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Pharmacovigilance in children: detecting adverse drug reactions in routine electronic healthcare records. A systematic review

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AIMS
A systematic review of the literature published in English over 10 years was undertaken in order to describe the use of electronic healthcare data in the identification of potential adverse drug reactions (ADRs) in children.

METHODS
MEDLINE and EMBASE were searched using MESH headings and text words. Titles, keywords and abstracts were checked for age <18 years, potential ADRs and electronic healthcare data. Information extracted included age, data source, pharmacovigilance method, medicines and ADRs. Studies were quality assessed.

RESULTS
From 14 804 titles, 314 had a full text review and 71 were included in the final review. Fifty were published in North America, 10 in Scandinavia. Study size ranged from less than 1000 children to more than 10 million. Sixty per cent of studies used data from one source. Comparative observational studies were most commonly reported (66.2%) with 15% using passive surveillance. Electronic healthcare data set linkage and the quality of the data source were poorly reported. ADRs were classified using the International Classification of Disease (ICD10). Multi-system reactions were most commonly studied, followed by central nervous system and mental and behavioural disorders. Vaccines were most frequently prescribed followed by corticosteroids, general anaesthetics and antidepressants.

CONCLUSIONS
Routine electronic healthcare records were increasingly reported to be used for pharmacovigilance in children. This growing and important health protection activity could be enhanced by consistent reporting of studies to improve the identification, interpretation and generalizability of the evidence base.

Introduction

The therapeutic use of medicines is one of the most significant contributors to adverse events associated with healthcare [1, 2]. The potential for adverse drug reactions (ADRs) in children is high [3] with a range of factors contributing to this vulnerability including the physiological changes which take place from birth to late adolescence, lack of evidence-based information regarding the safety and/or efficacy of medicines for paediatric use and high volume of off-label and unlicensed prescribing [4–6].

The overall incidence of ADRs in hospitalized children has been reported in two systematic reviews (2001 and 2009) to be 9.5% and 10.9%, respectively. Admissions to hospital due to ADRs were estimated to be 1.8% to 2.1%, of which up to 39.3% were considered life threatening. The overall incidence in children attending out-patient clinics was 1.0% to 1.5% [7, 8].

A qualitative review in 2010 of ADRs in children highlighted the potential of data collected in national databases for detecting information about previously unknown ADRs [9] but a systematic literature review in 2010 [10] noted that a mixture of methods was used in the majority of studies (58/102) including drawing on case records, computerized records, attendance at ward rounds and interviewing patients. A large proportion (31/102) relied only on case note review. Despite the recognized limitation of under-reporting, spontaneous reports of ADRs continue to play an important role [11].

Given the high numbers of ADRs reported in children, some of which are life-threatening and many of which are preventable, efficient methods of identifying ADRs as part of routine practice are a critical part of improving patient care [12, 13]. There are 'no gold standards' for identifying ADRs in health systems and a range of approaches has been developed [6]. The use of electronic healthcare records in the detection of ADRs has increasingly appeared to have potential and the use for ADR detection in adults has been reported [14]. Electronic healthcare records include a wide range of data source types, from administrative data systems, dispensing data sets, disease registries and spontaneous reports where collated routinely.

In order to describe the use of routinely collected electronic healthcare data in the identification of potential ADRs in children we undertook a systematic review of the literature published in English over 10 years.

Methods

Literature search

Literature published in English was identified in EMBASE and MEDLINE databases between 1999 and 2010. The search was supplemented by searching reference lists of retrieved reviews. The initial search was conducted in September 2009 and updated in January 2010.

Inclusion and exclusion criteria

Papers were considered eligible for inclusion if they referred to ADRs in children (aged 0–18 years). A broad definition of ADR was used, accepting papers reporting the investigation of any potentially adverse clinical event (e.g. specific clinical signs, symptoms or diagnoses, or a clinical event such as an admission to hospital or a visit to a physician) associated with a medicinal product, including vaccines. Only papers reporting the use of routinely collected electronic healthcare data were included. 'Routine' was defined as either a) systems that were part of the day to day recording of clinical care (e.g. medical records, prescribing, administrative data and complaints) or b) special data collections where information collection was a well established part of clinical practice (e.g. specialist registries, incident reporting systems, post-marketing surveillance).

Papers were excluded if they reported a mix of adults and children but did not separate the results. Adverse reactions or complications occurring as a result of surgical or other physical procedures, medicine withdrawal, dietary treatment and supplementation and other non-drug therapy interventions were excluded. We did not include intended or accidental poisoning/overdose or papers concerned with adverse reactions following *in utero* drug exposure. Papers containing insufficient information about the data sources or definition of ADRs were also excluded.

A search strategy was developed, piloted and refined in collaboration with an experienced clinical librarian. Subject headings and subheadings from the MeSH vocabulary for MEDLINE were combined using Boolean terminology with a wide range of free text terms covering four domains: adverse reactions, drug therapy, observational studies and paediatric populations (Supplemental Appendix 1). The text term 'randomized' and MeSH term 'pregnancy' were used to remove randomized controlled studies and reports regarding drugs prescribed during pregnancy. The results were limited to 'all children (0 to 18 years)'. A similar search strategy was applied in EMBASE.

Duplicate publications were removed. Titles and abstracts of the remaining papers were examined against the inclusion/exclusion criteria by three reviewers. This initial screening was conducted using a conservative approach. Full-text papers were retrieved if titles/abstracts appeared to meet the eligibility criteria or if the decision could not be made based on the titles and abstracts alone. Assessment of the full texts of each retrieved paper was undertaken independently by two reviewers using the same criteria (percentage agreement 81%). Any disagreements about inclusion were resolved through discussion (19% of papers). Assessment by a third reviewer to resolve disagreements was not required.

Data extraction

Data extraction was carried out by two reviewers independently using a specifically designed extraction form. Information extracted included age, data source, pharmacovigilance method, medicines and ADRs. Particular attention was paid to the quality of reporting the data source and ADRs. A simple checklist was adapted from guidelines for reporting data linkage studies and selection of databases for pharmacoepidemiology [15, 16]. It included the following key quality issues: ethics review, data entry procedures, data quality assurance, data linkage methods and quality assurance, denominator information and completeness of exposure and outcome data.

The findings of the review were summarized narratively and key characteristics of the studies tabulated. Pharmacovigilance methods were categorized as passive surveillance, active surveillance or comparative observational studies [6] as shown in Box 1. The classification of data sources is summarized in Supplementary Table E1. Information about the size and population coverage was tabulated and summarized graphically. Medicines used in the studies were classified according to the British National Formulary (BNF) categories. If more than three classes of medication were reported in a single study, 'various drug groups' was recorded. ADRs were classified using the International Classification of Diseases (ICD-10). If more than three ICD classes were reported, the ADRs were classified as 'multisystem'.

Box 1

Pharmacovigilance methods: WHO classification (adapted) [6]

Passive surveillance

- Spontaneous reports*
  'an unsolicited communication that describes one or more adverse drug reactions (ADRs) in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme'
- Case series
- Stimulated reporting
  'methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g. in hospital settings) for new products or for limited time periods

'Active surveillance'
seeks to ascertain the exact number of adverse events via a continuous pre-organized process'

- Sentinel site
  'reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure that complete and accurate data on reported adverse events are collected'
- Medicine event monitoring
  'cohort-based and prospective and observational' using active follow up through regular surveys.
- Registries – based on disease or medicine exposure

Comparative observational studies
'There are a number of observational study designs that are useful in validating signals'

- Cross sectional surveys
- Case-control
- Cohort
  'patients for case–control studies and cohort studies can be identified from large automated databases or from data collected specifically for the study at hand'.

**Data-mining, proportional reporting ratios, Bayesian techniques included under spontaneous reports as methods for signal detection*

Results

Included studies

From a total of 14 804 titles retrieved by the initial electronic search strategy, 314 studies were identified for full text review. Of these, 243 papers were excluded because they did not meet the inclusion criteria or provide adequate information about data sources ($n = 23$) and ADRs. Seventy-one papers were included in the final review (Figure 1).

Characteristics of included studies

The main characteristics of the papers are summarized in Supplemental Digital Content Table E2 [17–87]. The number of published studies grew rapidly since 1999 with one third of the papers ($n = 23$, 32.4%) being published within the last 2 years of the review. Research was dominated by North America with 46 (64.8%) of the studies carried out in the USA, four in Canada and one based in both countries. Scandinavia contributed 10 (14.1%) and the UK, four papers (5.6%). Age ranged from birth to 18 years, with five papers focusing on neonates (first 28 days of life) exclusively (7.0%).

Pharmacovigilance methods

A range of pharmacovigilance methods was observed with six studies adopting more than one methodological approach. Comparative observational methods were the most commonly reported ($n = 47$, 66.2%), with 15 (21.1%) reporting passive surveillance methods and only three (4.0%) reporting active surveillance using routine healthcare data.

The predominant study design within comparative observational methodology was the cohort study ($n = 38$, 53.5%). The remaining studies used case–control ($n = 5$, 7%), cross-sectional ($n = 1$) or a combination of designs ($n = 3$, 4.0%).

Passive surveillance methods, in many cases, used national adverse event reporting schemes including some specific to the medication type, such as vaccines. Most

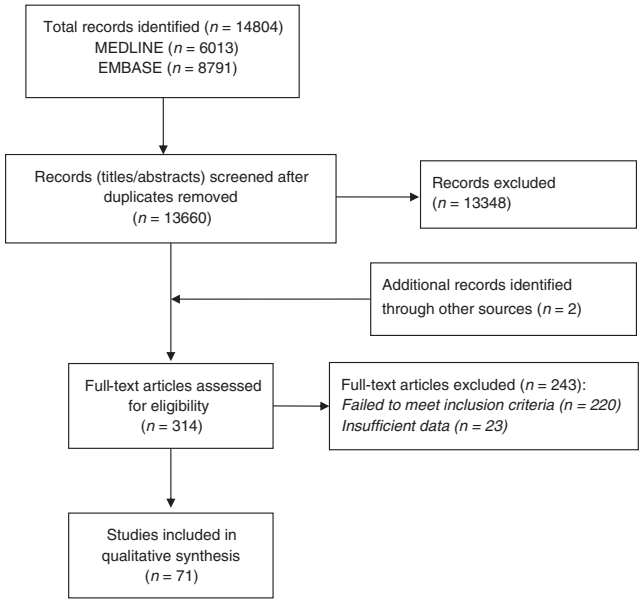

Figure 1
PRISMA flow diagram summarizing study selection process

studies adopted descriptive epidemiological methods, reporting the frequency of various potential ADRs. Some used information from prescribing or dispensing data to estimate the size of the "at risk" population thereby allowing event rates to be approximated. Data mining methods were applied to identify potential ADR signals.

In the studies reporting active surveillance methods, registers, as part of routine care, were kept for all patients taking specific medicines and ADR information was sought proactively by linkage to other healthcare data or by proactive follow-up and recording of ADRs in the register.

Data sources

A total of 68 different data sources were identified in the 71 studies which met the inclusion criteria (Supplemental Table E3). The majority of studies ($n = 42$, 59.1%) used data from a single data source, such as a financial reimbursement system ($n = 14$, 19.7%), hospital database ($n = 11$, 15.5%), or spontaneous reporting system ($n = 12$, 16.9%).

Studies based on more than one data source ($n = 29$, 40.9%) often included the use of registries, financial reimbursement systems and spontaneous reporting systems.

More than half of the studies which used multiple data sources used data linkage ($n = 15$, 51.2%), 10 ($n = 10$, 34.5%) studies used unlinked data and in the remaining four ($n = 4$, 13.8%) studies it could not be ascertained from the reported methods whether the data sources were linked. Where no formal linkage was undertaken, the multiple datasets were used to describe potential ecological associations or to provide estimates of the exposed population to accompany ADR reports in another data source.

Most of the 68 different data sources reported in the included studies were representative at a single country level ($n = 46$, 67.6%). Eleven ($n = 11$, 16.2%) were representative at regional level or above. With regard to the size of the data sources, information on 32 out of 68 (47.1%) was not reported within the included published paper and had to be obtained through extra searching. Data sources were reported either based on the population covered ($n = 54$; 79.4%) or the number of events reported per year/within the study period ($n = 15$, 22.1%) (Figure 2 and Supplemental Table E3).

Quality of reporting data sources

The amount of information and level of detail reported for the data source varied greatly across studies (Figure 3). Ethics permissions were well reported. Most studies used unconsented data (e.g. without individual patient consent for the data to be used in research in general or specifically in a given research project). Data entry methods were poorly reported in most of the studies with many reliant on data collection as part of routine clinical care but little information about who entered the data. Very few commented on the completeness or quality assurance of the source data. Validation against clinical registries or other sources were noted by some authors, in the main relating to well established

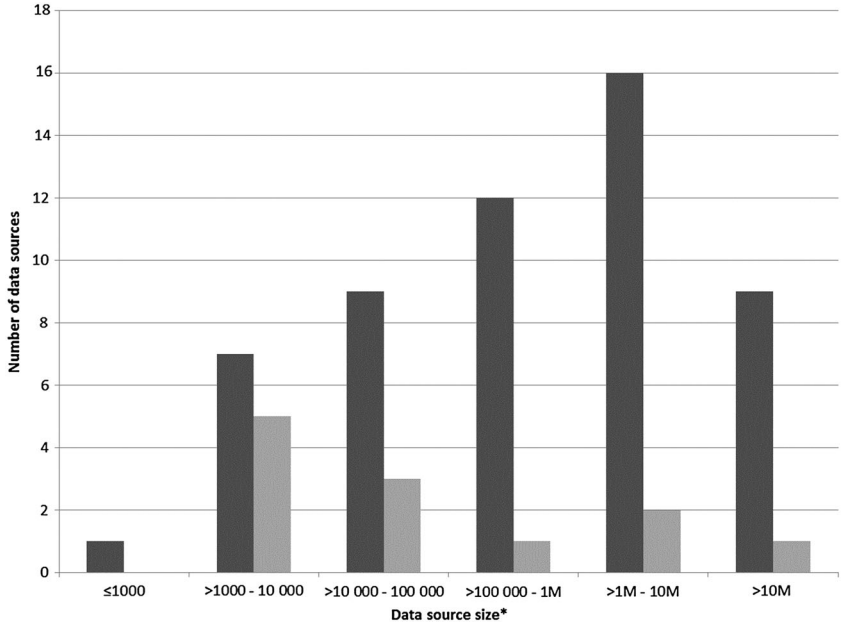

Figure 2

Size of the 68 data sources reported by population covered or the number of events reported per year/within the study period. M, Millions *two data sources did not report size. ■, Population; ■, Records/Reports

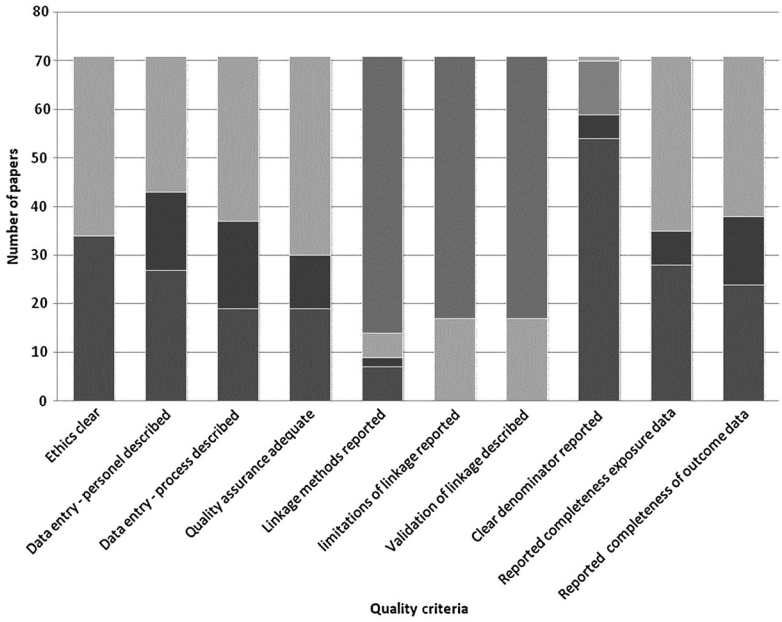

Figure 3

Summary of the quality assessment. ■, Not applicable; ■, Not reported; ■, Did not meet criteria; ■, Partially met criteria; ■, Met criteria

administrative and healthcare databases used regularly for research.

Linkage methods were poorly described and the limitations were rarely quantified. None of the studies reported on whether deterministic or probabilistic matching was undertaken. The completeness and accuracy of the linkage identifiers or the validation checks undertaken to ensure robust linkage were also poorly reported.

Some important limitations were noted by the reviewers, particularly with the passive surveillance methods reliant on potential ADRs being reported by various professional groups and patients to a central registry. The relationship between reporting and various factors including publicity in relation to an ADR were acknowledged. The lack of a robust denominator (how many were exposed) was recognized but largely complete pharmacy dispensing data in some countries allowed this limitation to be overcome. ADR recording in routine data was noted, by many authors, to be poor. The application of disease or ADR definitions and coding of conditions was not uniform within and between studies. The impact this had on generalizability was recognized. The need for high quality information about the date of onset of symptoms in relation to the timing of medicine use was also noted as a limitation by some. However, there was a consistent recognition of the importance of electronic healthcare data as a mechanism to follow up large numbers of medicine users over long periods of time in a real life care setting. This was considered to be critical for both good governance of the introduction of new medicines for long term ADR monitoring and for rare ADR detection.

ADRs and therapeutic groups of medicines studied in routine healthcare data

The definition of ADR varied between studies with some including all ADRs and adverse events, and others restricted to serious, life threatening ADRs or specific clinical outcomes. The studies reported the investigation of a spectrum of potential ADRs involving different organ systems. In 23 (32.4%) studies, electronic healthcare data were used to identify potential ADRs across multiple organ systems (Supplementary Table E2). Where studies focused on three or less ICD classes, the most commonly studied were mental/behavioural disorders ($n = 10$, 14.1%), central nervous system ($n = 10$, 14.1%) and digestive system ($n = 8$, 11.3%). One study reported using laboratory results.

Almost 40% of included studies ($n = 27$) were concerned with investigation of potential ADRs to vaccines (Figure 4). Antidepressants, antipsychotics and other central nervous system (CNS) drugs were the second most commonly studied therapeutic class ($n = 13$, 18.3%), followed by corticosteroids ($n = 7$, 9.9%), antibiotics and antivirals ($n = 7$, 9.9%) and general anaesthetics ($n = 7$; 9.9%).

Discussion

In this systematic review, we identified many pharmacovigilance studies in children using routine electronic healthcare data. The number of studies increased over the period of the review and reflected pharmacovigilance activity in many countries in

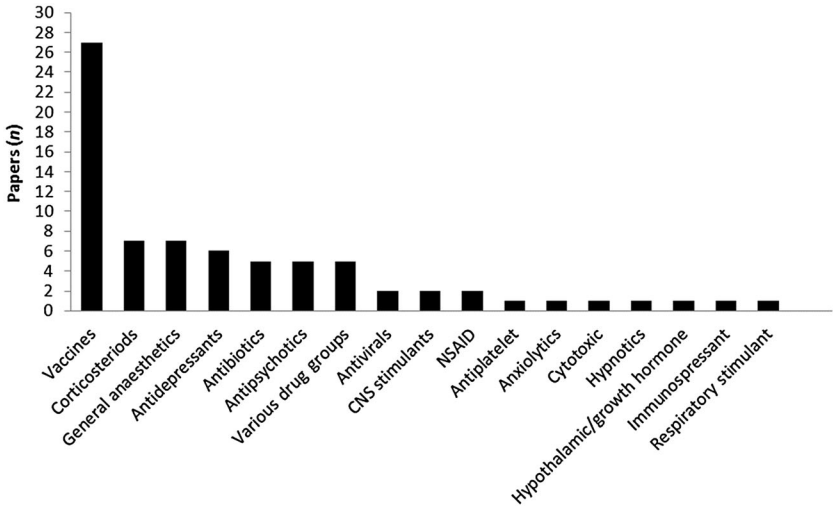

Figure 4

Therapeutic groups of medicines studied for potential ADRs in routine electronic healthcare data

particular North America. A wide variety of routine electronic healthcare data sets were used. Traditional, passive ADR reporting databases were used in 17% of the studies but there was also substantial evidence of the use of single and linked administrative datasets and specialist registries to detect ADRs. Methods such as data mining and comparative observational studies were applied to a wide range of data sources but signal generation, as an early alert to potential ADRs, still very much relied on passive reporting to ADR registries such as the UK Yellow Card Scheme or the US Vaccine Adverse Event reporting System.

This review, by focusing on ADR studies in children using electronic healthcare data, highlights the potential for proactive surveillance for ADRs utilizing the growth in digital medication data and the ability to link to health event data. This approach is complimentary to passive surveillance programmes. Our review also highlights the need for better quality reporting ADR literature.

Proactive ADR surveillance

The Erice Manifesto for Global Reform of the Safety of Medicines in Patient Care (2006) documented challenges in developing pharmacovigilance from a largely reactive activity to proactive study in routine clinical practice. It highlighted the need to develop new ways of collecting, analyzing and communicating information in relation to drug safety and the importance of quality assured research in databases and registries. Despite the WHO making the case for integrated pharmacovigilance as an essential component of public health programmes, we found little reporting of the integration of active surveillance using routine administrative, healthcare or laboratory data to generate potential signals [88].

Recognizing ADR literature

In this review we used a sensitive search strategy and systematically reviewed a large number of titles and abstracts seeking relevant studies, approaches similar to other reviews in this area [10, 89]. Using search terms, either MeSH headings or as free text, proved of limited value in focusing a search strategy without losing key references. In general, studies did not clearly identify that they were studying ADRs. The methodological approach of the study was also rarely reported clearly in the title, keywords or abstract. Guidance for the reporting of other study designs now clearly states the importance of including a statement about study design and aim in the title to improve the ability to retrieve relevant evidence from bibliographic databases [90] and similar guidance would benefit the reporting of studies of ADRs.

ADR detection methods

The WHO classifies ADR detection methods based on data collection procedures as well as study methodology (Box 1) [6]. Here, we found a more mixed picture, particularly with the growth in data linkage of passive spontaneous reports and active registries to administrative data. The range of analytical methodologies where then determined not by the approach to gathering the data, but by the research question with descriptive epidemiology through to data mining for signal generation being applied as appropriate. The WHO classification no longer well categorizes the way researchers are approaching ADR studies.

Quality of reporting

Despite restricting our review to studies with sufficient information about the data sources, we still found substantial variation in the detail and quality of reporting. There was particularly limited information recorded

about the robustness and validity of the datasets. Michel *et al*. [91], reviewing methods for assessing the nature and scale of harm caused by the health system, previously drew attention to the importance of the reliability of healthcare data and emphasized in particular the need for information about the completeness of data in medical records.

Bohensky *et al*. [16] recently published guidelines for the reporting of data linkage studies. Here, the included studies performed poorly against such criteria. Box 2 summarizes recommendations for authors reporting pharmacovigilance studies using routine electronic healthcare data.

Box 2

Recommendations for authors reporting pharmacovigilance studies using routine electronic healthcare data.

Title and abstract
Identify study as pharmacovigilance or ADR detection using electronic healthcare data.
Data source details
In the methods, describe the data source(s) including details of:
Purpose of the data collection
Who entered the data
Data entry process
Quality checks on data entry
Linkage
In the methods, describe linkage process including:
Methods for linkage
Quality of linkage and checks made to ensure validity
ADR detection method
In the methods, report whether
a) Active or passive surveillance approach used to gather ADR data
b) Signal detection, data mining, observational reporting or comparative observational analysis to identify ADRs

Exposure details
In the methods, describe the exposure:
Definition
Completeness of recording
ADR details:
In the methods, describe the ADR:
Definition
Completeness of recording
Denominator definition
In the methods, describe who was included in the dataset and any baises
Ethical review
The ethical review process should be reported

Strengths and limitations of the review

We report a large systematic review of the methods and electronic healthcare data sources used for ADR detection in children but there were a number of limitations to our review. We undertook a sensitive search but this resulted in a large number of titles and abstracts for review. As a result, only one researcher reviewed each title. To minimize inconsistencies, we used detailed inclusion and exclusion criteria and adopted a conservative approach of including studies for full text review where uncertainty existed. We know that other studies of ADRs in children using electronic routine healthcare data have been published but were not identified in our review often because they were reported as the association between a specific medicine and a disease or symptom and as a result were not clearly identifiable as a study of ADRs.

Post-marketing surveillance using electronic healthcare data

Surveillance of drugs in the post-marketing phase since the thalidomide disaster in the 1960s [92] has depended largely on analyses of spontaneous reports to identify new adverse drug events and of observational healthcare studies to confirm or refute suspected adverse events. The withdrawal of rofecoxib in 2004 reinforced again the importance of adverse drug event monitoring to identify as early as possible serious unwanted adverse effects of drugs [93].

The potential of using routine electronic healthcare data to identify adverse events has increasingly been recognised and during the period of this review significant progress has been made in North America and Europe [94, 95].

Conclusion

This systematic literature review identified a large number of routine electronic healthcare datasets worldwide used to study a wide range of medicines and potential ADRs in children. The increasing utility of routine electronic healthcare datasets for pharmacovigilance in children was evident and this growing and important health protection activity could be enhanced by consistent reporting of studies to improve the identification, interpretation and generalizability of the evidence base. Titles, key words and abstracts rarely identified the methodology. A clear classification system should be developed to aid consistent definition of ADR detection methods. Published guidelines should be used for reporting data linkage studies. Reporting of key quality issues should be improved. There is a wealth of electronic healthcare data and realisation of its potential could contribute significantly to pharmacovigilance.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare CB, PH, NTM had support (as part of the CHIMES study) from the Scottish Government, Chief Scientist Office [Grant Number: ARPG/07/4] and Lily Charlton Trust for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

We would like to acknowledge the methodological and clinical contribution of the Child Medical Records for Safer Medicines (CHIMES) study team to the design of the review protocol.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1
MEDLINE Search Strategy 11 September 2009
Table S1
Classification of data sources
Table S2
The key characteristics of the included studies
Table S3
Classification of data sources