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

Authors: C Black, N Tagiyeva-Milne, P Helms, D Moir.

Corresponding author : Corri Black

Contact details:

Dr C Black

Senior Clinical Lecturer in Public Health Medicine

Institute of Applied Health Science

School of Medicine

University of Aberdeen

Foresterhill

Aberdeen

AB25 2ZD

Corri.black@abdn.ac.uk

Keywords: Adverse drug reactions, children, electronic healthcare data, systematic review

Acknowledgments

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 this review.

Conflict of 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 Scottish Government, Chief Scientist Office [Grant Number: ARPG/07/4] and Lily Charlton Trust for the submitted work; no financial relationships with any organisations 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.

STRUCTURED SUMMARY

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, key words and abstracts were checked for age <18, 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

Electronic healthcare records are increasingly used to detect ADRs in children. Titles, keywords or abstracts of papers rarely identified the methodology. Performance against published guidelines for reporting data linkage studies was poor. A classification system to aid consistent definition of study design and improved reporting of key quality issues would improve pharmacovigilance in children.

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 ~~those of~~ birth to late adolescence, the lack of evidence-based information regarding the safety and/or efficacy of medicine for paediatric use and the high volume of off-label and unlicensed prescribing[4-6] .

The overall incidence of ADRs in hospitalised 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%

~~In 2001, a systematic review of ADRs in hospitalised children reported the overall incidence as 9.53%, the overall rate of paediatric hospital admissions due to ADRs as 2.09%, of which 39.3% were life-threatening and the overall incidence in children attending out-patient clinics was 1.46%~~[7~~];.~~ ~~A review in 2009 of prospective studies and safety alerts~~[8]~~. reported the overall incidence of ADRs in hospitalised children as 10.9% and 1.0% in those attending as out-patients while the rate of hospital admissions due to ADRs was 1.8%.~~

~~-~~A qualitative review in 2010 of ~~information about~~ adverse drug reactions reported in children highlighted the potential ~~in 2010~~ of data collected in national databases for detecting information about previously unknown ADRs[9].

Smyth in a systematic literature review of adverse drug reactions in children[10] noted ~~in 2012 additional information on how ADRs in children were reported~~methods for ADR

Formatted: Justified

Formatted: Left

detection. Combinations of methods were used in the majority (58/102) including drawing on case records, and computerised records, attendance at ward rounds and interviewing patients but a large proportion (31/102) relied only on case note review. Lopez-Gonzalez (2009) reporting a systematic review in 2009 onhighlighted the determinants of under-reporting of ADRs demonstrated that whilethrough spontaneous reporting of adverse events and that spontaneous reports identified a small proportion of the total, but, nevertheless, it continued to play an important role in their detection[11].

Given the high numbers of ADR 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 adverse drug reactions in health systems and a range of approaches have been developed[6]. The use of electronic healthcare records in the detection of adverse reactions has increasingly appeared to have potential and the use of 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

~~A systematic review of literature~~Literature published in English was identified in EMBASE and MEDLINE databases between 1999 and 2010. The database 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 ~~in the review~~ if they referred to ADRs in children (aged 0-18 years). A broad definition of ADR was used ~~in this review~~, 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 ~~by age~~. 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 (see Appendix 1, Supplemental Digital Content). The text term 'randomised' and MeSH term 'pregnancy' were used to remove randomised 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.

~~**Box 1** Pharmacovigilance Methods: WHO classification (adapted[4])~~

Duplicate publications were removed. Titles and abstracts of the remaining papers were examined against the inclusion/exclusion criteria by the three reviewers. This initial screening was conducted using a conservative approach: full-text papers were retrieved if ~~their~~ 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 ~~and piloted~~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.

Box 1 Pharmacovigilance Methods: WHO classification (adapted) [6]

The findings of the review were summarised narratively and key characteristics of the studies tabulated. Pharmacovigilance methods were categorised as: passive surveillance, active surveillance or comparative observational studies[6] as shown in Box 1. The classification of data sources is summarised in Table 1. Information about the size and population coverage was tabulated and summarised 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".

Table 1 Classification of data sources reported in the included studies.

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 and ADRs. Seventy-one papers were included in the final review (Figure 1).

Figure 1 PRISMA Flow Diagram of study selection process

Characteristics of included studies

The main characteristics of the papers are summarised in Appendix Table E1 (Supplemental Digital Content)~~Table 2~~. The number of published studies grew rapidly since 1999 with one third of the papers (n=23; 32.4%) being published within the last two years of the review. Research was dominated by North American ~~countries~~ with 46 (64.8%) of the studies carried out in the USA and 4 in Canada and one based in both countries. Scandinavia (Sweden, Denmark, Finland) contributed 10 (14.1%) and the UK, 4 papers (5.6%). Age ranged from birth to 18 years, with 5 papers focusing on neonates (first 28 days of life) exclusively (7.0%).

Pharmacovigilance methods

A range of pharmacovigilance methods were observed with 6 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 3 (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 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 (Appendix Table ~~E1~~ E2 Supplemental Digital Content). 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 4 (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%); 11 (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%) were 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 Digital Content Table E1).

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 *2 data sources did not report size*

Quality of reporting data sources

The amount of information and level of detail reported for the data source varied greatly across studies (see 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 administrative and healthcare databases used regularly for research (such as GPRD, Kaiser Permante, Dutch national datasets).

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 recognised 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 generalisability was recognised. 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.

Figure 3 Summary of the quality assessment

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 twenty three (32.4%) studies electronic healthcare data were used to identify potential ADRs across multiple organ systems (see Table 2). Where studies focused on three or less ICD classes, the most commonly studied were mental/behavioural disorders (n=10; 14.1%), central nervous system (10; 14.1%) and digestive system (n=8; 11.3%), (Table 2). One study reported on abnormal 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%).

Figure 4 Therapeutic groups of medicines studied for potential ADRs in routine electronic healthcare data

Table 2 The key characteristics of the included studies.

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

Search Strategy

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. Smyth

et al[10], in their systematic review of ADRs in children, also retrieved a large number of titles from which the majority were excluded. In general, studies did not clearly identify that they were studying ADRs. Sometimes ADRs were reported only as one of a number of outcomes, but even where ADR detection was the main focus, studies were often poorly identified as such. 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 in the title to improve the ability to retrieve relevant evidence from bibliographic databases. The CONSORT statement promotes the inclusion of the study design in the title for randomised controlled trials[90] and similar guidance on titles and key word coding 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]. For example, passive surveillance is described both in terms of the recording of the data – through spontaneous reporting, and in terms of the analytical approaches of data mining that might be applied to such data. The practical application of this classification is, however, challenging as technology and methodology has evolved. Traditional passive ADR recording systems, where ADRs are submitted to a central register by prescribers, health professionals or patients were increasingly interrogated proactively to provide early warning signals of ADRs employing various methods including data mining techniques or linkage to other data sources to establish the numbers exposed to a drug. Routinely collected administrative healthcare data were not being used to proactively seek signals for potential ADRs but rather to test hypotheses of associations between medicines and symptoms or diseases using traditional epidemiological observational study designs. The WHO classification mixes methods for

collecting the data with methods for interrogating the data that no longer well categorise the way researchers are approaching ADR studies. In this review we utilised the high level methodologies to categorise approaches: passive surveillance, active surveillance and comparative observational studies. This recognises that for each methodological approach there are a wide range of potential data collection methods and analytical methods that could be applied.

Quality Assessment

We undertook quality assessment of the included studies using criteria focusing on the assessment of whether key methodological aspects were reported clearly. Smyth et al[10], who were unable to find a validated quality assessment tool, similarly developed a quality assessment form for their review. Despite restricting our review to studies with sufficient information about the data sources and methods used, 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 providing data. 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 the limitations of health records as a source of information about ADRs and emphasised in particular the need for information about the completeness of data in medical records.

Where more than one dataset was linked, the methods for linkage and validation of the linkage process was generally not described. Bohensky et al[16] recently published guidelines for the reporting of data linkage studies. The studies we included in this review performed poorly against such criteria. The ethical use of the data was considered and most studies included a statement about the ethical review process. The included studies did, however, undergo a variety of different ethical review processes ranging from

statements that "ethical review was not required" because data were "anonymous" through to full ethics committee review and approval for each use of a dataset. Box 2 summarises recommendations for authors reporting pharmacovigilance studies using routine electronic healthcare data.

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 minimise 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. Twenty three studies were excluded because there was insufficient information provided about the data sources for the purpose of this review.

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. Curtis et al described in 2012 how the Food and Drug Administration (FDA) established the Sentinel System a nationwide network of databases in the United States of America and the use of the Mini-Sentinel distributed data system to inform and facilitate the development of active surveillance for monitoring the use and safety of medicinal products[94]. The European Commission likewise funded a project, EU-ADR, to demonstrate the feasibility of combining datasets from various countries to identify unwanted adverse drug events and has developed advanced techniques for harmonisation of data [95].

The use of electronic healthcare data in the study of potential Adverse Drug Reactions is increasingly developed in America and Europe but as serious adverse drug reactions are usually identified initially in small numbers, the pooling and analysis of larger electronic healthcare data sets will facilitate their early detection. The United Kingdom has contributed General Practice data to the EU-ADR project while many administrative systems, dispensing data sets, disease registries and spontaneous reporting systems are also well developed and could increase the potential of electronic healthcare data sets in the identification of previously unidentified ADRs.

Conclusion

This systematic literature review identified a large number of resources 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 generalisability 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 as part of a wider pooling process.

References

1. Leape, LL., Brennan, T. A., Laird, N., Lawthers, A. G., Localio, A. R., Barnes, B. A., Hebert, L., Newhouse, J. P., Weiler, P. C., and Hiatt, H. The nature of adverse events in hospitalized patients-results of the Harvard Medical Practice Study II. *N. Engl. J. Med.* **324**:377-384, 1991.

2. Thomas, E. J., Studdert, D. M., Burstin, H. R., Orav, E. J., Zeena, T., Williams, E. J., Howard, K. M., Weiler, P. C., and Brennan, T. A. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care* **38**:261-271, 2000.

3. WHO. Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action. WHO/EDM/QSM/2002.2. 2002. Geneva, World Health Organization.
4. Horen, B., Montastruc, J. L., and Lapeyre-Mestre, M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* **54**:665-670, 2002.

5. Impicciatore, P., Mohn, A., Chiarelli, F., Pandolfini, C., and Bonati, M. Adverse Drug Reactions to Off-label Drugs on a Paediatric Ward: an Italian Prospective Pilot Study. Paediatric and Perinatal Drug Therapy 5[1], 19-24. 2002.
6. WHO. Promoting safety of medicines for children. 2007. 20 Avenue Appia, 1211 Geneva 27, Switzerland, WHO Press, World Health Organization.
7. Impicciatore, P., Choonara, I., Clarkson, A., Provasi, D., Pandolfini, C., and Bonati, M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* **52**:77-83, 2001.

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

9. Aagaard, L., Christensen, A., and Hansen, E. H. Information about adverse drug reactions reported in children: a qualitative review of empirical studies. *Br. J Clin. Pharmacol.* **70**:481-491, 2010.

10. Smyth, R. M. D., Gargon, E., Kirkham, J., Cresswell, L., Golder, S., Smyth, R., and Williamson, P. Adverse Drug Reactions in Children - A Systematic Review. *PLoS One* **7**:e24061, 2012.

11. Lopez-Gonzalez, E., Herdeiro, M. T., and Figueiras, A. Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Saf* **32**:19-31, 2009.

12. Al Tajir, G. K. and Kelly, W. N. Epidemiology, comparative methods of detection, and preventability of adverse drug events. *Ann. Pharmacother.* **39**:1169-1174, 2005.

13. Kunac, D. L., Kennedy, J., Austin, N., and Reith, D. Incidence, preventability, and impact of adverse drug events (ADEs) and potential ADEs in hospitalized children in New Zealand: A prospective observational cohort study. *Pediatric Drugs* **11**:153-160, 2009.

14. Suling, M. and Pigeot, I. Signal detection and monitoring based on longitudinal healthcare data. *Pharmaceutics.* **4**:607-640, 2012.

15. Hall, G. C., Sauer, B., Bourke, A., Brown, J. S., Reynolds, M. W., and Casale, R. L. Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol. Drug Saf* **21**:1-10, 2012.

16. Bohensky, M. A., Jolley, D., Sundararajan, V., Evans, S., Ibrahim, J., and Brand, C. Development and validation of reporting guidelines for studies involving data linkage. *Aust N Z J Public Health* **35**:486-489, 2011.

17. Andrews, N., Miller, E., Grant, A., Stowe, J., Osborne, V., and Taylor, B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association. *Pediatrics* **114**:584-591, 2004.

18. Attridge, J. T., Clark, R., Walker, M. W., and Gordon, P. V. New insights into spontaneous intestinal perforation using a national data set: (2) two populations of patients with perforations. *J. Perinatol.* **26**:185-188, 2006.

19. Attridge, J. T., Clark, R., Walker, M. W., and Gordon, P. V. New insights into spontaneous intestinal perforation using a national data set: (1) SIP is associated with early indomethacin exposure. *J. Perinatol.* **26**:93-99, 2006.

20. Baxter, A. L., Mallory, M. D., Spandorfer, P. R., Sharma, S., Freilich, S. H., Cravero, J., and Pediatric Sedation Research, C. Etomidate versus pentobarbital for computed tomography sedations: report from the Pediatric Sedation Research Consortium. *Pediatr. Emerg. Care* **23**:690-695, 2007.

21. Black, S., Shinefield, H., Ray, P., Lewis, E., Hansen, J., Schwalbe, J., Coplan, P., Sharrar, R., and Guess, H. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr. Infect. Dis. J.* **18**:1041-1046, 1999.

22. Blumentals, W. A. and Song, X. The safety of oseltamivir in patients with influenza: Analysis of healthcare claims data from six influenza seasons. *MedGenMed Medscape General Medicine* **9**:Arte, 2007.

23. Brunlof, G., Tukukino, C., and Wallerstedt, S. M. Individual case safety reports in children in commonly used drug groups - signal detection. *BMC Clinical Pharmacology* **8**:1, 2008.

24. Casscells, S. W., Granger, E., Kress, A. M., and Linton, A. The association between oseltamivir use and adverse neuropsychiatric outcomes among TRICARE beneficiaries, ages 1 through 21 years diagnosed with influenza. *Int. J. Adolesc. Med. Health* **21**:79-89, 2009.

25. Center, K. J., Hansen, J. R., Lewis, E., Fireman, B. H., and Hilton, B. Lack of association of kawasaki disease after immunization in a cohort of infants followed for multiple autoimmune diagnoses in a large, phase-4 observational database safety study of 7-valent

pneumococcal conjugate vaccine: Lack of association between kawasaki disease and seven-valent pneumococcal conjugate vaccine. *Pediatr. Infect. Dis. J.* **28**:438-440, 2009.

26. Chaves, S. S., Haber, P., Walton, K., Wise, R. P., Izurieta, H. S., Schmid, D. S., and Seward, J. F. Safety of varicella vaccine after licensure in the United States: experience from reports to the vaccine adverse event reporting system, 1995-2005. *J. Infect. Dis.* **197**:S170-S177, 2008.

27. Chong, E., Greenspan, J., Kirkby, S., Culhane, J., and Dysart, K. Changing use of surfactant over 6 years and its relationship to chronic lung disease. *Pediatrics* **122**:e917-e921, 2008.

28. Clark, R. H., Bloom, B. T., Spitzer, A. R., and Gerstmann, D. R. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. *Pediatrics* **117**:67-74, 2006.

29. Clarkson, A., Choonara, I., and Marcovitch, H. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch. Dis. Child.* **87**:462-467, 2002.

30. Davis, R. L., Black, S., Shinefield, H., Mahoney, L., Zavitkovsky, A., Lewis, E., Nikas, A., Guess, H., and Coplan, P. Post-marketing evaluation of the short term safety of COMVAX. *Vaccine* **22**:536-543, 2004.

31. De Vries, T. W., Langen-Wouterse, J. J., van Puijenbroek, E., Duiverman, E. J., and De Jong-Van Den Berg Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. *Eur. J. Clin. Pharmacol.* **62**:343-346, 2006.

32. De Vries, T. W., Langen-Wouterse, J. J., De Jong-Van Den Berg, and Duiverman, E. J. Hypertrichosis as a side effect of inhaled steroids in children. *Pediatr. Pulmonol.* **42**:370-373, 2007.

33. Deeks, S. L., Clark, M., Scheifele, D. W., Law, B. J., Dawar, M., Ahmadipour, N., Walop, W., Ellis, C. E., and King, A. Serious adverse events associated with bacille Calmette-Guerin vaccine in Canada. *Pediatr. Infect. Dis. J.* **24**:538-541, 2005.

34. Dharnidharka, V. R., Ho, P. L., Stablein, D. M., Harmon, W. E., and Tejani, A. H. Mycophenolate, tacrolimus and posttransplant lymphoproliferative disorder: A report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr. Transplant.* **6**:396-399, 2002.

35. Donahue, J. G., Kieke, B. A., Yih, W. K., Berger, N. R., McCauley, J. S., Baggs, J., Zangwill, K. M., Baxter, R., Eriksen, E. M., Glanz, J. M., Hambidge, S. J., Klein, N. P., Lewis, E. M., Marcy, S. M., Naleway, A. L., Nordin, J. D., Ray, P., and Belongia, E. A. Varicella vaccination and ischemic stroke in children: Is there an association? *Pediatrics* **123**:e228-e234, 2009.

36. France, E. K., Glanz, J. M., Xu, S., Davis, R. L., Black, S. B., Shinefield, H. R., Zangwill, K. M., Marcy, S. M., Mullooly, J. P., Jackson, L. A., and Chen, R. Safety of the trivalent inactivated influenza vaccine among children: A population-based study. *Arch. Pediatr. Adolesc. Med.* **158**:1031-1036, 2004.

37. France, E. K., Glanz, J., Xu, S., Hambidge, S., Yamasaki, K., Black, S. B., Marcy, M., Mullooly, J. P., Jackson, L. A., Nordin, J., Belongia, E. A., Hohman, K., Chen, R. T., and Davis, R. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics* **121**:e687-e692, 2008.

38. Geier, D. A., King, P. G., Sykes, L. K., and Geier, M. R. RotaTeq vaccine adverse events and policy considerations. *Medical Science Monitor* **14**:H9-16, 2008.

39. Gold, M. S., Noonan, S., Osbourn, M., Precepa, S., and Kempe, A. E. Local reactions after the fourth dose of acellular pertussis vaccine in South Australia. *Med. J. Aust.* **179**:191-194, 2003.

40. Gonzalez-Heydrich, J., Raches, D., Wilens, T. E., Leichtner, A., and Mezzacappa, E. Retrospective study of hepatic enzyme elevations in children treated with olanzapine, divalproex, and their combination. *Journal of the American Academy of Child & Adolescent Psychiatry* **42**:1227-1233, 2003.

41. Haber, P., Patel, M., Izurieta, H. S., Baggs, J., Gargiullo, P., Weintraub, E., Cortese, M., Braun, M. M., Belongia, E. A., Miller, E., Ball, R., Iskander, J., and Parashar, U. D. Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, february 1, 2006, to september 25, 2007. *Pediatrics* **121**:1206-1212, 2008.

42. Hambidge, S. J., Glanz, J. M., France, E. K., McClure, D., Xu, S., Yamasaki, K., Jackson, L., Mullooly, J. P., Zangwill, K. M., Marcy, S. M., Black, S. B., Lewis, E. M., Shinefield, H. R., Belongia, E., Nordin, J., Chen, R. T., Shay, D. K., Davis, R. L., and DeStefano, F. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *J. Am. Med. Assoc.* **296**:1990-1997, 2006.

43. Haukka, J., Arffman, M., Partonen, T., Sihvo, S., Elovainio, M., Tiihonen, J., Lonnqvist, J., and Keskimaki, I. Antidepressant use and mortality in Finland: a register-linkage study from a nationwide cohort. *Eur. J. Clin. Pharmacol.* **65**:715-720, 2009.

44. Hviid, A., Stellfeld, M., Wohlfahrt, J., and Melbye, M. Association between Thimerosal-Containing Vaccine and Autism. *J. Am. Med. Assoc.* **290**:1763-1766, 2003.

45. Hviid, A., Stellfeld, M., Wohlfahrt, J., and Melbye, M. Childhood Vaccination and Type 1 Diabetes. *N. Engl. J. Med.* **350**:1398-1404, 2004.

46. Hviid, A. and Svanstrom, H. Antibiotic use and type 1 diabetes in childhood. *Am. J. Epidemiol.* **169**:1079-1084, 2009.

47. Inskip, P. D. and Curtis, R. E. New malignancies following childhood cancer in the United States, 1973-2002. *Int. J. Cancer* **121**:2233-2240, 2007.

48. Jacobsen, S. J., Ackerson, B. K., Sy, L. S., Tran, T. N., Jones, T. L., Yao, J. F., Xie, F., Craig Cheetham, T., and Saddier, P. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine* **27**:4656-4661, 2009.

49. Jerrell, J. M. and McIntyre, R. S. Adverse events in children and adolescents treated with antipsychotic medications. *Human Psychopharmacology* **23**:283-290, 2008.

50. Jerrell, J. M., Hwang, T. L., and Livingston, T. S. Neurological adverse events associated with antipsychotic treatment in children and adolescents. *J. Child Neurol.* **23**:1392-1399, 2008.

51. Jerrell, J. M. and McIntyre, R. S. Cardiovascular and neurological adverse events associated with antidepressant treatment in children and adolescents. *J. Child Neurol.* **24**:297-304, 2009.

52. Karian, V. E., Burrows, P. E., Zurakowski, D., Connor, L., and Mason, K. P. Sedation for pediatric radiological procedures: analysis of potential causes of sedation failure and paradoxical reactions. *Pediatr. Radiol.* **29**:869-873, 1999.

53. Kemp, S. F., Kuntze, J., Attie, K. M., Maneatis, T., Butler, S., Frane, J., and Lippe, B. Efficacy and safety results of long-term growth hormone treatment of idiopathic short stature. *Journal of Clinical Endocrinology & Metabolism* **90**:5247-5253, 2005.

54. Kimland, E., Rane, A., Ufer, M., and Panagiotidis, G. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiology & Drug Safety* **14**:493-499, 2005.

55. Kozyrskyj, A. L., Ernst, P., and Becker, A. B. Increased risk of childhood asthma from antibiotic use in early life. *Chest* **131**:1753-1759, 2007.

56. Kuno-Sakai, H. and Kimura, M. Removal of gelatin from live vaccines and DTaP-an ultimate solution for vaccine-related gelatin allergy. *Biologicals* **31**:245-249, 2003.

57. Lewis, E., Shinefield, H. R., Woodruff, B. A., Black, S. B., DeStefano, F., Chen, R. T., Ensor, R., and Vaccine Safety Datalink, W. Safety of neonatal hepatitis B vaccine administration. *Pediatr. Infect. Dis. J.* **20**:1049-1054, 2001.

58. Makela, A., Nuorti, J. P., and Peltola, H. Neurologic disorders after measles-mumps-rubella vaccination. *Pediatrics* **110**:957-963, 2002.

59. Maltz, L. A., Gauvreau, K., Connor, J. A., and Jenkins, K. J. Clopidogrel in a pediatric population: prescribing practice and outcomes from a single center. *Pediatr. Cardiol.* **30**:99-105, 2009.

60. Mancini, J., Thirion, X., Masut, A., Saillard, C., Pradel, V., Romain, F., Pastor, M. J., Coudert, C., and Micallef, J. Anxiolytics, hypnotics, and antidepressants dispensed to adolescents in a French region in 2002. *Pharmacoepidemiology & Drug Safety* **15**:494-503, 2006.

61. Marra, F., Marra, C. A., Richardson, K., Lynd, L. D., Kozyrskyj, A., Patrick, D. M., Bowie, W. R., and Fitzgerald, J. M. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics* **123**:1003-1010, 2009.

62. Mason, K. P., Zurakowski, D., Karian, V. E., Connor, L., Fontaine, P. J., and Burrows, P. E. Sedatives used in pediatric imaging: comparison of IV pentobarbital with IV pentobarbital with midazolam added. *AJR. Am. J. Roentgenol.* **177**:427-430, 2001.

63. Mason, K. P., Sanborn, P., Zurakowski, D., Karian, V. E., Connor, L., Fontaine, P. J., and Burrows, P. E. Superiority of pentobarbital versus chloral hydrate for sedation in infants during imaging. *Radiology* **230**:537-542, 2004.

64. Mason, K. P., Zurakowski, D., Connor, L., Karian, V. E., Fontaine, P. J., Sanborn, P. A., and Burrows, P. E. Infant sedation for MR imaging and CT: oral versus intravenous pentobarbital. *Radiology* **233**:723-728, 2004.

65. Mason, K. P., Zurakowski, D., Zgleszewski, S. E., Robson, C. D., Carrier, M., Hickey, P. R., and DiNardo, J. A. High dose dexmedetomidine as the sole sedative for pediatric MRI. *Paediatr. Anaesth.* **18**:403-411, 2008.

66. Mason, K. P., Padua, H., Fontaine, P. J., and Zurakowski, D. Radiologist-supervised ketamine sedation for solid organ biopsies in children and adolescents. *AJR. Am. J. Roentgenol.* **192**:1261-1265, 2009.

67. McDonald, K. L., Huq, S. I., Lix, L. M., Becker, A. B., and Kozyrskyj, A. L. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *Journal of Allergy & Clinical Immunology* **121**:626-631, 2008.

68. McMahon, A. W., Iskander, J. K., Haber, P., Braun, M. M., and Ball, R. Inactivated influenza vaccine (IIV) in children <2 years of age: examination of selected adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) after thimerosal-free or thimerosal-containing vaccine. *Vaccine* **26**:427-429, 2008.

69. Moore, T. J., Weiss, S. R., Kaplan, S., and Blaisdell, C. J. Reported adverse drug events in infants and children under 2 years of age. *Pediatrics* **110**:e53, 2002.

70. Niu, M. T., Erwin, D. E., and Braun, M. M. Data mining in the US Vaccine Adverse Event Reporting System (VAERS): early detection of intussusception and other events after rotavirus vaccination. *Vaccine* **19**:4627-4634, 2001.

71. Olfson, M., Marcus, S. C., and Shaffer, D. Antidepressant drug therapy and suicide in severely depressed children and adults: A case-control study. *Arch. Gen. Psychiatry* **63**:865-872, 2006.

72. Olfson, M. and Marcus, S. C. A case-control study of antidepressants and attempted suicide during early phase treatment of major depressive episodes. *J. Clin. Psychiatry* **69**:425-432, 2008.

73. Safer, D. J., Zito, J. M., and Gardner, J. F. Pemoline hepatotoxicity and postmarketing surveillance. *J. Am. Acad. Child Adolesc. Psychiatry* **40**:622-629, 2001.

74. Schirm, E., Tobi, H., van Puijenbroek, E. P., Monster-Simons, M. H., and De Jong-Van Den Berg Reported adverse drug reactions and their determinants in Dutch children outside the hospital. *Pharmacoepidemiology & Drug Safety* **13**:159-165, 2004.

75. Schlienger, R. G., Jick, S. S., and Meier, C. R. Inhaled corticosteroids and the risk of fractures in children and adolescents. *Pediatrics* **114**:469-473, 2004.

76. Simonsen, L., Viboud, C., Elixhauser, A., Taylor, R. J., and Kapikian, A. Z. More on RotaShield and intussusception: the role of age at the time of vaccination. *J. Infect. Dis.* **192**:S36-S43, 2005.

77. Sondergard, L., Kvist, K., Andersen, P. K., and Kessing, L. V. Do antidepressants precipitate youth suicide?: a nationwide pharmacoepidemiological study. *European child & adolescent psychiatry* **15**:232-240, 2006.

78. Szarfman, A., Tonning, J. M., Levine, J. G., and Doraiswamy, P. M. Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. *Pharmacotherapy* **26**:748-758, 2006.

79. van Staa, T. P., Cooper, C., Leufkens, H. G., and Bishop, N. Children and the risk of fractures caused by oral corticosteroids. *Journal of Bone & Mineral Research* **18**:913-918, 2003.

80. Verstraeten, T., Baughman, A. L., Cadwell, B., Zanardi, L., Haber, P., Chen, R. T., and Vaccine Adverse Event Reporting System, T. Enhancing vaccine safety surveillance: a

capture-recapture analysis of intussusception after rotavirus vaccination. *Am. J. Epidemiol.* **154**:1006-1012, 2001.

81. Vestergaard, M., Hviid, A., Madsen, K. M., Wohlfahrt, J., Thorsen, P., Schendel, D., Melbye, M., and Olsen, J. MMR Vaccination and Febrile Seizures: Evaluation of Susceptible Subgroups and Long-term Prognosis. *JAMA: The Journal of the American Medical Association* **292**:351-357, 2004.

82. Walsh, M. C., Yao, Q., Horbar, J. D., Carpenter, J. H., Lee, S. K., and Ohlsson, A. Changes in the use of postnatal steroids for bronchopulmonary dysplasia in 3 large neonatal networks. *Pediatrics* **118**:e1328-e1335, 2006.

83. Wattigney, W. A., Mootrey, G. T., Braun, M. M., and Chen, R. T. Surveillance for poliovirus vaccine adverse events, 1991 to 1998: impact of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. *Pediatrics* **107**:E83, 2001.

84. Winterstein, A. G., Gerhard, T., Shuster, J., Johnson, M., Zito, J. M., and Saidi, A. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics* **120**:e1494-e1501, 2007.

85. Woods, S. W., Martin, A., Spector, S. G., and McGlashan, T. H. Effects of development on olanzapine-associated adverse events. *J. Am. Acad. Child Adolesc. Psychiatry* **41**:1439-1446, 2002.

86. Young, H. A., Geier, D. A., and Geier, M. R. Thimerosal exposure in infants and neurodevelopmental disorders: an assessment of computerized medical records in the Vaccine Safety Datalink. *J. Neurol. Sci.* **271**:110-118, 2008.

87. Zhang, Q., Matsumura, Y., Teratani, T., Yoshimoto, S., Mineno, T., Nakagawa, K., Nagahama, M., Kuwata, S., and Takeda, H. The application of an institutional clinical data warehouse to the assessment of adverse drug reactions (ADRs). Evaluation of

aminoglycoside and cephalosporin associated nephrotoxicity. *Methods Inf. Med.* **46**:516-522, 2007.

88. WHO. The safety of medicines in public health programmes: Pharmacovigilance: an essential tool. 2006. WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland, WHO Essential Medicines and Pharmaceutical Policies Department.
89. Luo, X., Cappelleri, J. C., and Frush, K. A systematic review on the application of pharmacoepidemiology in assessing prescription drug-related adverse events in pediatrics. *Curr Med Res Opin* **23**:1015-1024, 2007.
90. CONSORT. The CONSORT Statement . Consolidated Standards of Reporting Trials . 2012. 1-2-2012.
91. Michel, P. Strengths and weaknesses of available methods for assessing the nature and scale of harm caused by the health system: literature review. 2003. Geneva, World Health Organization.
92. Dally, A. Thalidomide: was the tragedy preventable? *The Lancet* **351**:1197-1199, 1998.
93. Juni, P., Nartey, L., Reichenbach, S., Sterchi, R., Dieppe, P. A., and Egger, M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *The Lancet* **364**:2021-2029, 2004.
94. Curtis, L. H., Weiner, M. G., Boudreau, D. M., Cooper, W. O., Daniel, G. W., Nair, V. P., Raebel, M. A., Beaulieu, N. U., Rosofsky, R., Woodworth, T. S., and Brown, J. S. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. *Pharmacoepidemiol Drug Saf* **21**:23-31, 2012.
95. Coloma, P. M., Schuemie, M. J., Trifiro, G., Gini, R., Herings, R., Hippisley-Cox, J., Mazzaglia, G., Giaquinto, C., Corrao, G., Pedersen, L., van der, L. J., and Sturkenboom, M. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. *Pharmacoepidemiol. Drug Saf* **20**:1-11, 2011.