YCP16). Others were unsure about what happened to the data after they had submitted it. Most parents did not report expecting to receive feedback from the MHRA in response to their Yellow Card but those that had received a response were pleased: 'What I'm delighted about is the response it makes you feel very pleased, glad that I followed it up' (YCP3). As noted in Part 1, many Yellow Card parents emphasised how the health practitioners they consulted had not taken their concerns about their child's ADRs seriously. In this context, the opportunity the Yellow Card Scheme offered a welcome opportunity for parents to voice their concerns about medicines in a way that was not filtered or influenced by practitioners: 'I felt very pleased that I could [. . .] take control of it really and let someone know regardless of whether the doctor thought' (YCP8). Other parents spoke of how submitting a Yellow Card provided a form of redress: 'It's kind of restorative justice in a way' (YCP6) or helped to resolve their feelings of guilt about what had happened to their child: 'It felt that I might have failed [my child] so that's what I am doing it all for, really, to try and offload that information' (YCP10).

Views and experiences of participants who had not submitted Yellow Cards

As we note above, the children we interviewed and most ADRIC parents knew nothing of the Yellow Card Scheme prior to participating in this study. When we explained the Yellow Card Scheme to them during the interviews, like the Yellow Card parents, most of the children and ADRIC parents were generally positive about the Scheme 'I think that is a good idea as patients might think [an ADR] is important and doctors don't' (EC16) or spoke of the need for more to be done to publicise the Yellow Card Scheme: 'We should be told about things like this [the Yellow Card Scheme] [. . .] if anyone has a reaction to a drug then they need to know that something is going to happen about it. It should be recorded' (AC10). All but one parent said they would consider using the Yellow Card Scheme in future: 'Now that I know about it, yeah, I would do. I'll tell my friends about this actually' (AP23). Despite this positivity, none of the ADRIC parents said that they would like to complete a Yellow Card for the particular ADR that we had discussed during the interview. Parents' reluctance may be linked to their experiences of their child's ADR. As described above, both ADRIC and Yellow Card parents had been dissatisfied with how health practitioners had communicated about ADRs, but ADRIC parents also described confusion and uncertainty about roles and responsibilities for recording and reporting a suspected ADR. Some assumed this was a practitioner's role: '[I] just assume the doctor would sort it out' (AP14), or expected that practitioners would submit Yellow Cards as a matter of course: 'I would more than likely think that the doctors would do it [. . .] if the child has had a reaction they would automatically' (AP13). Others implied that practitioners might disapprove of parents who submitted Yellow Cards and regard such parents as stepping beyond their role: 'they might think that you are trying to do their job for them' (AP20).

Some ADRIC parents were also reluctant to submit a Yellow Card on this occasion because they were uncertain about whether an ADR had occurred: 'I don't think they linked it to an adverse reaction at the time' (AP25) or they felt that they or other members of the public were not equipped to decide if an ADR had occurred: 'I'm not medical so I wouldn't know what a reaction would be' (AP18); it [the side effect] may not be from the drug, and [a parent] might think it is and go onto the internet and say that on a Yellow Card' (AP22).

Discussion

Perspectives on communication about adverse drug reactions

Parents were generally disappointed with how clinicians communicated about suspected ADRs. Although children focused on the concern or distress the ADR had caused them, they voiced fewer problems with clinicians' communication. Children pointed to how their parents acted as intermediaries or conduits for communication about medicines and ADRs and this parental role may explain why children voiced fewer problems in communication compared with parents. The majority of parents reported receiving little or no advance explanation about the problems that might be associated with medicines. When information was provided, it was in ways that parents found hard to absorb. As a result, parents were taken by surprise when their child experienced a suspected ADR. This turned into frustration and confusion when clinicians were unresponsive to parents' concerns and some parents felt dismissed or abandoned as a result. In the absence of explanation about what steps could be taken to prevent further ADRs, a few parents were reluctant to give their children medicines in the future. The key exception to these negative parental accounts was parents of children with cancer, who, despite their intense fears about the illness and treatment, were generally highly satisfied with how clinicians communicated about ADRs.

As well as being a source of avoidable distress, poor clinician–parent communication about suspected ADRs will impact on what parents communicate to their children about the ADR, challenge parents' and children's confidence in medicine, and contribute to negative perceptions and misunderstandings of medicines.[257,258] This could lead to poor adherence in the future. We found considerable convergence among participants about the nature of helpful communication. Their suggestions, which are similar to those reported elsewhere, included the importance of the timing and pacing of information, as well as the need for clinicians to explicitly acknowledge what had happened and help families to understand events that they perceived to be significant, even if the event is not significant from the perspective of clinicians.[258–260] The accounts of parents of children being treated for cancer indicated that, despite the complexities involved in prospectively explaining about ADRs while not raising undue alarm about medicines, communication about ADRs can be conducted in ways that parents find informative, understandable and reassuring.

One important challenge facing clinicians who communicate about ADRs is the uncertainty involved in attributing symptoms to medicines. We found that families' accounts of how they linked symptoms to a medicine resembled the logic that underpins tools for assessing ADRs[53,188] in research and clinical practice. Participants noted temporal associations between a medicine's administration and the onset of symptoms, the receding of symptoms between doses and the absence of alternative explanations for symptoms. This common ground could be a starting point for improving communication about ADRs. Alongside our other findings – parents accepted that all medicines come with risks, appreciated the uncertainty in attributing symptoms to medicines and did not blame clinicians for suspected ADRs – we think there is reason to be optimistic about the potential to improve clinician–family communication about medicines. However, this needs to be confirmed by investigating clinicians' perspectives on communicating with parents about suspected ADRs.

Perspectives on spontaneous reporting of suspected adverse drug reactions

To our knowledge, this is the first study to specifically investigate how parents and children view the opportunity to report suspected ADRs directly to the MHRA. All participants saw value in direct reporting and those who had submitted Yellow Cards were satisfied with the Yellow Card Scheme. However, our key findings come from the ADRIC parents, none of whom had previously submitted a Yellow Card. These parents were generally supportive of the aims of the Yellow Card Scheme after it had been explained. Although they were positive about using the Scheme in the future, they were reluctant to use the Scheme to report the ADR discussed in their interviews. Comparing the settings, roles and perceptions of the Yellow Card and ADRIC parents helps to shed light on these findings. The Yellow Card parents generally reported events that had happened in the community, and linked to their professional roles, many were confident about using the Yellow Card Scheme. In contrast, the children of ADRIC parents had received

hospital care for their ADR or were hospital inpatients at the time the ADR occurred. As such, these parents either expected that it was the responsibility of the practitioners looking after their child to submit a Yellow Card, or they were uncertain about whether it was legitimate for parents to report the ADR. Moreover, only a few ADRIC parents had personal links to health practitioners or were themselves health practitioners.

Parents who submitted a Yellow Card reported multiple motivations. Altruistic motivations, such as a desire to contribute to the improving the safety of medicines at a population level, were particularly prominent in their accounts. This is similar to findings on other patient groups who have reported ADRs, to clinicians' motivations for submitting Yellow Cards[12,261,262] and it is also consistent with the goals of the MHRA.[223] Linked to their dissatisfaction with practitioners for not taking their concerns about suspected ADRs seriously, some parents experienced reporting as providing a form of redress or felt reassured, as others have also described,[12,261,262] by the availability of an independent vehicle for 'officially' recording ADRs. A few parents pointed to how submitting a Yellow Card had helped to resolve feelings of guilt (about the medicines they had given or allowed their child to take), a motivation that has not been previously described and may be unique to parents and others who care for vulnerable patients. In this way, the Yellow Card Scheme seemed to enable parents to take action that seemed psychologically important following their child's ADR, even if it would not directly benefit their child.

Consistent with previous research on adult patient reporters,[12,27,28] our findings indicate that awareness of the Yellow Card Scheme is limited and that further work is needed to promote the Yellow Card Scheme. Our study provides insight into the perspectives of parents and children who had not used the Yellow Card Scheme but were 'eligible' to do so. As we note above, participants supported the aims of the Yellow Card Scheme but they were reluctant to use it to report the ADR that we interviewed them about. The reasons for their reluctance may help inform strategies to widen participation in pharmacovigilance. The parents we interviewed were concerned that, because they lacked medical knowledge, their reports would be inaccurate or of little value. Emphasising that reports from members of the public can make a valuable contribution to drug safety would help to overcome such barriers, as would emphasising that people do not need to be certain that a medicine definitely caused a reaction in order to submit a report. Some parents expected that their child's practitioners would report the ADR, yet practitioner participation in spontaneous reporting and other forms of pharmacovigilance is poor.[40] Informing the public that their reports are an adjunct to practitioner reporting may help to motivate them to participate in pharmacovigilance. Parents also worried that their reports might be perceived as undermining practitioners. These concerns could be addressed by emphasising that the Yellow Card Scheme is confidential and that information will not be shared with practitioners without a reporter's consent.

Limitations

Our study had some limitations. First, we relied on clinical teams for access to children and ADRIC families. Clinical teams may have filtered out participants with whom their relationships were strained. To address this we sampled Yellow Card parents, as we could access them without consulting with clinicians. However, many Yellow Card parents were health professionals themselves, or had contacts who were, and their views on communication about ADRs and pharmacovigilance may be distinctive. Previous studies of patients' perspectives on spontaneous reporting pharmacovigilance schemes share similar limitations. This arises from the limited public awareness of the Yellow Card Scheme. In this context, our sampling of participants with experience of a suspected ADR but who had not used the Yellow Card Scheme is particularly important. The views of such groups have rarely been investigated, yet they are crucial in identifying how public participation in pharmacovigilance may be promoted. Moreover, the accounts of both ADRIC and Yellow Card parents triangulate in pointing to the difficulties parents experience in communication about ADRs. Finally, the interviews were conducted sometime after the suspected ADR, which may have shaped participants' accounts in certain ways. However, understanding the meanings that parents and children take away from their experiences of ADRs is crucial in learning how to enhance their experiences and it is these meanings that were the focus of our study.

Conclusions

Poor communication about children's ADRs was a source of significant difficulty for parents and our findings will help to guide clinicians regarding what topics to cover in their discussions about medicines and ADRs. At the time of prescription, parents wanted to know the potential risks associated with medicines. In the aftermath of a suspected ADR, both parents and children wanted to understand what had happened and in some cases this might include explicit acknowledgement that an ADR had possibly occurred. Parents also wanted know the potential future implications of the suspected ADR for their child. Parents and children linked symptoms to medicines in ways that resembled the reasoning used clinically for identifying ADRs. Clinicians could possibly use this common ground as a starting point for communicating with families when an ADR is suspected. However, our study's most important contributions may lie in providing insight for clinicians into how valuable discussions of ADRs can be for parents and the important role that parents have as a conduit for communicating with children about medicines and ADRs.

Parents who had used the Yellow Card Scheme found it straightforward and were satisfied with its aims. Participants who had not used the Yellow Card Scheme were also satisfied with its aims but parents were uncertain about their role in reporting ADRs and many assumed that submitting a Yellow Card was the responsibility of practitioners. Therefore, although raising public awareness of reporting schemes is important, our findings indicate that this will not improve public participation by itself and that pharmacovigilance agencies will need to present their schemes in ways that empower and support lay reporters. Based on our findings, we recommend that agencies emphasise the following points when publicising their schemes: (1) the value of laypeople's reports in promoting drug safety; (2) that reports will not be shared with practitioners without the reporter's permission; and (3) that reports can be submitted even when there is uncertainty about whether or not a medicine caused a reaction.

Chapter 8 Developing a communication strategy about suspected adverse drug reactions affecting children

Abstract

Background
Families have unmet information needs following a suspected ADR in a child or young person.

Aims
To develop a strategy to support communication about suspected ADRs between families and clinicians by:

1. identifying any barriers to effective communication with families from the perspective of clinicians following a suspected ADR
2. developing information leaflets about ADRs for parents, children and young people to support their communication with clinicians.

Methods
Semistructured qualitative interviews with 42 clinicians about their experiences of ADRs in children. Face-to-face interviews were audio-recorded and transcribed. Analysis was informed by the principles of the constant comparative method. A parental leaflet on ADRs was developed, based on feedback from a range of stakeholders, including parents and clinicians. The usefulness of the leaflet was examined by conducting structured interviews with 17 clinicians after they had used the leaflet during routine parent–clinician discussions about suspected ADRs.

Results
Clinicians described using all the features of communication that parents wanted to see. However, clinicians made active decisions about when and what to communicate to families about suspected ADRs. These decisions mean that communication may not always match families' needs and expectations. Clinicians describe a number of complexities with effective communication, some of which are unique to paediatric settings. The complexities perceived by clinicians may explain, at least in part, the discordance between clinician and family perspectives. Clinicians found the leaflet useful in supporting discussions with parents about a suspected ADR in their child.

Conclusions
The parent leaflet was useful in supporting discussions between parents and clinicians about suspected ADRs. Further strategies to improve communication between families and clinicians should focus on aligning clinicians' decision-making about what and when to communicate with families following a suspected ADR rather than focusing on developing clinicians' communication skills.

Introduction

The ADRIC-QUAL interviews (see *Chapter 7*) elucidated the communication difficulties that many families experienced following a suspected ADR. In their interviews parents also indicated that written information about ADRs in the form of a leaflet may help to address their communication needs by supporting discussions between families and clinicians about suspected ADRs. In response to these findings, we developed information leaflets that could be given to parents and children following a suspected ADR and

used to support them in communicating with clinicians about ADRs. As well as being the catalyst for developing the leaflets, the findings from the families' interviews also informed the content of the leaflets.

The findings described in *Chapter 7* suggest that from the perspective of parents, there is a need to enhance communication about ADRs between clinicians and parents. However, as communication is a two-way process, it is important to also examine communication about ADRs from clinicians' perspectives, particularly to identify which strategies are likely to be feasible for use in everyday practice to enhance communication with families. Accordingly, this study aimed to describe clinicians' views of communicating with families about ADRs and to relate the findings to the accounts given by parents.

Methods: development of a leaflet for parents

Process

The parent leaflet was developed iteratively through numerous cycles of drafting, comment and redrafting, culminating in a pilot study to test the suitability of the leaflet for supporting communication about ADRs in clinical practice.

External review

The text and format of the parents' leaflet was reviewed externally through three routes:

1. During interviews with clinicians about their experiences of ADRs, clinicians were shown a copy of the leaflet and asked to comment on the content and the potential usability of the leaflet.
2. The leaflet was reviewed by parent members of the MCRN at Alder Hey and by parents from the Research User Group at Liverpool Women's Hospital.
3. The leaflet was reviewed by the Paediatric Medicines Expert Advisory Group at the MHRA.

Two prototype text-only versions of information leaflets for children were reviewed internally and revised within the ADRIC team. The children's leaflets were further reviewed and revised as follows:

1. Children's views of the leaflets were sought during some of the qualitative interviews that we conducted (see *Chapter 7*). In response to comments during these interviews we developed a third leaflet aimed at young people aged $\geq$ 16 years. This leaflet matched the level of information provided on the parents' leaflet.
2. We engaged a professional designer to enhance the age-appropriateness of the design of the leaflets to ensure their suitability for the target age groups.
3. Children and young people from the MCRN Young Person's Advisory Group at Alder Hey reviewed and commented upon the leaflets.
4. The revised children's and young people's leaflets were then reviewed by the ADRIC steering committee.
5. Following this review the leaflets were forwarded to the Paediatric Medicines Expert Advisory Group at the MHRA to mirror the review process that we had conducted for the parents' leaflets.

We approached the Royal College of Paediatricians and Child Health to ask if it would consider hosting the parents' leaflet on the publicly available Medicines for Children website (www.medicinesforchildren.org.uk). Including the leaflet on this website offers the advantage of making the leaflet available widely for parents and clinicians, as all hosted leaflets are freely available for download by anyone accessing the website. The leaflet was reviewed by the Patient Information Leaflet Committee, which requested that it be piloted to assess the suitability of the leaflet for use in clinical practice before its inclusion on the website.

Piloting the parent leaflet

The pilot study took place in Alder Hey. We conducted brief structured interviews with doctors and nurses after they had actually used the leaflet in the routine interactions that they had with families when they usually explained about any suspected ADRs.

Sample

The leaflet was used on 17 occasions. There were three further occasions when doctors declined to use the leaflet: either because they did not feel an ADR had occurred or they did not feel it was appropriate to introduce the concept of an ADR to a family at that particular time. Excerpts from interviews are presented to evidence our conclusions; in these excerpts omitted speech is indicated by [. . .] and explanatory text by [text], and excerpts are coded 'N' (nurse) or 'D' (doctor).

Pilot study results: development of a leaflet for parents

The pilot study indicated that from the perspective of clinicians, the leaflet was well designed and useful in supporting communication between parents and clinicians following a suspected ADR in a child. Clinicians commented that the leaflet was 'very well laid out and [. . .] jargon free' (P06:N) and 'simple to read' (P09:N). They also reported that the leaflet supported conversations with families by prompting clinicians to include information that they would not normally have covered when discussing ADRs with parents. In this way, clinicians indicated that the leaflet helped them to offer additional reassurance to parents. Some clinicians also felt the leaflet empowered parents to ask questions that they might not have otherwise voiced or felt able to ask: 'Some of our other families [who had not seen the leaflet] [. . .] mightn't have thought of those things or they are thinking "oh [. . .] it is all right to ask this and ask that" ' (P06:N). All clinicians said they would use the leaflet again: 'Oh yeah, I would be quite happy to do it again' (P02:N); 'Yeah I would use it again' (P12:D).

Pilot study feedback and leaflet validation

The results of the pilot study were fed back to:

- the Patient Information Committee at the Royal College of Paediatricians and Child Health
- the Medicines Management Committee at Alder Hey
- the ADRIC Steering Group (including members of the MHRA).

The leaflet for parents is now available at www.medicinesforchildren.org.uk/search-for-a-leaflet/side-effects-from-childrens-medicines/.

Methods: clinicians' perspectives on communicating with families about suspected adverse drug reactions in children

The methods were similar to those used in *Chapter 7*, with the key elements noted below.

We purposively sampled clinicians across three sites for maximum variation[241] in terms of professional role (nurse, doctor or pharmacist), length of practice, seniority and specialty. Site 1 was a specialist regional paediatric hospital that had been actively involved in the ADRIC studies of the prevalence and characteristics of paediatric ADRs.[20,22] We were aware that clinicians at this hospital may have a heightened awareness of the subject because of the ADRIC studies. Therefore, to enhance the transferability of our findings we included two additional sites (sites 2 and 3), which were paediatric units in local district general hospitals.

Procedure

The researcher (JA) made initial contact with a senior research lead at each site, who helped the researcher to access a list of eligible clinicians. JA then contacted clinicians by e-mail with a brief outline of the study and an invitation to take part. Where a clinician did not reply they were sent one reminder e-mail. Clinicians who expressed an interest in the study were provided with a participant information sheet and their written consent was sought. One of two experienced qualitative researchers (JA and AR) conducted the interviews with each clinician at the hospitals where the clinicians worked.

A topic guide was developed to steer the interviews and this was adapted to reflect the different roles of each professional group in the sample. The topic guide included prompts to elicit clinicians' definitions and experiences of ADRs; their perceptions of how families' experienced ADRs; their accounts of communicating about potential ADRs with families, both at the time a medicine was prescribed and following a suspected ADR; and their accounts of recording and reporting ADRs. Interviews were audio-recorded and transcribed. The researchers also kept field notes of each interview detailing the interview context, including the setting and observations and reflections on the interview process.

Results: clinicians' perspectives on communicating with families about suspected adverse drug reactions in children

We invited 90 clinicians to participate; 46 did not respond to an initial and reminder invitation and one doctor agreed to take part but we were unable to arrange an interview. Non-respondents included doctors ($n = 28$), nurses ($n = 15$) and pharmacists ($n = 3$). We audio-recorded interviews with 42 clinicians, which included doctors ($n = 26$), nurses ($n = 12$) and pharmacists ($n = 4$). The mean length since registration to practice of our sample was 18.5 years (range 3–36 years). *Table 36* shows other sample demographics (interviews lasted approximately 70 minutes). We found no difference in participant characteristics or study findings between sites. In the following sections we present preliminary findings from our analysis.

Why communicate about adverse drug reactions?

Clinicians indicated that they viewed providing both prospective and retrospective information to families about ADRs as an important part of their clinical practice. They also talked of the need to optimise adherence to medicines and pointed to how prospective communication about ADRs helped to guard against the possibility that parents may refuse a medicine in the future because their child had experienced an ADR about which that they had not been warned. Only a few clinicians described how discussing ADRs prospectively was important in order to actively involve parents in their child's clinical care.

In their accounts of retrospective communication following a suspected ADR, clinicians more commonly pointed to the importance of the active involvement of parents. For example, a few clinicians mentioned how discussing ADRs retrospectively was important in order to overcome the circumstances of the ADR. Clinicians also spoke of how important it was to ensure that parents were adequately briefed about the ADR and the medicine implicated in its causation so that parents could pass on this information in future interactions with health teams.

Definitions of adverse drug reactions

In some cases, clinicians indicated that although they recognised and responded clinically to possible side effects to a medicine, they did not necessarily consciously 'label' these symptoms as an ADR. The descriptions of ADRs used by clinicians reflect the clinicians' thresholds for communication with parents. However, they did not mirror formal definitions of ADRs used in pharmacovigilance, such as in the MHRA Yellow Card system for reporting suspected reactions. We also noticed that some clinicians used the terms *allergic* and *side effect* interchangeably, and that this informed how and what clinicians communicated to families.

How much information to communicate about adverse drug reactions?

Clinicians' accounts pointed to factors that led them to constrain or filter the information that they communicated to families about ADRs. These constraints reflected commonly accepted practice and 'rules of thumb' in communicating about medicines, as well as their judgements about the characteristics of the drug reaction, such as how severe, common or expected clinicians perceived an ADR to be. Clinicians also indicated that they constrained their prospective communication about ADRs in order to promote adherence to medicines: 'If we read out the list of all potential reactions to parents, paracetamol for example, no-one would take paracetamol' (23:D). A common theme reported by clinicians was the need

TABLE 36 Sample demographics

Professional role	Level/grade	Specialty	Length of time since registration
Doctor	Non-consultant	General paediatrics	5–10 years
Doctor	Non-consultant	General paediatrics	< 5 years
Pharmacist	Consultant	General paediatrics	Missing
Nurse	Missing	General paediatrics	Missing
Nurse	Staff nurse	Paediatric A&E	Missing
Nurse	Specialist nurse practitioner	Paediatric oncology	> 10 years
Pharmacist	Senior	General paediatrics	> 10 years
Doctor	Consultant	Paediatric neurology	> 10 years
Doctor	Non-consultant	Community paediatrics	5–10 years
Pharmacist	Senior	General paediatrics and research	> 10 years
Pharmacist	Senior	General paediatrics	5–10 years
Nurse	Sister	Missing	> 10 years
Nurse	Specialist nurse practitioner	Pain and sedation	> 10 years
Nurse	Student	General medicine	N/A
Doctor	Missing	Missing	Missing
Doctor	Consultant	Paediatric allergies	> 10 years
Doctor	Consultant	Paediatric nephrology	> 10 years
Doctor	Consultant	Paediatric neurology	> 10 years
Doctor	Consultant	Paediatric general surgeon	> 10 years
Doctor	Consultant	General paediatrics	> 10 years
Doctor	Consultant	Paediatric nephrology	> 10 years
Doctor	Consultant	Paediatric respiratory/cystic fibrosis/ allergy/asthma	> 10 years
Doctor	Consultant	Neonatal	> 10 years
Nurse	RSCN	Paediatric A&E	5–10 years
Nurse	Sister	Paediatric	> 10 years
Doctor	Missing	Paediatric A&E	> 10 years
Nurse	Sister	Paediatric	> 10 years
Doctor	Non-consultant	Paediatric A&E	< 5 years
Doctor	Consultant	Paediatric cardiology	> 10 years
Nurse	Staff nurse	General paediatrics	< 5 years
Doctor	Consultant	Paediatric anaesthetist	> 10 years
Nurse	Sister	Paediatric diabetes	> 10 years
Doctor	Consultant	Paediatric respiratory	> 10 years
Nurse	Missing	General paediatrics	> 10 years
Doctor	Consultant	General paediatrics	> 10 years
Doctor	Consultant	Paediatric anaesthetist	> 10 years

continued

TABLE 36 Sample demographics (*continued*)

Professional role	Level/grade	Specialty	Length of time since registration
Doctor	Consultant	Missing	Missing
Doctor	Consultant	Paediatric rheumatology	> 10 years
Doctor	Consultant	General paediatrics	> 10 years
Doctor	Consultant	Paediatric rheumatology	> 10 years
Doctor	Consultant	Oncology	Missing
Doctor	Consultant	Paediatric rheumatology	> 10 years

N/A, not applicable; RSCN, Registered Sick Children's Nurse.

to balance the information they gave to parents about ADRs with the need to avoid causing parents any unnecessary anxiety at the time a medicine was prescribed.

Who should discuss suspected adverse drug reactions with families

Clinicians' views about who should discuss ADRs with parents were varied, although most emphasised that the member of staff who was 'seeing the child' (09:D) or responsible for the child's care should also be the one who takes responsibility for communicating about ADRs. The clinical severity of a suspected ADR also influenced clinicians' views about who should discuss a suspected ADR with a family retrospectively. Clinicians thought that nurses were well placed to discuss relatively minor, expected and transient ADRs with families, whereas ADRs that were more serious required a discussion between doctors and parents.

Discussion

This is the first study to report clinicians' perceptions of discussing ADRs with parents. Similar to the findings from studies about other populations,[263–267] the clinicians in this study reported that communication about ADRs was generally important in clinical practice. However, in specific cases they described filtering the information that they discussed with families. Clinicians' views about what constituted an ADR also influenced their communication. When clinicians felt ADRs were mild, transient and expected they reported either not discussing these with families or constraining the information that they gave families. Evidence from our study of parents' experiences of ADRs reported in *Chapter 7* suggests that the level of parental anxiety and concern may relate more to suboptimal communication than to the perceived severity of an ADR. For example, parents of children with cancer were reassured and confident managing in suspected ADRs, even although the ADRs such children experienced could be severe. In contrast, parents of children who experienced relatively minor ADRs reported feeling confused, dismissed and abandoned.[29]

Limitations of the study

This study explored clinicians' accounts of discussing ADRs with families and may be subject to recall bias. In addition, during interviews, we found clinicians tended to drift into normative or idealised descriptions rather that giving specific accounts of what they did in practice when discussing ADRs with families. Because of this, it is difficult to establish to what extent clinicians' accounts reflect day-to-day practice.

Strengths of the study

- Wide range of participants, including doctors, pharmacists and nurses.[267]
- Multicentred (specialist and non-specialist).
- Everyday interactions on busy wards in which the relationship with doctors was mainly episodic discrete rather than long term.

Conclusion

Taken together, the findings of this chapter and *Chapter 7* point to a mismatch between clinicians' and parents' accounts of communication about ADRs. Although the clinicians spoke of the importance of communicating with parents about ADRs, parents pointed to deficiencies in clinicians' approaches to communication. Our initial analyses suggest that this mismatch may relate, at least in part, to decisions made by clinicians about what and when to discuss ADRs with parents. Some of the difficulties experienced by parents may also have their roots in the different ways in which ADR terminology is used by clinicians. Our preliminary results suggest that clinicians use terms that describe ADRs in ways that reflect whether they need to tell parents about the incident, or whether they need to modify clinical management. The same terms are used by pharmacovigilance specialists with a broader drug safety agenda. This variation in the use of terminology may be one explanation for the low rates of reports to spontaneous pharmacovigilance systems. Further analysis is needed to clarify the results of these findings.

Conclusion and future research directions

Adverse Drug Reactions In Children was conceived and developed in 2006, which was the first year of operation of the NIHR MCRN and shortly before the European Regulation on Better Medicines for Children became law in January 2007.[268] The programme was an ambitious one and aimed, for the first time, to investigate the whole spectrum from when and where ADRs in children occurred to the development of solutions to reduce the burden of ADRs. As originally conceived, the key component parts were:

- *Identification* To identify the nature of ADRs in children and the drugs causing these ADRs in hospitalised patients.
- *Quantification* To determine the proportion of hospital admissions related to ADRs, and those occurring in hospital; to estimate the whole burden associated with local, specialist regional and national paediatric care.
- *Evaluation* To evaluate the risk factors for ADRs, including OLUL use of medicines.
- *Intervention* To develop tools and guidelines for improving the recognition and ultimately reducing the burden of ADRs through enhanced prevention.

At the time of submission, two important studies had been conducted by Pirmohamed *et al.*[198] in the adult population. First, a prospective study of 18,820 admissions to two adult hospitals showed that 6.5% of the admissions were due to ADRs, which led to death in 0.15% of adult patients (equivalent to 5700 deaths per year in the UK) at a cost to the NHS of £500M.[198] A further study, examining ADRs occurring in 3728 patients in hospital, showed that 15.8% of adult patients experienced an ADR after admission to hospital.[59] Importantly, > 70% of ADRs, in both the hospital admission study and the inpatient study, were potentially avoidable. Although the burden of disease and use of drugs in children is considerably lower than in adults, the majority of drugs are not evaluated in children, leading to a much higher proportion of drugs being used OLUL, with the consequent safety concerns.[3,269] Previous studies addressing ADRs in children had considerable limitations. The populations studied were poorly described, heterogeneous and the methodologies used to determine ADRs were unsatisfactory or inadequately reported, making incidence estimates highly unreliable. Assessment of causality, severity and avoidability was generally absent or inadequate and there was no assessment of risk factors for ADRs in children. There was a clear rationale for the first two studies proposed in ADRIC, which would be conducted at the

largest children's hospital in Europe with 12,600 children admitted per year and long term, each study conducted over 1 year.

Similarly, although systematic reviews of studies to identify ADRs in children had been conducted previously, there was a need for a systematic review, which was fully comprehensive and went beyond attempting to describe the aggregate incidence of ADRs, to examine the nature of ADRs in children and the drugs associated with them, and the quality of the methods used to detect, assess and avoid these ADRs.

We anticipated detecting a proportion of ADRs, which had not been previously described and which were unknown or unpredictable, from the known pharmacology of the drug and thus, originally planned to develop screening tools to improve recognition of such ADRs and of known ADRs. However, during the course of the first two studies, such unknown ADRs were not detected and we did not feel that development of such a screening tool was appropriate. However, a number of other problems were identified by the early studies, which required the development of tools for the benefit of patients in the NHS. These included the need to develop entirely new, validated tools to assess causality and avoidability, which became a focus of the later studies in ADRIC. In addition, the interviews with families whose children had experienced an ADR highlighted a disturbing degree of distress associated with this and some concern from them about the ways in which this diagnosis had been communicated by their health professionals. An additional focus of the later parts of the programme was to understand this better by conducting interviews with clinicians about how they communicate ADRs to families and to develop information leaflets for clinicians and families to help guide these discussions.

The prevalence of ADRs associated with admission to hospital was around 2.9%, lower than reported in a similar study in adults (6.5%).[198] When we assessed the origin of the prescriptions for the drugs responsible, the majority originated either directly from hospital or from protocols led by hospital practitioners. This also differed from experience in adults. Although many of the ADRs were predicted and the families were expecting them, for example in the children being treated with immunosuppressive therapy, other signals were more disturbing. These included the cases of respiratory depression associated with drugs used to treat status epilepticus and bleeding post tonsillectomy in children treated perioperatively with corticosteroids to prevent vomiting.

The most surprising findings were from the study of ADRs in hospital. First, we found that the incidence of ADRs in children is much greater than in adults. We included probable and definite ADRs, which gave an incidence of 17.7%; a comparable study, published by our group in adults,[59] reported an incidence of 14.7% but this included ADRs classified as definite, probable or possible. If we included possible ADRs in our numerator, the comparable figure is that > 25% children in hospital experience an ADR. We also observed that the risk of experiencing an ADR was increased over six times in children who had a general anaesthetic during their admission and over half of the drugs implicated in all ADRs were used either perianaesthetic or post anaesthetic. These drug groups have been under-represented in previous studies and our findings have important implications for all clinicians concerned with the perioperative and postoperative management of children, in particular in view of the recent moves to ambulatory surgery in the UK and elsewhere.

The signals in studies 1 and 2 (see *Chapters 2 and 3*) of ADRs associated with drugs used during and after surgery are the most novel and concerning findings of this programme. In study 2, we were able to include only children who had been in hospital for > 48 hours. Most children who have surgery are in hospital for shorter periods than this and a very high proportion are discharged on the day of surgery. The anaesthetic care of children receiving their surgery as 'day cases' is adapted to ensure adequate control of pain and vomiting in the home environment. One example of this is use of a single dose of a corticosteroid to control vomiting over the ensuing 24 hours period, which in turn may contribute to postoperative bleeding following procedures such as tonsillectomy. Our study has highlighted a need to understand better the morbidities associated with anaesthesia and surgery in children.

The nested case–control study found that drugs used OLUL were more likely to be implicated in an ADR than authorised medicines. This again highlights the implications for how drugs are used in children. Furthermore, we observed that drugs licensed for use in children but given to a child below the minimum age or weight had the greatest risk of being implicated in an ADR, emphasising the importance of studies to provide pharmacokinetic data in children of different ages.

The LCAT is now available and is being used in research and clinical practice. Further work is being conducted to assess, by a randomised controlled trial, whether or not a short training package in the use of the tool – available online – enhances this assessment. We believe that the LCAT is the best tool currently available for assessment of ADR causality. Importantly, it has been developed, not only for children, but also for assessment of ADRs in adults. The Liverpool AAT is at an earlier stage of development, but we have learnt much from the development of the LCAT, in particular the visual algorithm is user friendly and allows a more rapid assessment. By providing a simple tool that can be used by all clinicians, the ADRIC programme has made an important contribution to the future assessment of ADRs. Like LCAT, the Liverpool AAT has been developed to provide this assessment of ADRs in both children and adults.

We have learnt much during the course of this programme, about the problems in communicating ADRs to children and families. The materials produced to aid these discussions have either undergone full assessment and user testing (the information leaflet to inform clinicians' discussions) or will shortly do so, and we will make these leaflets available via the internet. More could be done to provide information to young people, for example via smartphone apps.

The ADRIC programme of research has highlighted a number of important implications for future research. The end of the ADRIC programme symposium included a workshop on the research implications of the burden of ADRs in paediatrics, and the key research questions from this are highlighted in *Appendix 7*. Following discussion within the ADRIC Steering Group, the recommendations for future research are prioritised below:

1. *Risk–benefit evaluation* There is a need to explore the balance of drug safety compared with drug efficacy and, potentially, there has been too much focus on safety and monitoring at the expense of potential benefit. More research is necessary to assess the values that parents and children place on the use of different medicines and the risks that they will find acceptable within these contexts. Indeed, the conceptual framework within which the balance between safety and efficacy of medicines and individual drugs presents is an important area for further research, and poses the question whether the weighting between efficacious outcomes and safety of patients is appropriately calibrated. This subject is currently less understood in children than adults. There is a clear need for innovative means to interrogate and evaluate the risk and benefit associated with use of drugs in children. Methodological developments mean that this theme could be rigorously addressed, for example through the use of discrete choice experiments incorporating the views of parents, adolescents and younger children, regulators and industry. Important questions also include how do the decision-making differences between children and parents for particular drugs differ, and how the individual's perspective may vary between the younger child and adolescent.
2. *Evaluation of ADRIC outputs* Two key ADRIC outputs are the LCAT and the Liverpool AAT. Although these tools are at different stages of development there is potential for further research with both. Following validation, the Liverpool AAT will be used to assess the avoidability of the ADRIC admissions study cases and the results will be compared with the Hallas[54] assessments carried out in *Chapter 2*. Similarly, for the inpatient study cases we will aim to assess a proportion of the cases using the new Liverpool AAT. This will help us to identify potentially avoidable ADRs. There is the potential to evaluate the use of both tools in a variety of settings including other paediatric and adult hospitals and clinical trial AE reporting. The applications of these tools in clinical practice and education could be explored. For example, a learning package which incorporates the LCAT has been developed in order to explore whether or not it can be used in this context to improve the causality assessment skills of clinicians.

3. *Dose optimisation* There is a clear need to reduce the burden of ADRs in children, and one component strategy is to optimise dosing in children and young people. A clear first step will be a comprehensive review of the literature to identify how extrapolations from adults to children are achieved, which methods have or have not been used, and an evaluation of the utility of those methods that have been used. The findings will help to inform a gold standard practice for extrapolation, which can be targeted towards drugs identified as high risk within ADRIC and other relevant studies, and in combination with alongside pharmacokinetic/pharmacodynamic (PK/PD) evaluation studies. Alongside studies of risk–benefit evaluation, enhanced methodologies for extrapolation would make a significant contribution to the potential of adaptive licensing within the regulatory framework for drugs in children.
4. *Enhanced ADR monitoring associated with surgery and anaesthesia in children* The signals in studies 1 and 2 (see *Chapters 2* and *3*) of ADRs associated with drugs used during and after surgery are the most novel and concerning findings of this programme, and have important implications for further research. Our study has highlighted a need to understand better the morbidities associated with anaesthesia and surgery in children. This will require a study that can follow up children in the community and in the home setting to assess the incidence of ADRs following surgery, and compare these according to the anaesthetic and postoperative drugs, surgical procedures and their comorbidities. Such an observational study could lead to an assessment of which children should be discharged on the day of surgery and, for those who are, randomised controlled trials will be able to assess the most appropriate treatment regimens to prevent pain, vomiting and other postoperative complications.
5. *Evaluation of strategies for communication about ADRs* We identified that families have unmet information needs following a suspected ADR in a child or young person and responded to this through the development of a series of leaflets. Further research should focus on the development of communication strategies, supported by the use of leaflets and other media. The reasons for the mismatch in the perceptions of families and clinicians about how ADRs are communicated should be investigated, inclusive of the uncertainties around terminology. The evaluation of any strategies developed should take into consideration how improvements in communication have a direct impact on the individuals involved (e.g. improved health outcomes for the patient) as well as their indirect impacts, for example, improve rates of ADR reporting by families and clinicians.
6. *Quantification of ADRs in children in other settings* The ADRIC programme generated rich data in a number of settings relevant to paediatric practice, but there remain significant gaps in the knowledge of the quantification of ADRs in children in a variety of settings. In addition to understanding the burden of ADRs in particular settings, such as theatres and critical care, and populations (most notably neonates), there is also a need to undertake comprehensive studies of the burden and impact of long-term side effects, which was not an objective within the ADRIC programme.

Finally, ADRIC has provided an important focus on this important and neglected area of paediatric medicine. It has provided the most comprehensive assessment to date of the size and nature of this problem in children presenting to, and cared for in, hospital, and the outputs that have resulted will improve the management and understanding of ADRs in children and adults within the NHS.

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Contributions of authors

Rosalind L Smyth (Head, Institute of Child Health, University of Liverpool) Conceived and designed the studies, supervised all aspects of the conduct of the studies and analysis of the data, planned, led and contributed to all aspects of writing of the report.

Matthew Peak (Director of Research, Alder Hey Children's NHS Foundation Trust) Conceived and designed the experiments and contributed to the writing of this report.

Mark A Turner (Head of Research and Development, Liverpool Women's Hospital) Conceived and designed the experiments, performed the experiments, analysed the data and contributed to the writing of this report.

Anthony J Nunn (Honorary Professor, University of Liverpool) Conceived and designed the experiments, performed the experiments and contributed to the writing of this report.

Paula R Williamson (Head of Biostatistics, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

Bridget Young (Professor and Director of Communication Skills, University of Liverpool) Conceived and designed the experiments, analysed the data and contributed to the writing of this report.

Janine Arnott (Research Associate, University of Liverpool) Performed the experiments, analysed the data and contributed to the writing of this report.

Jennifer R Bellis (Research Pharmacist, Alder Hey Children's NHS Foundation Trust) Conceived and designed the experiments, performed the experiments, analysed the data and contributed to the writing of this report.

Kim A Bird (Research Nurse, Alder Hey Children's NHS Foundation Trust) Conceived and designed the experiments, performed the experiments and contributed to the writing of this report.

Louise E Bracken (Research Pharmacist, Alder Hey Children's NHS Foundation Trust) Performed the experiments, analysed the data and contributed to the writing of this report.

Elizabeth J Conroy (Research Statistician, University of Liverpool) Analysed the data and contributed to the writing of this report.

Lynne Cresswell (Research Statistician, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

Jennifer C Duncan (Research Pharmacist, Alder Hey Children's NHS Foundation Trust) Performed the experiments.

Ruairi M Gallagher (Clinical Research Fellow, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

Elizabeth Gargon (Assistant Systematic Reviewer, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

Hannah Hesselgreaves (Research Associate, University of Liverpool) Performed the experiments.

Jamie J Kirkham (Research Statistician, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

Helena Mannix (Research Nurse, Alder Hey Children's NHS Foundation Trust) Performed the experiments.

Rebecca MD Smyth (Systematic Reviewer, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

Signe Thiesen (Clinical Research Fellow, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

Munir Pirmohamed (Head of the Department of Molecular and Clinical Pharmacology, University of Liverpool) Conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools and contributed to the writing of this report.

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Appendix 1 Databases searched

Database	Period covered
MEDLINE via Ovid	1950 to October 2010
EMBASE via NHS Evidence Health Information Resource	1980 to October 2010
CINAHL via NHS Evidence Health Information Resources	1981 to October 2010
Science Citation Index	1990 to October 2010
Biological Abstracts	1926 to October 2010
International Pharmaceutical Abstracts	1970 to October 2010
Toxicology Literature Online – USA National Library of Medicine	Searched October 2010
Iowa Drug Information Service	1966 to October 2010
Allied and Complementary Medicine Database	1985 to October 2010
General Practice Research Database	1987 to October 2010
Database of Systematic Reviews (The Cochrane Library)	Searched October 2010
Database of Abstracts of Reviews of Effects	Searched October 2010
Health Technology Assessment programme	Searched October 2010
National Institutes of Health	Searched October 2010
EMA	Searched October 2010
US FDA	Searched October 2010
ClinicalTrials.gov	Searched October 2010
Agency for Healthcare Research and Quality	Searched October 2010
Incidence and Prevalence	Searched November 2010

Appendix 2 Search strategy

First concept: general terms used to describe the participants – infants and children

1. exp Child/
2. exp Adolescent/
3. (young adj (person$ or people or adult$ or individual$ or women or woman or men or man)).ti,ab.
4. (child$ or adolescen$ or kid or kids or youth$ or youngster$ or minor or minors or teen$ or juvenile$ or student$ or pupil$ or boy$ or girl$).ti,ab.
5. exp Students/
6. Puberty/
7. Pediatrics/
8. (infan$ or newborn$ or new born$ or baby$ or babies or child$ or schoolchild$ or kid or kids or toddler$ or adoles$ or teen$ or boy$ or girl$ or minor$ or juvenil$ or youth$ or kindergar$ or nurser$ or puber$ or prepuber$ or pre puber$ or pubescen$ or prepubescen$ or pre pubescen$ or pediatric$ or paediatric$ or schoolage$).ti,ab.

Second concept: including terms relating to adverse drug reactions

9. side effect$.ti,ab.
10. (drug induced or drug related or drug safety).ti,ab.
11. tolerability.ti,ab.
12. toxicity.ti,ab.
13. Harm$.ti,ab.
14. adrs.ti,ab.
15. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
16. (toxic adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
17. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp drug toxicity/ or exp abnormalities, drug induced/ or exp drug hypersensitivity/

Third concept: terms relating to the occurrence of adverse drug reactions

18. incidence/ or prevalence/
19. (incidence$ or prevalence$ or occurrence or admission$ or admitted or visit$ or hospitalisation or hospitalised or hospitalization or hospitalized).ti,ab.

Fourth concept: terms that encompass the intervention

20. (drug$ or pharmaceutical$ or medicin$).ti,ab.
21. Pharmaceutical Preparations/
22. (herbal$ or plant or plants or herb or herbs or aromatherap$ or aroma therap$).ti,ab.
23. Medicine, Chinese Traditional/ or Plant Preparations/ or Plants, Medicinal/ or Plant Extracts/ or Drugs, Chinese Herbal/
24. Aromatherapy/

Fifth concept: study design

25. Health Care Surveys/
26. Retrospective Studies/
27. Prospective Studies/
28. Cohort Studies/
29. Observational stud$.ti,ab.
30. (prospectiv$ adj3 review$).ti,ab.
31. (prospectiv$ adj3 stud$).ti,ab.
32. (retrospectiv$ adj3 stud$).ti,ab.
33. (retrospectiv$ adj3 review$).ti,ab.
34. population-based stud$.ti,ab.
35. cohort stud$.ti,ab.
36. incidence stud$.ti,ab.
37. Sn.fs.
38. Ep.fs.
39. monitor$.ti,ab.
40. surveillance.ti,ab.

Appendix 3 Study characteristics

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
ADRIC	UK	12 months Prospective	Causing admission, large tertiary – paediatric hospital	Children	Naranjo LCAT	Hallas 1990[54]
Agarwal (2010)[164]	USA	4 months Retrospective	In hospital, PICU	Children	Not reported	ADEs assessed, non-preventable = ADR. Determined by individual sites based on local interpretations; in general was based on the premise that the ADE may have been avoidable, given the appropriate implementation of evidence-based medicine and/or appropriate use of available services
Al-Olah (2008)[147]	Saudi Arabia	28 days Prospective	Causing admission, emergency department	Children and adults	Naranjo	Definite preventable and definite non-preventable defined as three evaluators in agreement; possible preventable and possible non-preventable – two in agreement
Al-Tajir (2005)[109]	United Arab Emirates	12 months Prospective	Causing admission, in hospital and in community, general paediatric ward	Children and adults	Naranjo score algorithm	Schumock 1992[44]
Baniasadi (2008)[110]	Iran	12 months Prospective	Causing admission and in hospital, multidisciplinary hospital	Children and adults	Naranjo score algorithm	Schumock 1992[44]
Barstow (1988)[156]	USA	4 months Prospective	Paediatric units	Children and adults	Not reported	Not reported
Benkirane (2009)[163]	Morocco	3 months Prospective	In hospital, intensive care unit	Children and adults	Not reported	ADEs assessed, non-preventable = ADR
Bordet (2001)[142]	France	18 months Prospective	Causing admission and in hospital General paediatric ward	Children and adults	Begaud 1985[270]	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Buajordet (2002)[45]	Norway	5 months Prospective	Causing admission, in hospital and in community, general paediatric ward	Children	Naranjo score algorithm	Not reported
Buckley (2007)[162]	USA	12 days Prospective	In hospital, PICU	Children	Not reported	ADEs assessed using Bates 1995,[271] non-preventable ADE = ADR
Calderon-Ospina (2008)[170]	Colombia	12 days Prospective	In community, A&E visits	Children and adults	WHO	Schumock 1992[44]
Campbell (1978)[187]	USA	48 months Prospective	In community, medical care contacts	Children and adults	Not reported	Not reported
Choonara (1984)[111]	UK	6 months Prospective	In hospital, general paediatric ward	Children	Seidl 1966[150]	Six avoidable because three doses prescribed too high, one treatment not necessary, two applications of pharmacological principles would have prevented reactions
Cirko-Begovic (1989)[124]	Croatia	3 months Prospective	In community, general paediatric outpatient unit	Children	Hutchinson 1979[272]	Not reported
Classen (1991)[151]	USA	18 months Prospective	Causing admission, acute care referral hospital	Children and adults	Naranjo score algorithm	Not reported
Dennehy (1996)[171]	USA	1 month Retrospective	In community, emergency department	Children and adults	Strand 1990[273]	Considered preventable if they could have been avoided through appropriate prescribing, outpatient monitoring or patient compliance
Dharnidharka (1993)[112]	India	18 months Prospective	In hospital, paediatric unit	Children	Stephens 1998[274]	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Doomra (2001)[168]	India	15 months Prospective	In hospital and in community General paediatric outpatient unit	Children and adults	Naranjo score algorithm	Not reported
dos Santos (2009)[114]	Brazil	2 years Prospective	In hospital, general paediatric ward	Children	Naranjo	Not reported
dos Santos (2006)[113]	Brazil	5 months Prospective	In hospital, general paediatric ward	Children	WHO	Not reported
Doval (1981)[172]	India	Not reported Prospective	In community, outpatient department	Children and adults	Not reported	Not reported
Duczmal (2006)[105]	Poland	Not reported Retrospective	Causing admission, paediatric department	Children	Naranjo	Not reported
Easton (1998)[41]	Australia	56 days Prospective	Causing admission, medical ward	Children	Naranjo score algorithm	Schumock 1992[44]
Easton (2004)[102]	Australia	22 weeks Prospective	Causing admission, specialist paediatric teaching hospital and general regional teaching hospital	Children	Dartnell 1996[275]	Schumock 1992[44]
Easton-Carter (2003)[115]	Australia	18 weeks Prospective	In community, emergency department	Children	Dartnell 1996[275]	Schumock 1992[44]
Easton-Carter (2003)[125]	Australia	39 weeks Prospective and retrospective	In hospital, general paediatric ward	Children	Naranjo score algorithm	Schumock 1992[44]

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Farrokhi (2006)[92]	Iran	5 months Prospective	In hospital, paediatric surgery	Children	Not reported	Not reported
Fattahi (2005)[107]	Iran	5 months Prospective	Causing admission and in hospital Paediatric disease referral centre, paediatric infectious diseases department	Children	WHO	Not reported
Fincham (1989)[152]	USA	Not reported Not reported	Causing admission and in hospital; hospital and private practice	Children and adults	Not reported	Not reported
Gallagher 2011[20]	UK	2 weeks Prospective	Causing admission, large tertiary – paediatric hospital	Children	Naranjo	Hallas 1990[54]
Ganeva 2007[106]	Bulgaria	5 years Prospective	Causing admission, dermatology and venereology	Children and adults	Naranjo score algorithm	Not reported
Gill (1995)[108]	UK	28 months Prospective	Causing admission and in hospital, PICU	Children	Kramer 1979[276]	Not reported
Gonzalez-Martin 1998[116]	Chile	1 year Prospective	In hospital, paediatric wards	Children	Naranjo score algorithm	Naranjo 1989[277]
Haffner (2005)[134]	Germany	91 days; 80 days; overlap of 52 days Prospective	Causing admission and in hospital ICU, general paediatric ward, department of paediatrics	Children	WHO	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Hewitt (1995)[138]	Australia	4 months Retrospective	Causing admission, general teaching hospital	Children and adults	Not reported	Not reported
Horen (2002)[77]	France	Not reported Prospective	In community, office-based practice	Children	Begaud 1985[270]	Not reported
Imbs (1999)[167]	France	1 day Prospective	In hospital, departments of medicine, surgery and geriatrics	Children and adults	Two members of the pharmacovigilance team validated each ADR	Not reported
Impicciatore (2002)[48]	Italy	9 months Prospective	Causing admission and in hospital, paediatric unit	Children	WHO – confirmed by author	Not reported
Ives (1987)[139]	USA	1 year Retrospective	Causing admission, family medicine inpatient service at hospital	Children and adults	Naranjo score algorithm	Not reported
Jha (2007)[117]	Nepal	5 months Prospective	In hospital, general paediatric ward	Children and adults	Naranjo score algorithm	Not reported
Jonville-Bera (2002)[37]	France	1 week Prospective	Causing admission, in hospital and in community, paediatric wards, A&E, private paediatricians	Children	Begaud 1985[270]	Not reported
Jose and Rao (2006)[155]	India	12 months Prospective	Causing admission, in hospital and in community, various departments (not stated)	Children and adults	Naranjo score algorithm	Lau 2003[278]
Juntti-Patinen (2006)[126]	Finland	6 months Prospective	In community, emergency department visits	Children and adults	WHO	Not reported
Kaushal (2001)[157]	USA	36 days Prospective	In hospital, general paediatric ward	Children and adults	Naranjo score algorithm	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Kaushal (2007)[127] – two citations (Zandieh 2008[279])	USA	2 month blocks Prospective	In community, office-based practice	Children	Not reported	Not reported
Kramer (1985)[78]	Canada	1 year Prospective	In community, private group practice	Children	Kramer 1979[276]	Highly preventable – realistic non-drug alternative available Probably preventable – safer alternative drug available or lower dosage/possibly preventable – dose might have been modified/unpreventable – would not have changed the choice or dose of drug
Kunac – two citations (2008,[280] 2009[143])	New Zealand	12 weeks Prospective	Causing admission, paediatric	Children	Naranjo score algorithm	Schumock 1992[44]
Kushwaha (1994)[136]	India	2 years Prospective	In community, department of paediatrics	Children	Not reported	Not reported
Lamabadusuriya (2003)[47]	Sri Lanka	11 months Prospective	Causing admission, medical ward	Children	Naranjo score algorithm	Not reported
Le – two citations (2005,[144] 2006[36])	USA	10 years Retrospective	Causing admission and in hospital, children's hospital	Children	Definite; probable; possible; conditional	Not reported
Leach (1998)[118]	UK	14 months Prospective	In hospital, regional ICU, a general medical ward, cardiac ICU and cardiac medical ward	Children	Naranjo 1981,[23] Karch 1977,[281] and Kramer 1979[276]	Not reported
Lemer (2009)[182]	USA	10 months Prospective	In community, attending GP	Children	ADEs assessed, non-preventable = ADR	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Lewinski (2010)[185]	Germany	3 months Prospective	In community, community pharmacy	Children and adults	Strand 1990[273]	Not reported
Maistrello (1999)[120]	Italy	6 months Prospective	In hospital, emergency ward, infectivology ward, general paediatric ward, pneumology ward	Children	Not reported	Not reported
Major (1998)[103]	Lebanon	6 months Prospective	Causing admission, medical, paediatric	Children and adults	Naranjo score algorithm	Not reported
Martinez-Mir – two citations (1996,[42] 1999[121])	Spain	105 days; and 99 days Prospective	Causing admission and in hospital Paediatric hospital; paediatric isolation ward, lactants B ward	Children	Spanish Drug Surveillance Scheme (Meyboom 1992)[282]	Not reported
Martys (1979)[181]	UK	2 years Prospective	In community, general practice	Children and adults	Not reported	Not reported
McDonnell (2002)[140]	USA	11 months Retrospective	Causing admission, university affiliated teaching hospital	Children and adults	Naranjo score algorithm	Adapted from Schumock 1992[44]
McKenzie (1973)[137]	USA	8 months Prospective	Causing admission and in hospital University affiliated teaching hospital, paediatric medicine services	Children	Definite – directly attributable to drug Probable – a known direct relationship Possible – nebulous aspects that could be explained by the illness; no reference provided	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
McKenzie (1976)[32]	USA	3 years Prospective	Causing admission and in hospital University affiliated teaching hospital	Children	Definite – directly attributable to drug Probable – a known direct relationship Possible – temporally related to drug; no reference provided	Not reported
Menniti-Ippolito (2000)[128]	Italy	1 year Prospective	In community, family paediatricians	Children	Not reported	Not reported
Miller (2006)[183]	Australia	10 months Prospective	In community, general practice	Children and adults	Not reported	Thomas 2000[283]
Mitchell (1979)[119]	USA	4 years Prospective	In hospital, general medical, oncology, NICU	Children	Not reported	Not reported
Mitchell (1988)[33] – two citations (Lacouture 1986)[284]	USA	11 years Prospective	Causing admission, teaching and community hospitals	Children	Definite – clear implicated drug caused the reaction Possible – other factors might have caused the reaction	Not reported
Mulroy (1973)[184]	UK	1 year Prospective	In community, general practice	Children and adults	Not reported	Not reported
Munoz (1998)[131]	Spain	25 months Prospective	In community, emergency room	Children	Karch 1977[281]	Not reported
Neubert (2004)[75]	Germany	8 months Prospective	In hospital, paediatric isolation ward	Children	Naranjo score algorithm	Schumock 1992[44]

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Neubert (2006)[165]	Germany	6 months Prospective	In hospital, paediatric isolation ward	Children and adults	Naranjo score algorithm	Not reported
Oshikoya (2007)[46]	Nigeria	3 years Both	Causing admission and in hospital General paediatric ward	Children	Jones 1982[285]	Done but no reference provided
Otero Lopez (1999)[178]	Spain	6 months Prospective	In community, emergency department	Children and adults	Karch-Lasagna modified algorithm that uses the Spanish Pharmacovigilance System	Schumock 1992[44]
Phan (2010)[169]	USA	5 months Retrospective	In community, emergency department	Children	Naranjo	Not reported
Planchamp (2009)[129]	France	6 months Prospective	In community, emergency department	Children	Begaud 1985[270]	Olivier 2005[216]
Pouyanne (2000)[146]	France	14 days Prospective	Causing admission, medical, public hospital	Children and adults	Not reported	Not reported
Prince (1992)[173]	USA	4 months Retrospective	In community, emergency department	Children and adults	Michel 1986[286]	Not reported
Ramesh (2003)[153]	India	7 months Prospective	Causing admission and in hospital, memorial hospital	Children and adults	WHO	Not reported
Rebelo Gomes (2008)[174]	Portugal	4 months Prospective	In community, general paediatric outpatient unit	Children	Not reported	Not reported
Santos (2000)[104,108] – two citations	Philippines	3 months Prospective	Causing admission, paediatric unit	Children	Naranjo score algorithm	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Sanz (1987)[130]	Spain	6 months Prospective	In community, general practice, outpatient paediatricians	Children	Karch 1977,[281] Venulet 1986,[287] Dangoumau 1978,[288] Kramer 1979,[276] Naranjo 1981[23] and Blanc 1979[289]	Not reported
Schneeweiss (2002)[148]	Germany	2 years and 5 months Prospective	Causing admission, internal medicine or emergency departments of all hospitals	Children and adults	Begaud 1985[270]	Not reported
Seidl (1966)[150]	USA	3 months Prospective	Causing admission and in hospital, general medical service	Children and adults	Documented confirmatory rechallenge test or a lab result indicating the unwanted effect. Probable – improvement or cessation of symptoms upon withdrawal of drug	Not reported
Sharma (2007)[175]	India	4 months Prospective	In community, medicine outpatient department	Children and adults	WHO	Not reported
Shockrollah (2009)[122]	Iran	3 months Prospective	In hospital, ICU	Children	Not reported	Not reported
Smidt and McQueen – two citations (1972,[154] 1973[290])	New Zealand	6 months Prospective	Causing admission and in hospital, general hospital	Children and adults	Not reported	Not reported
Smith (1997)[179]	USA	1 month Retrospective	In community, emergency department	Children and adults	Not reported	Not reported
Speranza (2008)[135]	Uruguay	1 week Prospective	Causing admission and in hospital Paediatric hospital	Children	Karch 1977[281]	Not reported
Stoukides (1993)[176]	USA	6 months Retrospective	In community, emergency department	Children and adults	Not reported	Not reported

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Takata (2008)[158]	USA	3 months Retrospective	In hospital, paediatric hospitals	Children	Not reported	Assessed but no detail provided, non-preventable ADE = ADR
Takata (2008)[159]	USA	6 months Prospective	In hospital, paediatric teaching hospitals	Children	Naranjo score algorithm	Assessed but no detail provided, non-preventable ADE = ADR
Telechea (2010)[a]	Uruguay	2 months Prospective	In hospital, ICU	Children	Karch 1977[281]	Not reported
Turner (1999)[3]	UK	13 weeks Prospective	In hospital, surgical ward, medical ward, neonatal surgical ward, cardiac ICU, general paediatric intensive care units	Children	Choonara 1984[134]	Not reported
Uppal (2000)[160]	India	3 years Prospective	In hospital, general paediatric ward	Children and adults	Karch 1977[281]	Not reported
Valladares (1992)[177]	Spain	4 years Prospective	In community, ear, nose and throat outpatient unit	Children and adults	Karch 1977[281]	Not reported
Van der Hooft (2006)[141]	Netherlands	1 year Retrospective	Causing admission, academic and general hospitals	Children and adults	Not reported	Not reported
Van der Hooft (2008)[149]	Netherlands	1 year Retrospective	Causing admission and in hospital, Integrated Primary Care Information Database	Children and adults	WHO	Hallas 1990[54]
Vazquez de la Villa (1989)[123]	Spain	12 months Prospective	In hospital, paediatrics service	Children	Naranjo score algorithm	Not reported
Wang (2007)[161]	USA	3 months Prospective	In hospital, ICU, general paediatric ward, NICU	Children	Not reported	ADEs assessed, non-preventable = ADR

Study	Country	Study duration/ design	Clinical setting	Population	Causality assessment	Avoidability assessment
Weiss (2002)[166]	Germany	8 months Prospective	In hospital, paediatric isolation ward	Children	Adapted Naranjo 1981,[23] Evans 1994[291]	Avoidable or tolerated – toxicity, drug interactions, secondary effects Unavoidable – idiosyncratic or allergic reactions and intolerance No reference
Whyte (1977)[145]	UK	10 months Prospective	In hospital, causing admission Paediatric unit	Children	Not reported	Not reported
Woods (1987)[132]	UK	26 weeks Prospective	In community, infant care and educational establishments	Children	Not reported	Not reported
Yosselson-Superstine (1982)[43]	Israel	7 months Prospective	Causing admission, general paediatric ward	Children	Seidl 1965,[292] Seidl 1966,[127] McKenzie 1973,[115] McKenzie 1976,[32] Whyte 1977[112]	Not reported
Zahroui (2010)[133]	Morocco	7 months Prospective	In community, visits to A&E	Children	Not reported	Not reported

GP, general practice; ICU, intensive care unit.
a Telechea M, Lucas N, Nanni G, Menchaca A. Importance of drug-induced pathology in an intensive care unit of children. 2010, unpublished data.

Appendix 4 Liverpool Avoidability Assessment Tool glossary

Appropriate management plan(s) This could include *any* local, national or international guideline available, for example hospital guidelines, NICE, Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society (BTS), the British Society for Paediatric and Adolescent Rheumatology (BSPAR), World Health Organization (WHO) or the National Guideline Clearinghouse (NGC). For example, in the case of postoperative nausea and vomiting, appropriate management plans could include Alder Hey Children's NHS Trust guideline on postoperative nausea and vomiting, or the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA) guideline on the prevention of postoperative vomiting in children.

Known preventative strategies Prophylactic or concomitant medicines or any necessary monitoring.

Information about the ADR and its avoidance: does the management plan mention any preventative measures to be taken to avoid the ADR, including medicines to be given prophylactically or concomitantly or any necessary monitoring, etc. (electrolytes, full blood count or blood pressure)? A management plan may or may not contain information regarding prevention of ADRs but more often than not they contain no information regarding the prevention of ADRs.

Other information sources Examples include the *British National Formulary for Children* (BNFC), SmPC, advice from colleagues, history from the parents/patients or information from a journal article, etc.

Unassessable The case could not be assessed owing to lack of information about the case and/or treatment or conflicting information.

Not avoidable The ADR was unavoidable based on the information available at the time of the reaction. There are four scenarios that lead to an ADR being categorised as 'not avoidable':

- If the reaction was unpredictable and there was no known history of previous similar reaction or allergy to the drug.
- If there was an appropriate management plan with information about the ADR and its avoidance and it was followed.
- If there was no appropriate management plan, with information about the ADR and its avoidance available, there were no other information sources available to consult and there was no information in the history available for prevention of the ADR.
- If there was no appropriate management plan, with information about the ADR and its avoidance available but there were other information sources available to consult or information in the history available for prevention of the ADR and appropriate action was taken to avoid the ADR.

Possibly avoidable There was no appropriate management plan available to follow but there were other information sources or information in the history available to prevent the ADR and these were not followed.

Definitely avoidable There were known preventative strategies or an appropriate management plan was available with information about the avoidance of the ADR but the strategies and or management plan were not followed.

Guide to questions in the avoidability tool

Is there sufficient information available about the case and the treatment to allow assessment?

If the answer is 'yes' then there is sufficient information available about the case and the treatment, and the assessor can proceed to the next question; if the answer is 'no', either due to lack of information or conflicting information, the case becomes 'unassessable'.

Was the reaction predictable on the basis of the known pharmacology of the drug(s)?

This question relates to whether the ADR is predictable on the basis of known pharmacology, as there is lots of unknown pharmacology. If the answer is 'no' then you proceed to the question asking if there was a known history of a previous similar reaction. If the answer is 'yes' then you proceed down the left-hand side of the flow diagram, which asks questions regarding availability of appropriate management plans and if they were followed.

Was there a known history of allergy or previous similar reaction to the drug?

The purpose of this question is to establish if the patient has experienced a similar reaction in the past, and answering 'no' to the question takes you to 'not avoidable', as an unpredictable reaction where the patient had no previous history of occurrence means that the reaction could not have been prevented on this occasion. In theory this reaction could be avoided in the future.

Were other information sources, or information in the history available for prevention of the adverse drug reaction that could have been followed?

This is an important question to establish if there was something else that could have been done to avoid the ADR either by consulting a more senior clinician for advice or looking in other reference source examples including (but not limited to) BNFC, SmPC, consulting the parents or conducting a quick search for journal article, etc. If the answer is 'no' to this question then the reaction is categorised as 'not avoidable'; if the answer is 'yes' then you proceed to the next question.

Was appropriate action taken to avoid the adverse drug reaction?

This question allows the reaction to be categorised as 'not avoidable' if appropriate action was taken to avoid the ADR but it occurred anyway, and in cases for which other information sources were available but the appropriate action was not taken, i.e. answering 'no' to the question, the ADR is categorised as 'possibly avoidable'.

Were there known preventative strategies and/or appropriate management plan(s) available with information about the adverse drug reaction and its avoidance?

This question is designed to establish if there was an appropriate treatment guideline available. This could include *any* local, national or international guideline available: for example hospital guidelines, NICE, SIGN, BTS, WHO, NGC. If there was information available regarding the management of the condition but the guidance made no reference to the ADR or its prevention then by answering 'no' to the question you are directed to answer the question about whether other information sources were available. This allows for the application of other measures. If the answer is 'yes' to this question then you proceed to the next question below.

Were the strategies and/or management plan(s) followed?

If there was an appropriate management plan available and it contained information about the avoidance of the ADR but it was not followed then this would mean that answering 'no' to this question would categorise the ADR as 'definitely avoidable'; if the answer is 'yes' that the drug(s) was used in accordance with the management plan then the ADR is categorised as 'not avoidable'.

Appendix 5 Participant characteristics

ID[a]	Child age (years)[b]	Child gender	Ranked IMD scores[c]	Type of drug associated with suspected ADR	Body system affected by suspected ADR
AP1	3–5	Female	403	Antibiotics	Skin and mucous membranes
AP2/AC2	12+	Male	10,787	NSAID	Musculoskeletal
AP3	3–5	Male	306	Corticosteroids, cytotoxics	Haematological
AP4/AC4	12+	Female	2482	Cytotoxics	Gastrointestinal
AP5	0–2	Female	12,821	Antibiotics	Skin and mucous membranes
AP6	0–2	Male	1574	Cytotoxics	Haematological
AP7	0–2	Male	15,485	Corticosteroids, cytotoxics	Haematological, immune system
AP8	3–5	Female	383	Vaccines	Skin and mucous membrane
AP9/AC9	6–11	Male	6091	Corticosteroids	Immune
AP10	0–2	Female	12,223	Vaccines	Immune/infection
AP11	6–11	Female	16,778	Antibiotics	Skin and mucous membranes
AP12	3–5	Female	271	Antiepileptic	Hepatic
AP13	0–2	Male	NA	Antibiotics	Skin and mucous membranes
AP14/AC14	6–11	Male	19,865	Opioid analgesia	Nervous
AP15/AC15	12+	Female	24,299	Opioid analgesia plus other postoperative analgesia	Nervous
AP16	0–2	Female	24,447	Opioid analgesia	Skin and mucous membranes
AP17/AC17	12+	Male	108	Opioid analgesia	Gastrointestinal
AP18	12+	Male	NA	Antibiotics	Manifestation was flushing of skin but underlying cause was immune
AP19	0–2	Male	18,461	Antibiotics	Manifestation was flushing of skin but underlying cause was immune
AP20	6–11	Female	14,971	Drugs used in status epilepticus	Nervous
AP21/AC21	12+	Male	19,823	Opioid analgesia	Gastrointestinal
AP22/AC22	6–11	Male	29,022	Opioid analgesia	Respiratory
AP23	3–5	Male	5171	Opioid analgesia	Gastrointestinal
AP24	12+	Male	NA	Corticosteroid	Cardiovascular
AP25/AC25	6–11	Male	26,028	Opioid analgesia	Nervous
AP26/AC26	12+	Female	11,667	Drugs affecting the cardiovascular system	Nervous
AP27/AC27	6–11	Female	24,071	Antibiotics; non-opioid analgesia	Skin and mucous membranes
YCP1	12+	Male	32,210	Immunological products and vaccines	Endocrine

ID[a]	Child age (years)[b]	Child gender	Ranked IMD scores[c]	Type of drug associated with suspected ADR	Body system affected by suspected ADR
YCP2	12+	Male	17,251	Drugs used for attention deficit disorder	Neurological
YCP3	12+	Female	20,387	Immunological products and vaccines	Haematological
YCP4	12+	Male	31,691	Non-opioid analgesia	Renal
YCP5	12+	Female	20,737	Immunological products and vaccines	Neurological, musculoskeletal, gastrointestinal, skin and mucous membranes, mental health
YCP6	12+	Female	31,439	Immunological products and vaccines	Neurological, immune, musculoskeletal
YCP7	6–11	Female	NA	Respiratory	Mental health
YCP8	12+	Female	29,831	Immunological products and vaccines	Musculoskeletal, neurological
YCP9	6–11	Male	22,922	Immunological products and vaccines	Gastrointestinal
YCP10	12+	Female	30,656	Immunological products and vaccines	Neurological, musculoskeletal, immune
YCP11	0–2	Male	31,508	Immunological products and vaccines	Haematological
YCP12	12+	Female	30,775	Immunological products and vaccines	Immune, neurological
YCP13	2–6	Male	9436	Respiratory	Behavioural changes
YCP14	2–6	Male	31,612	Respiratory	Behavioural changes
YCP15	6–11	Male	29,750	Drugs used for attention deficit disorder	Neurological
YCP16	12+	Male	25,366	Insulin	Behaviour changes, gastrointestinal
YCP17	6–11	Female	15,380	Antibiotic	Skin and mucous membranes
EC12	12+	Female	19,959	Opioid and other analgesia	Gastrointestinal/skin and mucous membranes
EC13	12+	Female	20,454	Opioid analgesia	Neurological
EC14	6–11	Male	15,771	Cytotoxics	Gastrointestinal
EC15	12+	Male	NA	Opioid and other analgesia	Gastrointestinal/skin and mucous membranes
EC16	12+	Male	24,092	Anaesthetics	Gastrointestinal
EC17	12+	Male	2350	Anaesthetic	Neurological/gastrointestinal
EC18	12+	Male	26,978	Opiate analgesia	Withdrawal
EC19	12+	Female	NA	Intravenous paracetamol	Collapsed/fainted? Need to review notes

AC, ADRIC children; AP, ADRIC parents; EC, extended child sample; NA, not available; YCP, Yellow Card parents.

a Where a parent and child from the same family were interviewed we include both participants' identifiers in the same row.

b Age reported in year groups: 0–2; 3–5; 6–11; ≥ 12 years.

c Calculated using Lower Super Output Area 2007 ranked score data, whereby lower scores indicate greater deprivation (data for families outside England are not reported and marked NA owing to incompatibility between IMD scoring systems within UK).

Appendix 6 Study protocols

Study 1 Protocol: Adverse Drug Reactions among children admitted acutely to hospital

Study description

Document history

This protocol is based on version 1 of the protocol for Study 1 drawn up by Mark Turner on 6th July 2007 and amended on 26th September 2007 and 19th January 2008. It was revised in the light of a pilot study by Ruairi Gallagher on 28th May 2008.

1 Study description

1.1 Study design

Cohort study

1.2 Subject selection

Single site: Alder Hey Children's Hospital

1.3 *Inclusion criteria.*

The overall study population will be all children acutely admitted to hospital as an emergency. This will be emergency admissions either via the Emergency Department or directly to a Ward. The subgroup of interest, "cases", will be children with suspected ADRs after exposure to any systemic or topical medicinal product (including alternative remedies such as herbals and aromatherapy) at the time of admission or within the preceding two weeks. Suspected ADRs will be defined as those admissions which involve any event that study team consider could possibly be an adverse drug reaction.

1.4 Criteria for not recruiting children to the study.

Elective surgical and medical admissions, including elective day-case admissions.

Intentional/unintentional drug overdose.

Admission due to drug misuse (of prescribed and illicit drugs) by patient and/or parent.

1.5 Recruitment

Participants will be recruited on the basis of a data entry tool embedded in routine admissions processes. This data tool will be paper based and will capture identifying information, source of admission and the medication history. Admissions will be identified on a daily basis by use of downloads from the hospital computer system.

1.6 Monitoring of recruitment

Hospital computer systems will be queried to determine whether all admissions have been recruited.

1.7 Sample size

This is a sample of convenience. We expect c. 12,600 admissions during this year-long study. This compares with a sample size of 18,820 in a similar study among adults admitted to hospital. Some of these admissions will be for children with more than one admission during the study period.

1.8 Data collection

As per methods below.

1.9 Awareness raising:

1.9.1 Run in period

A comprehensive training and awareness-raising programme will commence one month before the start of the study. This programme will ensure that all staff who admit patients are educated in taking and recording a full drug history, indicate common ADRs and demonstrate the information required to identify novel ADRs. It will be provided within existing programmes and by personal contact with relevant professionals.

1.9.2 During the study

Ongoing reminders will include posters and messages on the hospital's electronic patient data management system.

1.10 Methods

1.10.1 During admission process (i.e. routine clinical care)

A medication for all eligible admissions will be taken by the admitting clinicians as admissions occur and will include:

1. Identify all children acutely admitted to AHCH.
2. Obtain drug history relating to the 2 weeks immediately prior to admission.
3. Document whether member of staff admitting the child suspects an ADR.

The medication histories obtained by the admitting teams will be verified after the first 2 weeks of the study and periodically thereafter. This verification process will be undertaken by the study team who will interview a sample of parents and the family GPs in order to determine whether medication histories taken by the admitting team are complete.

1.10.2 Daily review of admissions by study team

At least one member of the study team will review all admissions on the next working day (including Saturdays). This will include:

1. Find clinical records of all children acutely admitted to AHCH.
2. Double check on exclusions.
3. Explore whether a medication error was present and classify as to whether it was a therapeutic error, dispensing error or administration error.
4. Define whether suspected ADR is present.

4a) examine list of known ADRs compiled from BNF / eMC

4b) identify any suspected ADRs identified on the basis of the clinical picture by admitting staff or review by study team.

5. If suspected ADR is present, gather relevant information from clinical record.
6. If necessary seek supplementary information from family / hospital team / primary care team about children in whom a suspected ADR is present.

The process of identifying suspected ADRs will be verified by the senior investigators two weeks after the start of the study and periodically thereafter. This verification will involve a selection of admissions in the first 2 weeks of the study. Senior Investigators will review all relevant data in a manner that is blinded to the outcome of the conclusions reached by the study team. This verification process will involve a mixture of cases that the study team designate as suspected ADRs and those designated as not suspected ADRs.

1.10.3 Review of suspected ADRs

Review meetings will take place twice a week. Initially, at least one senior investigator will attend each of these meetings in order to provide education and guidance. As the study team become more experienced, the senior investigators will be less involved in these meetings, but will continue to attend periodically to ensure quality control.

An initial triage of suspected ADRs will be done by at least 2 members of the study team during the week of the admission. This will include:

1. Naranjo's algorithm to identify likelihood of ADR when clinical information is complete

If definite / probable / possible:

2. Hartwig scale of severity
3. Type A / B (predictable in the light of pharmacology / idiosyncratic)

4. Hallas scale of Avoidability (this will be a consensus decision)
5. Yellow card submitted to MHRA

Suspected ADRs will be evaluated in several steps:

Step 1: decision made by study team

Step 2: decision made by programme team

Step 3: decision made by external reviewers

At each step, the evaluation will result in one of three decisions:

Definite, probable or possible ADR

Unassessable

not an ADR

When the status of the suspected ADR is not clear, the next step will be invoked.

1.10.4 Communicate ADRs to responsible clinicians

Whenever a definite, probable or possible ADR is identified, the study team will report the ADR to the clinical team responsible for the child's admission using a proforma sent to the clinician's secretary. The responsible clinicians will decide on subsequent clinical actions.

If a clinician informs a family about an ADR, the study team will ask clinical teams to communicate to families about an associated research project and gain feedback on permission to approach them about it (i.e. the qualitative research study).

The study team will identify which families have been informed about the ADR and where appropriate will inform the qualitative research team.

1.10.5 Data about children affected by ADRs

Following discharge the following data will be collected from the clinical record by the study team for all children affected by a definite, probable or possible ADR:

1. Did ADR cause admission or was it incidental?
2. Length of stay
3. Duration of intensive care
4. Investigations related to the ADR
5. Need for follow-up

a. Secondary care

b. primary care

1.10.6 Data about children not affected by ADRs

For all children admitted during the study period the following data will be obtained from electronic records.

1. Length of stay

a. stratified by age +/- presentation

2. Duration of intensive care

1.10.7 Senior review of ADRs

As part of quality control, decisions about ADRs will be reviewed periodically by senior members of the programme team. This is in addition to the initial validation procedures described in sections 9.10.2 and 9.10.3 above. After the initial phase of the study, senior members of the programme team will review all ADR cases where there is discrepancy between causality scores between study team members.

A sample of 10% of admissions in which a suspected ADR was not found will be reviewed by a the study team and a senior investigator.

1.10.8 Data handling

The study team will have responsibility for: data collection, recording and quality acting under Standard Operating Procedures (SOP) in accord with the Data Protection Act.

Data will be stored securely on Trust and University servers with back-up procedures described in an SOP.

Data will be retained in perpetuity in light of the possibility that ADRs in children may have consequences in later life.

All identifiable data will be held on the Trust computer network.

1.11 Analysis

1. Clean data and archive it in preparation for development of screening tool
2. Further analysis will use two denominator values (total acute admissions; admissions exposed to medication) to give:

a) proportions of ADRs for each class of drugs

b) proportions of ADRs according to licensing status

c) proportion of ADRs deemed to result from drug interactions.

3. Tabulate numbers of medication errors (including therapeutic, dispensing and administration errors) according to total admissions, medication class and age of child

Statistical analysis will be by the chi-square test.

Demographic data of patients with and without ADRs will be summarised using the mean and standard deviation for normally distributed data, the median and inter quartile range for skewed data, together with 95% confidence intervals. Similar statistics will be prepared for ADRs that are incidental to hospital admission.

We will assess the number of yellow cards generated over the study period in comparison to yellow card reports for the previous 5 years (using data from MHRA) in order to provide an estimate of the degree of under-reporting.

1.12 Stopping / discontinuation rules

We do not anticipate the need for stopping or discontinuation rules. If circumstances change, the Programme Executive Group will consult the Programme Steering Committee.

2 Research Governance

Study organization: Alder Hey Children's Hospital, Liverpool, UK.

The study lead(s) will be: Prof R Smyth.

The programme management group will be: Prof R Smyth, Prof M Pirmohamed, Prof AT Nunn, Prof P Williamson, Dr Mark Turner and Dr M Peak and will meet monthly.

The study steering committee will comprise: Prof Sir A Breckenridge, Prof M Rieder, Prof D Ashby and Dr J Raine.

The study team are: Kim Bird, Jennifer Mason, and Dr Ruairi Gallagher and will report to the Programme Executive Group each month.

3 Ethical considerations.

This is an audit project, as confirmed by NRES (letter on file). This is a review of existing data held in routine clinical records. The aim of the study is to enhance existing services using information and approaches that have been used elsewhere.

4 Approvals

This study will be done in accord with approvals from Audit, Clinical Governance and the R&D Department at AHCH

5 Finance

Funded by National Institutes of Health Research through a Programme Grant in Applied Health Research to the Investigators and administered by the R&D Department at RLC

6 Indemnity

Standard NHS provisions

7 Reporting and dissemination

Results of this study will be:

- reported to Trust bodies regularly (e.g. General Paediatric Forum)
- presented at regional meetings
- submitted to MHRA
- submitted for publication by peer-reviewed journals.

Study 2 Protocol: Adverse Drug Reactions among paediatric inpatients

1. Background

Alder Hey Children's NHS Foundation Trust treats 200,000 children a year from the North West of England, North Wales, Shropshire and the Isle of Man. The Accident and Emergency department treats 65,000 children every year. There are 309 in-patient and day case beds. During 2008 there were 33,905 in-patient episodes. This includes emergency admissions, elective admissions and day-case attendances. On an average day Alder Hey Hospital treats 167 patients in the Accident & Emergency Department, admits 121 patients, and cares for 230 In-patients.

For the period 1st January 2008 – 31st December 2008 the number of patients whose stay was longer than 48 hours was 7137.

In this study, we will use the definition of Edwards and Aronson. An ADR 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 dose regimen, or withdrawal of the product."

2 Study Objectives

1. To determine the incidence of ADRs in a paediatric inpatient population.
2. To characterise those ADRs identified in terms of type, causality, avoidability, severity, management required, duration and contribution to prolonged hospitalisation

3 Study Description

3.1 Study Design

A prospective cohort study carried out over 1 year.

3.2 Study Setting

Single Centre: Alder Hey Children's NHS Foundation Trust

3.3 Study Population

Children aged 0-16 years, who are inpatients for more than 48 hours.

3.3.1 Definition of ADR cases

ADR Cases will be deemed children with suspected ADRs to any systemic or topical medicinal product occurring during their inpatient stay whilst they are on a ward. This will include medication administered in the A&E Department.

If the same suspected reaction to the same medication occurs in the same patient on several occasions during a single inpatient stay this will be recorded as one ADR episode.

If the same suspected reaction to the same medication occurs in the same patient on a subsequent admission, this will be recorded as a new episode. A reference to the previous and subsequent admissions will be made respectively.

3.3.2 Inclusion Criteria Patients

Any child admitted to the hospital after the start of the study who then remains an inpatient for more than 48 hours will be reviewed.

3.3.3 Exclusion criteria Patients and Rationale

a) All patients in the transitional care unit

These patients are classified as inpatients on the hospital records system. They all have complex medical and nursing needs but are clinically stable. In general, they are awaiting transfer home or to a placement in the community. If they become acutely unwell they will be admitted for treatment to one of the wards included in this study.

b) All patients receiving medicines as part of their follow on treatment at home.

These patients are classified as inpatients on the hospital records system. They are receiving treatment at home from the community nursing team. The study team will not be able to make a daily review of these patients and so will not be able to fully assess any suspected ADRs.

c) All patients treated on the paediatric intensive care unit (PICU)

These patients are classified as inpatients in the hospital record system. They are managed with a high level of medical and nursing expertise. The proposed methodology does not cover all aspects of the clinical complexity and expertise required in an intensive care environment. The study team will therefore not be able to fully assess suspected ADRs. Patients who are inpatients before and/or after their PICU stay will be included

3.3.4 Inclusion and Exclusion Criteria Medication and Rationale

a) Prescribing or administration error

Excluded are all reactions which occur as a consequence of a prescribing or administration error including administration of a medication to a patient with a known allergy to this medication.

Rationale: These are adverse drug events resulting from medication errors.

b) Accidental ingestion of medication or deliberate medication overdose

Excluded are all reactions which occur as a consequence of an
accidental ingestion of medication or deliberate self-harm.

Rationale: These are adverse drug events resulting from medication errors.

c) Suspected reactions to total parenteral nutrition (TPN)

Excluded are reactions to TPN.

Included are reactions to any medicines added to TPN.

Rationale: The anticipated reactions to TPN include electrolyte imbalances which are difficult to assess for causality in complex patients. When prescribing TPN, clinicians assess electrolyte imbalances and amend the prescription in anticipation of, or response to these. The individualised nature of TPN prescribing means that a large amount of detailed data would need be collected for every patient receiving TPN.

d) Suspected reactions to intravenous hydration fluids

Excluded are reactions to intravenous hydration fluids.

Included are reactions to any medicines added to intravenous fluids.

Rationale: Similar to TPN.

e) Suspected reactions to medicines administered in theatre or in the department of radiology

Excluded are suspected reactions occurring whilst the patient is in theatre (including recovery) or in the department of radiology.

Included are suspected reactions to medicines administered in these departments which become apparent after the patient's return to a ward.

Rationale: Reactions which resolve quickly or which are considered to be expected or minor are not consistently recorded in these settings. It is therefore not possible to capture

information on all suspected ADRs using the proposed methodology. Suspected ADRs occurring on a ward will be picked up by the study team using the proposed methodology.

f) Suspected reactions to certain blood products

Suspected reactions to the following products are

Excluded:

- Red cells
- Platelets
- Cryoprecipitate
- Albumin solutions
- Fresh Frozen Plasma

Rationale: These products are not medicines. They are obtained from the transfusion service.

Included:

- Antithrombin III Concentrate
- Dried Prothrombin Complex
- Drotrecogin Alfa (activated)
- Factor VIIa (recombinant)
- Factor VIII Fraction, dried
- Factor VIII Inhibitor By-passing Fraction
- Factor IX Fraction, Dried
- Factor XIII Fraction, Dried
- Protein C Concentrate

Rationale: These products are listed in the BNF and some are under intensive surveillance by the MHRA

g) Suspected reactions to oxygen treatment

Excluded are reactions to oxygen therapy.

Rationale: Oxygen is not prescribed on the regular medication prescription charts. It will be difficult to obtain and record data of the amount of oxygen administered.

3.4 Sample size

This is a sample of convenience. We are expecting approximately 7000 patients to meet our criteria of having an inpatient stay lasting more than 48 hours during this year-long study. Some of these inpatient episodes will be for children with more than one episode during the study period.

3.5 Recruitment

We will use the already established hospital database HCIS MEDITECH for the recruitment of patients to the study. Electronic files containing a list of all children in the study population who meet the inclusion criteria will be automatically generated every 12 hours. All patients in the study population who meet the inclusion criteria will thus be enrolled. For ethical considerations see below (7).

3.6 Data collection

As per methods below.

3.7 Awareness raising

3.7.1 Run in period

A training and awareness-raising programme will commence before the start of the study. The study team will present Study 2 at appropriate meetings e.g. grand round, ward managers' meetings, doctor's induction, pharmacy clinical forum.

3.7.2 During the study

Ongoing reminders will include posters, and messages on the hospital's electronic patient data management system, intranet and internal communications. The study team will also continue to present Study 2 at appropriate meetings e.g. grand round, ward managers' meetings, doctors induction, pharmacy clinical forum

4 Methods

4.1 Data to be collected for analysis

The following data will be recorded in the study database for all patients in the cohort, with or without ADR, and will be used for the analysis of this study.

- Age on admission
- Gender
- Admission type (surgical, medical or both)
- Clinical team (surgical, medical or both) for each day of stay
- Time spent outside the hospital as part of daytime leave, weekend leave or overnight leave for each day of the stay.
- Duration of PICU or HDU stay in days
- Total length of stay in days
- Medication History
- Name of medication and preparation with BNF code, license status, black triangle status and off label status
- Route of Administration
- Indication
- Date given
- Dose and number of times given per 24hr period if administered intermittently ; dose or concentration and rate if given continuously

During the child's stay and following discharge the following additional data will be collected for all children affected by a suspected ADR:

- Trigger to suspect ADR e.g. nursing notes, laboratory results, observations
- Description of ADR
- Measurements relevant to the identification and evaluation of the ADR e.g. radiology reports, laboratory results and observations
- Specific treatment for ADR
- Type A/B
- Serious as specified by MHRA
- Action taken with drug as specified by MHRA
- Severity (Modified Hartwig Scale of Severity; see Appendix 2)
- Outcome (recovered/recovering/continuing/death/unknown)

If the reaction is ongoing at time of discharge and the patient had no further documented hospital visits (admission, A&E attendances or clinic appointment) the outcome will be

unknown. If the patient had further documented visits and the reaction is not documented then, the outcome will be recorded as recovered

- Duration of the ADR if known

This will be recorded in days. A reaction lasting <24hrs = 1 day; 24-48hrs = 2 days, etc.

- Drug interaction

We will not highlight the summative effects in this section

We will highlight the following drug interaction types in this section

1) Pharmacodynamic reactions, e.g. loop diuretic and digoxin

2) Pharmacokinetic reactions i.e. reactions affecting absorption, distribution, metabolism or elimination.

- Whether the ADR prolonged the admission and by how long
- Whether the ADR influenced the level of care (Admission to HDU cause or co-factor; Admission to PICU cause or co-factor) and if so by how long. This information will usually be readily available from the medical notes. In all other cases this will be discussed with the clinician. It will be documented whether clinician was contacted or not.

4.2 Data recorded in the study database but not used for analysis

Some data entered into the study database will be required for purposes other than analysis of the study, namely:

1) To identify each patient in the study cohort during and after the study. and to distinguish between multiple admissions for the same patient. Examples of these data would include patient name, hospital and account number.

2) To facilitate the daily review process and aid communication between members of the study team. Examples of these data would include past medical history and r**eason for admission.**

4.3 Data Sources

a) Personal details, admission and discharge details

These are routinely recorded in the hospital database HCIS Meditech.

b) Medical notes

These are recorded on paper and filed in the case notes.

c) Nursing notes

These are usually recorded electronically in the hospital database HCIS Meditech. For certain conditions or procedures designated patient care pathways combine both medical and nursing notes. These are paper records and will be available in the case notes.

d) Laboratory results

Details of all laboratory samples taken at Alder Hey and sent for analysis are available in the hospital database. Most reports will also be available in the hospital database. In all other cases a paper copy of the report will be available in the case notes.

e) Imaging results

Details and reports of all imaging results taken are available in the hospital database. The exception is any imaging undertaken in theatre where a formal radiological report is not available, for example cardiac catheter investigations and central line placements.

f) Observation and other charts

Observation charts including PICU charts, fluid balance charts, pain control charts and withdrawal charts are paper records which are usually kept separately from the medical notes. After discharge, these are filed together with the medical notes.

g) Prescription charts

As for observation charts.

4.4 Timing of data collection:

Data will be collected and entered into the database on a daily basis.

Baseline data will be collected at time of enrolment into the study as outlined in "New patient review" (5a) and 5.2)

Follow up data and data for ADR cases will be collected on a daily to weekly basis until discharge as outlined in "Follow up Review" and "ADR case review" (5b)

Data collection will be completed at time of discharge for all non-ADR cases. For ADR cases data collection might not be completed until after discharge from hospital, as outlined in "ADR review process".

4.5 Data handling

Data will be entered directly into the study database created for this study. The study database is stored securely on the Trust server with back up procedures described in an SOP. (to be attached)

The study team will have responsibility for: data collection, recording and quality acting under Standard Operating Procedures (SOP) in accordance with the Data Protection Act.

Data will be retained in perpetuity in light of the possibility that ADRs in children may have consequences in later life.

5 Outline of review process

Data collection will be completed by designated researchers within the study team, currently JM, KB and ST. Each week, one or two researchers will undertake new patient reviews and follow up reviews, whereas the third researcher will undertake ADR evaluations

Eligible patients will fall into one of 3 review categories:

a) New patient review (including patients discharged from PICU who were admitted to PICU from outside the hospital)

b) Follow up review (including patients discharged from PICU who were inpatient prior to PICU admission)

c) ADR suspected

a) New patient review

A new patient review involves baseline data collection and a first clinical progress review.

The purpose of the baseline data collection is to record basic demographic data required for the analysis and to create a patient profile in the study database that will enable study team members to carry out follow up reviews.

The purpose of the clinical progress review is to highlight any suspected ADRs. The focus lies on assessing any new symptoms or worsening of existing symptoms as well as assessing abnormal laboratory or imaging results in the context of all administered medication.

b) Follow up review

A follow up review involves updating the medication history and ward status and undertaking a clinical progress review to highlight any suspected ADRs.

c) ADR suspected

Any reaction highlighted as ADR suspected will be evaluated and an ADR case report will be completed.

5.1.2 Timing of new patient review and follow up review

New patients will be added to ADRIC caseload every 12 hours. New patient reviews will be carried twice daily by two members of the study team on weekdays and one member of the study team on weekends and bank holidays. New patient reviews may be postponed for 24hr or 48hrs if only one member of the study team is available and/or the workload is unusually high.

Follow up reviews will be carried out by two members of the research team on weekdays, one member of the research team on weekends and bank holidays and three members of the research team after weekends and bank holidays.

The next review date will be decided for each patient individually on a review-to-review basis. This will usually be 2 days from the time of last review.

We will aim to minimise the number reviews on weekends and bank holidays when only one member of the research team will be available for data collection. Consequently the number of reviews will be increased after Weekends and Bank Holidays when three members of the research team will be available for data collection.

5.1.3 Communicating ADRs to clinicians

Whenever a definite, probable or possible ADR is identified, the study team will report the ADR to the consultant responsible for the child's care. However, it will not be possible, practical or appropriate to inform consultants immediately about every ADR identified. Examples would include post-operative nausea and vomiting, pruritus with morphine and nausea and vomiting following chemotherapy.

These are all expected and frequent reactions we have identified during pilot work of which consultants are well aware. We will therefore only contact the consultant responsible for the child's care directly to discuss the ADR at the time the ADR is identified if

1) The ADR causality is uncertain and the case requires further discussion

2) There is a clinical reason to alert the clinician to a problem

3) We would like to recruit patient into ADRIC-QUAL (for details see ADRIC-QUAL protocol)

The consultant will receive a paper copy of the yellow card for all ADRs (5.1.4) This is expected to be the main way of communicating ADRs to clinicians who are not already aware of the ADR and where it was not necessary to contact them directly.

5.1.4 ADR reporting to the MHRA

All possible, probable or definite ADRs will be reported to the MHRA through the yellow card online reporting system on a monthly basis by one member.

5.1.5 Causality assessment

Causality assessment will be carried out using the Liverpool Causality Tool to identify the likelihood of ADR

5.1.6 Classification of suspected reactions

All suspected reactions will be coded using a standard set of MedDRA terms.

5.1.7 Review of cases deemed non-ADRs

A structured review of these cases will be undertaken to determine the number of missed ADR cases.

5% of admissions without ADRs will be assessed independently by 2 study team members.

5.1.8 Fatalities occurring within 48 hours of admission

A list of fatalities occurring within 48 hours of admission for the period of this study will be obtained from the hospital database every 4 months. The case notes of those individuals will be obtained and reviewed, in retrospect, and the database record completed as outlined in new patient review.

5.2 New patient review process: A step-by-step guide

A Meditech data file will be generated automatically for all patients newly added to ADRIC caseload (stay reaches > 48 hours). This has to be imported into the study database by the study team. The patient will then be listed in the "blank record" report.

Each new patient will fall in one of the 3 following categories and should be prioritised in the order shown:

- Patient discharged and case notes still on ward:

Complete baseline data collection, clinical progress review and enter discharge date.
If no ADR is suspected mark 'patient discharged'.
If an ADR is suspected alert ADR evaluator of the week.

- Patient still an inpatient.

Complete baseline data collection and complete clinical progress review for each completed 24hr period as outlined below.
If no ADR is suspected mark 'incomplete' and review date 'DDMMYY'. This will usually be in two days' time but researcher can elect to make it one day, three days or four days if they think this is appropriate.

- Patient discharged and case notes still not on ward.

Enter discharge date and mark 'notes needed'.

5.2.1 Baseline data

a) Personal details, admission and discharge details

Source: Meditech (These data are contained in the Meditech file for each patient which is imported into the study database at enrolment.)
Study database section: Meditech

- Hospital Unit Number
- Account number
- Name
- Date of birth
- Ward at time of import into the study base
- Age
- Gender male or female.
- Admission date
- Discharge date
- Admitting consultant
- Admitting speciality
- Admission source
- Admission time
- Duration of stay at time of import into the study database

b) Weight

Source: Meditech, patient record, observation or prescription chart
Study database section: Meditech
If the recorded weight is an estimate mark 'estimate'
If no weight has been recorded estimate weight according to Alder Hey emergency prescribing guidance [(age in years + 4) x 2] and mark 'estimate'.
Values for weight estimates will be replaced by accurate weights once these become available. The database entry cannot be closed without entering a value for weight.

c) Allergies

Source of data: Medical notes, nursing notes, prescription chart
Study database section: Allergies
Record the name of the medication the patient is allergic to.
Record type of reaction if known
If the patient is not known to have allergies mark 'NKDA' (no known drug allergies)

d) Admission type

Source: Medical notes admission
Study database section: PMH

The type of admission is determined by the reason for admission the clinical team responsible for the patient's care during admission (consultant NOT ward type).
If the patient is primarily cared for by a surgical team mark 'surgical'
If the patient is primarily cared for by a medical team mark 'medical.
If care arrangements are shared equally between both teams (for example if the patient is reviewed daily by a medical and a surgical team) mark 'both'

e) Current ward, PICU and HDU stay

Source: Meditech
Study database section: Meditech and Clinical progress section
Update name of current ward in the Meditech section if different from ward at time of enrolment. The location of the patient on any report will be linked to the current ward status.
Mark HDU or PICU for every day of stay as part of the structured clinical progress review in the following way:
Mark as 'PICU' or 'HDU' in the clinical progress section.
HDU stay does include the high dependency areas on the cardiology and neurosurgical wards and the bone marrow transplant cubicles on the oncology ward.
If the patient has been transferred from PICU or HDU to a ward with lower level of care, record the ward with the highest level of care within the given 24hr period.

f) Past Medical History and reason for admission

Source: Medical notes and nursing notes
Study database section: PMH
These data will be recorded in free text. The entry could be coded with MedDRA preferred terms in retrospect at a later stage to describe both the ADR and the non-ADR population in more detail.
Reason for admission

- For elective admissions this will be the name of the planned procedure, operation or investigation.
- For emergency admissions this will be the presenting complaint such as new presentation or exacerbation or of one or several symptoms.

Past medical history

- Any current diagnoses
- Any chronic symptoms which are still under investigation or where it has not been possible to attribute these to a diagnosis
- Previous operations
- Birth history for neonates if appropriate (gestational age at delivery, type of delivery, significant problems during delivery, details of admission to neonatal unit)

g) Medication History

Source: Prescription chart, medical notes and nursing notes
Study database section: Drug history
If the patient has not received any medication mark "no medication"
Record any topical or systemic medication administered since admission (Inclusion criteria see above) by choosing the generic name of the medication and preparation from the provided medicines list and entering the following details:

- Route of Administration
- Indication - if unclear review medical notes, nursing notes or ask member of clinical team
- Date given - for each completed 24hr period at time of review

- Dose and Number of times given per 24hr period if administered intermittently
- Dose or concentration and rate if given continuously.

If the medication administered is not in the medicines list inform JM to amend the medicines list. Complete the medication history at time of next review. The medicines list has been compiled by JM, Research Pharmacist. Every medication entry in the database will be accompanied by:

- BNF code as per current electronic BNFC version (http://bnfc.org/bnfc/)
- License status – license yes or no
- Black triangle status – black triangle yes or no
- Off label - off label prescription yes or no

For the majority of medications in the current list BNF code, licence status and black triangle status are already entered. They will auto-populate once the medication name and preparation has been entered. Any missing data as well as the off-label status will be completed by JM on a regular basis.

h) Recording of Medication administered before admission

If the patient has taken medication at home which is also prescribed during the inpatient stay mark 'on before admission'

No ADR suspected

If patient has taken medication prior to admission that is not prescribed during inpatient stay this will not be recorded

If patient has been transferred from another hospital and medication other than medication taken at home has been administered this will not be recorded

ADR suspected

If patient has taken medication prior to admission that is not prescribed during inpatient stay which is suspected to have caused and ADR which was not apparent on admission this will be recorded in the clinical progress section and/or the ADR details section.

This includes medication administered at another hospital other than medication taken at home.

5.2.2 Structured Clinical progress review

Source: as outlined below

Study database entry: clinical progress

The following sources will be reviewed

- Nursing notes
- Laboratory reports
- Imaging results
- Observation charts
- Other charts
- Prescription charts

The review will focus on the following findings

- new symptoms
- worsening of existing symptoms
- abnormal laboratory results
- abnormal imaging results
- observations outside normal limits

The aim is to compare these findings with the adverse drug reaction profile of medicines administered. The team will refer to the Summary of Product Characteristics (http://emc.medicines.org.uk/medicine/2209/SPC/Efexor/) or, if not available, the BNFC http://bnfc.org/bnfc/

If a suspicious finding could be related the adverse drug reaction profile of anaesthetic mediation and the patient has had an anaesthetic (current or previous admission) the anaesthetic charts will also be reviewed.

Naturally there are two possible outcomes for each clinical progress review:

ADR suspected or no ADR suspected.

a) ADR suspected

Enter date for each day of structured clinical review since admission or last review in the clinical progress section. Review only completed 24hr periods unless patient has been discharged.

Record symptom or abnormal result related to suspected ADR and also any treatment given or investigations undertaken. This might be several entries if more than one ADR is suspected or the suspected ADR lasted longer than 24hrs or is ongoing.

Mark the suspected medication or medications in the 'ADR? Yes' medication history section.

b) No ADR suspected

Enter the date for each day of structured clinical review since admission or last review. Review only completed 24hr periods unless patient has been discharged

5.3 Follow up review: A step-by-step guide

Patient is listed in the "review today" report and will fall into one of the 3 following categories and should be prioritised in the order shown:

- Patient discharged and case notes still on ward:

Complete medication history and ward status for all days since last review as described above

Undertake a structured clinical progress review for all days since last review as described above and enter discharge date.

If data collection has been completed the mark report status as 'patient discharged'.

- Patient still an inpatient.

Update Medication history and ward status for each completed 24 hour period since last review as described above. Undertake a structured clinical progress review for each completed 24 hour period since last review, mark 'incomplete' and set review date DD/MM/YYYY.

If ADR is suspected, mark 'ADR suspected'.

- Patient discharged and case notes not on ward.

Enter discharge date and mark 'notes needed'.

5.4 ADR case review – a step-by-step guide

This will be carried out and completed by "the ADR evaluator of the week". If a patient experiences more than one possible, probable or definite ADR during the inpatient stay each ADR might be described by a different member of the research team.

Patient will fall into one of the 5 following categories :

- Patient discharged, no results pending and case notes still on ward

Complete ADR details section and mark ADR report status as "yellow card - incomplete".

If database entry status is marked 'complete' and discharge date is entered not further action is required.

If database entry status is marked as 'incomplete', complete data as outlined above (5.2.2), enter discharge data and mark 'complete'.

- Patient discharged, results pending and case notes still on ward

Complete ADR details section as far as possible and mark ADR report status as "yellow card - incomplete"

If database entry status is marked 'complete' and discharge date is entered not further action is required.

If database entry status is marked as 'incomplete', complete data as outlined above (5.2.2er), enter discharge data and mark 'complete'.

- Patient discharged and case notes not on ward

If database entry status is marked 'complete' and discharge date is entered not further action is required

If database entry status is marked as 'incomplete' change to 'notes needed'

- Patient still an inpatient, no results pending

Complete ADR details section and mark ADR report status as "yellow card".

5.4.1 ADR details section

The ADR clinical details section or the database includes 4 sub sections:

a) Clinical details

b) ADR info

c) Causality

d) Drugs ADR

a) Clinical details section of database referring to ADR case

Reaction – Describe ADR reaction and code any findings with MedDRA preferred term(s). Past medical history details do not have to be included as these are already recorded (5.2.1f)Summarise all relevant details including

- investigations relevant to the identification and evaluation of the ADR (radiology reports, laboratory results, observations
- specific treatment for ADR
- Outcome (recovered/recovering/continuing/death/unknown)
- Duration of the ADR (unless ongoing)
- Contribution of drug or food interactions to the ADR
- Whether the ADR prolonged the admission and by how long – this is usually decided after discussion with the clinical team.
- Whether the ADR influenced the level of care (Admission to HDU cause or co-factor; Admission to PICU cause or co-factor) and if so by how long – this is usually decided after discussion with the clinical team.

Record laboratory results in the bloods section of the database

Indicate name of Investigator

Once sections a) to c) are completed change ADR status 'yellow card'

b) ADR info

This section contains questions with predefined answers such as

"Was this a serious ADR yes/no"

c) Causality

This section contains questions with predefined answers such as

Is an ADR suspected yes/no Complete Liverpool causality tool

5.5 Analysis

The will be a separate protocol for the analysis of Study 2

We will assess the number of yellow cards generated over the study period in comparison to yellow card reports for the previous 5 years (using data from MHRA) in order to provide an estimate of the degree of under-reporting.

5.6 Stopping / discontinuation rules

We do not anticipate the need for stopping or discontinuation rules. If circumstances change, the Programme Executive Group will consult the Programme Steering Committee.

6 Research Governance

Study organization:

The study lead(s) will be Prof R L Smyth, Prof M Pirmohamed, Dr M Turner, Prof A Nunn, Prof P Williamson and Dr M Peak.

The programme management group will be Prof R L Smyth, Prof M Pirmohamed, Dr M Turner, Prof A Nunn, Prof P Williamson and Dr M Peak and will meet every 6-8 weeks.

The study steering committee will comprise Sir Alasdair Breckenridge (Chair), Prof R L Smyth, Prof M Pirmohamed, Dr M Turner, Prof A Nunn, Prof P Williamson, Dr M Peak, Dr B Young, Prof D Ashby, Prof M Rieder and Dr J Raine and will meet every annually.

The study team are: Kim Bird, Jennifer Mason and Signe Thiesen and will report to the programme management group every 6-8 weeks.

7 Ethical considerations

a) Ethics approval

This is an audit project, as confirmed by NRES (letter on file). This is a review of existing data held in routine clinical records. The aim of the study is to enhance existing services using information and approaches that have been used elsewhere.

b) Consent

The information to be used is available to the investigators without permission and will be maintained, analysed and reported in a fashion from which individuals cannot be identified.

Consent will be obtained for recruitment into ADRIC-QUAL in is described in the relevant protocol.

8 Approvals

This study will be done in accord with approvals from Audit, Clinical Governance and the R&D Department at AHCH

9 Finance

Funded by National Institutes of Health Research through a Programme Grant in Applied Health Research to the Investigators and administered by the R&D Department at Alder Hey.

10 Indemnity

Standard NHS provisions

11 Reporting and dissemination

Results of this study will be:

- reported to Trust bodies (e.g. General Paediatric Forum)
- presented at regional meetings
- submitted to MHRA
- submitted for publication by peer-reviewed journals.

12. Interventions excluded after study start

a) Suspected reactions to topical anaesthetics

Excluded are reactions to lidocaine 2.5%, prilocaine 2.5% cream (EMLA®) or tetracaine 4% gel (Ametop®)

Included are reactions to LAT gel (lidocaine 4% & adrenaline 0.1% & tetracaine 0.5% gel)

Rationale: EMLA® and Ametop® are not consistently prescribed on the regular medication prescription charts. It will be difficult to obtain and record reliable data of these medications. LAT gel however is prescribed on the regular medication prescription chart.

b) Suspected reactions to Ranitidine

Excluded are reactions to Ranitidine added to TPN.

Included are reactions to Ranitidine administered otherwise.

Rationale: Ranitidine added to TPN is not consistently prescribed on the regular medication prescription charts. It will be difficult to obtain and record reliable data of these medications.

c) Suspected reactions to Heparin

Excluded are reactions to Heparin administered as intermittent intravenous heparin flush.

Included are reactions to heparin administered as intermittent intravenous injection other than heparin flush, heparin administered as continuous intravenous infusion or as subcutaneous injection.

Rationale: Heparin flushes are not consistently prescribed on the regular medication prescription charts. It will be therefore be difficult to obtain and record reliable data. In all other cases heparin is prescribed on the regular medication prescription charts.

d) Suspected reactions to rectal washouts

Excluded are reactions to rectal washouts with Sodium Chloride 0.9%.

Rationale: These are not consistently prescribed on the regular medication prescription charts. It will be therefore be difficult to obtain and record reliable data.

e) Suspected reactions to medicines administered on PICU

Excluded are suspected reactions which are apparent at time of discharge to a ward.

Included are suspected reactions to medicines administered on PICU which only become apparent after the patient's return discharge to a ward.

Rationale: ADRs occurring in an intensive care setting cannot be fully assessed using the proposed methodology and patients are therefore excluded from the study for the duration of their intensive care stay. Suspected ADRs occurring on a ward will be picked up by the study team using the proposed methodology

f) Suspected phlebitis and infusion site reactions

Excluded phlebitis and infusion site reactions

Rationale: Factors found to be strong predictors of phlebitis such as size of cannula, anatomical site and prolonged catheterisation are not recorded and we would therefore be unable to obtain reliable data. Infusion site reactions are not consistently documented in a way that would enable the study team to distinguish a reaction due to error or extravasation from a true infusion site reaction.

Appendix 7 Research Implications from Adverse Drug Reactions In Children

Outputs from a discussion group: what are the research implications of the burden of adverse drug reactions in paediatrics?

Symposium: Drug Safety in Children – Adverse Drug Reactions In Children

Atlantic Tower by Thistle Hotel, Liverpool
Friday 26 April 2013
14.00–15.00

Participants

Professor Munir Pirmohamed (Moderator), Professor Matthew Peak, Professor Sir Alasdair Breckenridge, Professor Deborah Ashby, Professor Michael W Beresford, Dr Andrew Rose, Dr Jamie Kirkham, Dr Sudeep Pushpakom, Dr Amitabh Shankar, Dr Petr Jirasek, Dr Virginia Ramos-Martin, Charlie Orton, Norkasihan Ibrahim, Mohammed Amali, Dave Delaney, Catherine Birch, Beth Conroy.

Key implication	Key discussion points	Next steps summary
Dosing	Work with industry to develop adaptive licensing. In literature how do researchers extrapolate from adults to children? Explore what has been used, what has not been used and utility of methodologies. Use findings to develop a gold standard practice for extrapolation and apply to drugs identified as high risk within ADRIC Take forward drugs highlighted by ADRIC as a focus for further study, monitor the PK/PD of these drugs and aim to develop risk models – they may not differ across age	• What extrapolation methods have/have not been used in literature, of those used which are successful?
ADRIC outputs	LCAT and avoidability tools The discussion focused primarily on the LCAT as this tool is fully completed: 1. Develop an 'app' for assessment tools 2. Use tools in RCTs to improve ADR reporting 3. Use tools in real world sense to improve practice – would give a consistent approach to assessments 4. Test outputs elsewhere, e.g. other hospitals and settings LCAT e-learning tool 1. Test elsewhere 2. Conduct a larger RCT of LCAT e-learning tool to determine effect of clinician assessment of ADR causality 3. Use in real world and medical training could improve how the LCAT is used in practice	• Use outputs in randomised controlled trials to improve reporting • Use outputs in real world scenarios to improve practice • Hypothesis testing RCT of effect of LCAT e-learning tool on clinician assessment of ADR causality

Key implication	Key discussion points	Next steps summary
Quantification	There are knowledge gaps in the quantification of ADRs in a variety of settings not included in the ADRIC study: 1. Other sites outside specialist tertiary care (e.g. District General Hospitals) – explore variation across settings, variation across age at other sites 2. Neonates 3. Theatres and critical care 4. A&E 5. Long-term side effects 6. Post discharge and in the home setting 7. Other settings: primary and community care There are also benefits of evaluating long-term side effects, which was not looked at in ADRIC. What lessons from the adult studies can be extrapolated to children?	• Explore ADRs in settings where data are not yet described, e.g. neonates, critical care, community settings and primary care and long term/longitudinally
Risk–benefit evaluation	There is a need to explore the balance of safety vs. efficacy. Is there too much focus on safety in monitoring at the expense of potential benefit? Is the weight between efficacious outcomes and safety of patients always sensible? This subject is currently less understood in children than adults. For further work, one paediatric area could be focused on, e.g. paediatric oncology What are parental views of risk–benefit evaluation? What are the children's views? How do the decision making differences between children and parents for particular drugs differ? Does the benefit/risk comprehension and decision differ with age, e.g. from pre-school to adolescence?	• What are parents' views on risk–benefit evaluation? What are children's views on risk–benefit evaluation? How do these differ and vary across the child and young person's age spectrum?
Interventions	Development of interventions that could reduce harm to be given alongside high-risk drugs identified by ADRIC	• Development of targeted interventions for identified high-risk drugs
Monitoring	ADRIC has highlighted a need to understand better the morbidities associated with anaesthesia and surgery in children. This requires a study that can follow-up and monitor children in the community and home setting to assess the incidence of ADRs following surgery, compare these according to the anaesthetic and postoperative drugs, surgical procedures and their comorbidities. An observational study could lead to an assessment of which children should be discharged on the day of surgery and for those who are, RCTs will be able to assess the most appropriate treatment regimens to prevent pain, vomiting and other postoperative complications Explore active reporting, passive reporting and the difference between them Communicate and collaborate with industry in the development and refinement of monitoring systems within paediatric pharmacovigilance	• Observational study of ADRs in children following discharge after surgery • RCT of treatment regimens designed to minimise pain, vomiting and postoperative complications in early discharged children

RCT, randomised controlled trial.

Appendix 8 Leaflets

What questions can I ask?

YOU CAN ASK ANYTHING YOU LIKE!

Here are some questions you may want to ask:

- Can I take my medicine again?
- How long will the side effect last?
- If I take my medicine again, will I have the same side effect?
- Can I have a different medicine that doesn't give me side effects?
- What will happen if I don't take my medicine?
- How long will the side effect last?

What should I do if I think I've had a side effect?

If you think you have had a side effect it is really important that you tell others how you are feeling. Some side effects go away quickly but some stay, and some can be serious. You should talk to your mum or dad, or another grown up that you trust. If you are at school you could talk to a teacher.

Like Tom and Lily you may want to talk to your doctor or nurse about what to do next. They will listen to your problems and work out what's best for you. It might be best to keep taking the medicine like Lily, or it might be best to try another medicine like Tom.

This leaflet was developed as part of the ADRIC (Adverse Drug Reactions in Children) Programme which was funded by the National Institute for Health Research.

Talking about problems with medicines

Information leaflet about side effects for children aged 5-8 years

Alder Hey Children's NHS NHS Foundation Trust

Medicines usually help people get better. Many people take medicines without any problems. But sometimes medicines can make you feel poorly. When this happens it is called a side effect. If you think you have had a side effect it's really important that you tell others how you are feeling.

What is a side effect?

Tom's Story

Tom had an operation on his tummy. Dr Wood gave Tom some medicine to stop his tummy hurting. The medicine worked and Tom's tummy didn't hurt. But a bit later, Tom started feeling very itchy. He couldn't stop scratching! Dr Wood said that the medicine was good at stopping pains but it made some people itchy. This is a side effect of the medicine. Tom's itching was so bad that Dr Wood stopped the medicine and gave Tom a new medicine. After that Tom felt much better. He didn't feel itchy anymore and his tummy didn't hurt.

Is it easy to spot a side effect?

Medicines can cause different side effects in different people. Some side effects are bad and some are mild. Knowing if a side effect has really happened (or not) can be hard. Lily was taking a medicine and started to feel worse. Her mum wasn't sure if it was a side effect so she asked Lily's doctor.

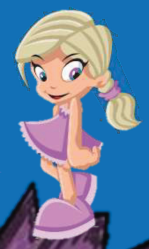
Who is this leaflet for?

Are you worried that a medicine is making you feel worse? It might be a side effect. This leaflet is for children to read with a parent or grown up. The leaflet is to help you talk with a doctor or nurse about any worries that you have about medicines.

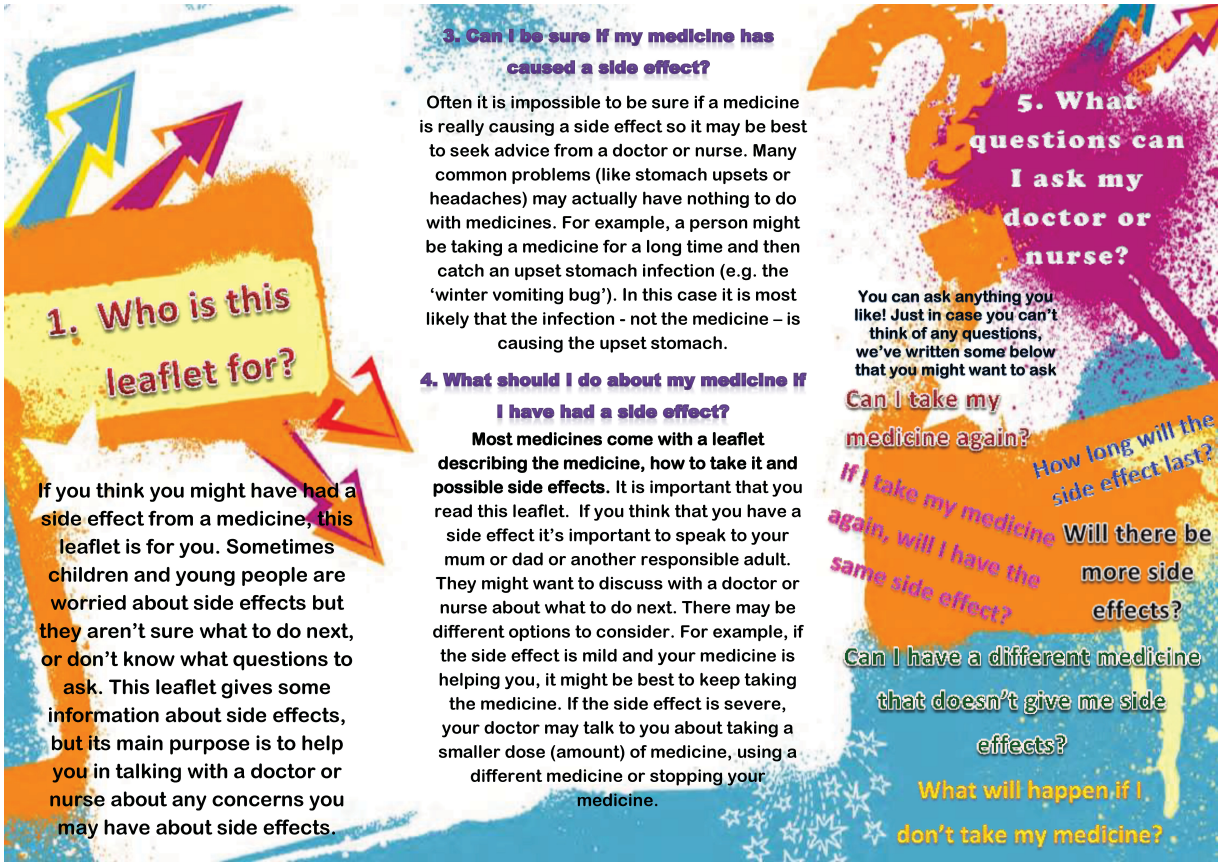
Lily's Story

Lily's ear was hurting. She went with her mum to see the doctor. Dr Jones said that a germ was making Lily's ear ache. She gave Lily some medicine to make the germ go away go away. Dr Jones said the medicine would take a few days to work. Lily didn't mind taking the medicine – it was yellow and tasted a like banana!

The next day Lily had earache and a headache too! Lily's mum thought the headache might be a side effect of the medicine so Lily and her mum went back to see Dr Jones. Dr Jones told Lily that it was very rare for this medicine to give people headaches. She said, "The same germ that is making your ear ache is also making your head ache. The medicine will soon make both aches go away." Lily and her mum agreed that she should keep taking the banana medicine. When Lily woke up the next day she felt much better. Her earache and headache had both gone away!




2. What is a side effect?
Medicines are designed to help you but sometimes they can cause problems. For example, a medicine to stop a bad pain might make you feel sick or cause a headache. These unwanted problems are called side effects. You may also hear them called 'adverse drug reactions'. Side effects can range from being common to very rare. They can also range from mild to severe. So, if you think you're having a side effect from your medicine, it's really important that you tell others how you're feeling.
6. Apart from my doctors and nurses, who else watches out for side effects?
The Medicines and Health Care products Regulatory Agency (MHRA) watches out for side effects. Anyone can report a side effect to the MHRA either by going to their website http://www.mhra.gov.uk/ or phoning them free on 0808 100 3352. If you decide to report your side effect to the MHRA you might want to ask your parent for help.
7. Where can I find out more information?
For more information about side effects, please see the information leaflet that came with your medicine. If you did not get a leaflet, please ask a doctor or nurse for one, or visit the website http://www.medicinesforchildren.org.uk/
This leaflet was developed as part of the ADRIC (Adverse Drug Reactions in Children) Programme which was funded by the National Institute for Health Research.
NHS
Talking about side effects from medicines
Information leaflet for children and young people aged 9 and over
Alder Hey Children's
NHS
Foundation Trust


1. Who is this leaflet for?
If you think you might have had a side effect from a medicine, this leaflet is for you. Sometimes children and young people are worried about side effects but they aren't sure what to do next, or don't know what questions to ask. This leaflet gives some information about side effects, but its main purpose is to help you in talking with a doctor or nurse about any concerns you may have about side effects.
3. Can I be sure if my medicine has caused a side effect?
Often it is impossible to be sure if a medicine is really causing a side effect so it may be best to seek advice from a doctor or nurse. Many common problems (like stomach upsets or headaches) may actually have nothing to do with medicines. For example, a person might be taking a medicine for a long time and then catch an upset stomach infection (e.g. the 'winter vomiting bug'). In this case it is most likely that the infection - not the medicine – is causing the upset stomach.
4. What should I do about my medicine if I have had a side effect?
Most medicines come with a leaflet describing the medicine, how to take it and possible side effects. It is important that you read this leaflet. If you think that you have a side effect it's important to speak to your mum or dad or another responsible adult. They might want to discuss with a doctor or nurse about what to do next. There may be different options to consider. For example, if the side effect is mild and your medicine is helping you, it might be best to keep taking the medicine. If the side effect is severe, your doctor may talk to you about taking a smaller dose (amount) of medicine, using a different medicine or stopping your medicine.
5. What questions can I ask my doctor or nurse?
You can ask anything you like! Just in case you can't think of any questions, we've written some below that you might want to ask
Can I take my medicine again?
How long will the side effect last?
If I take my medicine again, will I have the same side effect?
Will there be more side effects?
Can I have a different medicine that doesn't give me side effects?
What will happen if I don't take my medicine?

Medicines for Children information for parents and carers

Side-effects from children's medicines

This leaflet gives information about is about side-effects from children's medicines. It will support you in discussing with your doctor or nurse any concerns you have about your child's medicine.

This leaflet has been written for parents and carers about medicines in children. Keep it somewhere safe so that you can read it again.

What is a side-effect?

Medicines are important in preventing and treating children's illnesses, but sometimes they can cause problems. For example, medicines can sometimes make people feel sick or cause an itchy rash. This is called a side-effect.

A side-effect is an unwanted reaction or symptom caused by taking a medicine. You may have also heard this called an 'adverse drug reaction'. A side-effect may happen straight away, or it may happen a few days or weeks after your child has taken a medicine.

Can I be certain that a medicine has caused my child's symptoms?

Often it is difficult to be certain whether a medicine has definitely caused a side-effect. This is because a child's symptoms could be due to an illness or another cause. If your child is taking lots of different medicines, it can be difficult to pinpoint which (if any) medicine or medicines may have caused the symptoms. This uncertainty can be very frustrating for parents, children and health professionals.

To work out what might be causing your child's symptoms, here are some questions that you and your child's doctor or nurse might discuss:

- When did you first notice the symptoms?
- Is there anything else that might have caused the symptoms?
- Has your child ever had symptoms like this before?
- Are the symptoms a known side-effect of the medicine?

Risks and benefits of children's medicines

All medicines can have side-effects but it is important to balance these against the benefits of medicines. No one wants a child to miss out on a medicine when the benefits of taking it are greater than the side-effects. If your child has had a mild side-effect, she or he might still be able to keep taking the medicine. If they have had a serious side-effect, then you and your child's doctor will want to discuss other options, such as changing the dose, stopping the medicine or switching to a different medicine.

Questions to consider asking your doctor or nurse

If your child has had problems after taking a medicine, it is natural to have concerns and questions.

Here are some questions you might want to ask your doctor or nurse:

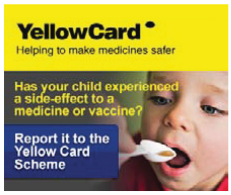
- How certain is it that my child's medicine has caused a side-effect?
- Should my child stop taking the medicine?
- Will somebody record this side-effect in my child's medical notes?
- Will my child ever be able to have the medicine again?
- Will my child have any long-term problems due to any side-effects?
- Will my other children get similar side-effects if they need to take the same medicine?
- Is there an alternative medicine that my child could take?

Will there be a record of my concerns?

You can ask your child's doctor to record any concerns about your child's medicines in his or her medical records. If the doctor recommends stopping the medicine, he or she will usually put an alert in your child's records. This will tell other health professionals that your child should not have the medicine.

If you think your child has had a side-effect to a medicine, you should mention this next time your child sees a doctor or nurse.

Reporting side-effects to the medicines safety 'watchdog'



The Medicines and Health Care products Regulatory Agency (MHRA) watches out for side-effects. Anyone can report a side-effect to the MHRA via its Yellow Card Scheme:

- Website – http://www.mhra.gov.uk/yellowcard
- Freephone – 0808 100 3352 (10am to 2pm Monday-Friday only)

The Yellow Card Scheme acts as an early warning system to

identify new side-effects and get more information about other problems which might not have been known about before.

If a new side-effect is found, the MHRA will review the way that the medicine can be used, and the warnings that are given to people taking it to minimise risk and maximise benefit to the patient.

Where can I find out more information?

It is important to read about possible side-effects when getting a new medicine.

Detailed information about side-effects is given in the leaflet for each medicine on the Medicines for Children website, www.medicinesforchildren.org.uk.

www.medicinesforchildren.org.uk

RCPCH Royal College of Paediatrics and Child Health

WellChild the national charity for sick children

NPPG Neonatal & Paediatric Pharmacists Group

Health & care information you can trust

This information is co-produced by: ADRIC; NHS National Institute for Health Research

The primary source for the information in this leaflet is the British National Formulary for Children. For details on any other sources used for this leaflet, please contact us through our website, www.medicinesforchildren.org.uk

We take great care to make sure that the information in this leaflet is correct and up-to-date. However, medicines can be used in different ways for different patients. It is important that you ask the advice of your doctor or pharmacist if you are not sure about something. This leaflet is about the use of these medicines in the UK, and may not apply to other countries. The Royal College of Paediatrics and Child Health (RCPCH), the Neonatal and Paediatric Pharmacists Group (NPPG), WellChild and the contributors and editors cannot be held responsible for the accuracy of information, omissions of information, or any actions that may be taken as a consequence of reading this leaflet.

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