Studying Disease Occurrence and Drug Effects in Children: *A global approach*

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For reasons of consistency within this thesis, some terms have been standardized throughout the text. As a consequence, the text may differ in this respect from the articles that have been published.

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Studying Disease Occurrence and Drug Effects in Children: *A global approach*

Onderzoek naar ziekte en geneesmiddeleffecten in kinderen: *een wereldwijde aanpak*

Thesis

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To my son, *Noah*

and

my parents, *Emmanuel (RIP) and Victoria*

Chapter 1 General Introduction

The paragraphs that follow provide an introduction to this thesis which is about a global approach to studying disease occurrence and drug effects in children.

Diseases in children: burden and characteristics on a global scale

Usually, children are healthy when they are born. In the first 6-12 months of life, they are protected against infections mainly by maternal antibodies acquired during pregnancy[1-4]. Although they ultimately develop their own immunity, this takes time. Meanwhile, they get exposed to various environmental pathogens and therefore can become infected. Newborns and older children can also experience diseases and injuries resulting from genetic or multifactorial causes[5-8]. Some childhood infections are common, transient and recurrent i.e. acute otitis media (AOM). On the other end of the spectrum of recurrent diseases there may be rare conditions i.e. acute pyelonephritis (APN)[9 10]. Other infections are highly contagious but seldom recur i.e. measles[11]. Non-infectious, multifactorial diseases that affect children may be chronic and differ in frequency: asthma is common and chronic unlike type 1 diabetes (DM) which is also chronic but less common[12,13]. Complications may occur, including death and disability.

According to findings from a study that was conducted in 188 countries[14], the leading causes of death (globally) among children *aged <5 years* in 2013 were lower respiratory tract infections (LRTIs), preterm birth complications, neonatal encephalopathy following birth trauma and asphyxia, malaria, and diarrheal diseases. Altogether, these causes accounted for 3.4 million deaths (54% of all deaths) in this age group. Preterm birth complications and congenital anomalies were the leading causes of death among countries in North America, Australasia, Europe, East Asia, and most countries in Latin America and the Caribbean. LRTIs, malaria, and diarrheal diseases were the leading causes of death in sub-Saharan African countries. Lower respiratory tract infections were also the leading cause for some countries in Asia. Neonatal encephalopathy was the most common cause of death in some South Asian countries.

Among children *aged 5-9 years*, the most common cause of death in 2013 was diarrheal disease, followed by LRTIs, road injuries, intestinal infectious diseases (mainly typhoid and paratyphoid), and malaria. Altogether, these causes accounted for 181 000 deaths (39% of all deaths) in this age group. Road injuries were the leading cause of death for countries in North America, Latin America and the Caribbean, and Australasia, while drowning was the most common cause of death in most countries in Eastern Europe, East Asia, and Southeast Asia. Intestinal infectious diseases and LRTIs were the leading causes for countries in South Asia, while diarrheal diseases, HIV/AIDS, and malaria were the leading causes for countries in sub-Saharan Africa.

Among children *aged 10-19 years*, the leading causes of death in 2013 were road injuries, HIV/AIDS, self-harm, drowning, and intestinal infectious diseases; accounting for 34% of all deaths in this age group. Injury-related deaths were the leading causes in most countries except for those in sub-Saharan Africa, where HIV/AIDS was the leading cause of death. Self-harm was the most common cause of death for some parts of Asia and Eastern Europe.

Regarding disability, iron deficiency anemia was the most common cause of years lived with disability (YLDs) among children and adolescents. Fifty countries with the largest child and adolescent population contributed to 86% of global iron deficiency anemia cases with India, China and Nigeria being the top three countries. Skin diseases and depression were the second and third leading causes of YLDs.

Drugs for children: Inadequate evidence supporting safe and effective use, and legislations aimed at generating better evidence

Many childhood diseases can be treated using (essential) medicines. Following the thalidomide scandal[15]; regulations were introduced that require evaluation of quality, benefits and risks of medicines, prior to marketing. In the past, children were often excluded from randomized clinical trials (RCTs) because of ethical considerations leading to a high rate of unlicensed or off-label use of drugs in pediatrics. Unlicensed drug use is the use of medications that are not approved for use by the relevant national authority while off-label use means the use of pharmaceutical drugs outside the product license for an unapproved indication, an unapproved age group, unapproved dosage, or unapproved form of administration[16,17]. In an overview of

different studies Conroy et. al (1999) reported unlicensed or off-label drug use to be as high as 90%[18]. In Australia, 47% of prescriptions in the neonatal intensive care unit was off-label, while in France, 42% prevalence was reported. Radley et al (2006) reported that 21% prescriptions were off-label while Shah et al (2007) reported that 78.9% of discharged children were taking at least one off-label drug[19,20]. In a survey conducted in the pediatric wards of five European countries, Conroy et al (2000) reported that 67% of admitted children received drugs prescribed either unlicensed or used in an off-label manner[21]. Analgesics and bronchodilators were most commonly prescribed off-label. In three of the five countries, off-label drug use most often pertained to dose and frequency accounting for more than half of off-label use. Almost half (46%) of all prescriptions (2262) were either unlicensed or off-label. According to Pandolfini et al (2005), out of 30 studies conducted between 1985 to 2004, off-label and unlicensed prescription rates ranged from 11% to 80% with higher rates found in younger patients than older ones[22].

The importance of pediatric drugs as a global health issue was recognized in the World Health Assembly resolution WHA60.20 "Better medicines for children" (http://www.who.int/gb/ebwha/pdf_files/WHA60/A60_R20-en) in 2007[23]. The increased awareness of the need for improved drugs for children has led to legislation in the US and Europe, and aimed at facilitating the development of drugs for children specifically. In the US the legislation include the Food and Drug Administration Modernization Act (1997), Best Pharmaceuticals for Children Act (BPCA) (2002), Pediatric Research Equity Act (PREA) (2003) and the Food and Drug Administration Amendments Act (FDAAA) (2007)[24-27]. In Europe pediatric drugs has been an area of focus in: European Medicines Agency (EMA) Round Table of experts (1997), Note for Guidance on the Clinical Investigation of Medicinal products in Children (1999), Council of the Ministers of Health Resolution (2000), Regulation no. 141/2000 (2000) and Directive EC/2001/20 (2000). Finally, the European regulation on Medicinal products for pediatrics, which was introduced in January 2007, represented a major breakthrough in pediatric drug development[28,29].

Currently, both the US Federal Drug Administration (FDA) and EMA require that each drug in development that may be used in children should be investigated specifically in children. The

procedures include waivers for diseases that affect only adults or deferrals if studies in children are not appropriate or would lead to unnecessary delay in the authorization of drugs for adults. Both the FDA and EMA can offer extended patent protection to marketing authorization holders who have tested new drugs in children and meet other criteria. In addition, in Europe, the 'Paediatric Use Marketing Authorization' (PUMA), provides a specific marketing authorization and 10 years of data protection for off-patent drugs when MA holders test such drugs in children specifically. The importance of supporting the development of orphan drugs (those that can only ever be used in a small population of patients) is underlined by both EMA and the FDA. The FDA ruled that children constitute a medically plausible subset of patient population to be granted an orphan designation. In Europe, a Pediatric Orphan indication grants 12 instead of 10 years market exclusivity.

For these regulations it is important that estimates of disease occurrence in children are provided in the pediatric investigation plans (PIPs). A PIP should not only include identifying information about the drug to be developed but also information about the proposed indication in children including details of the potential therapeutic benefit of the drug in relation to unmet needs[30]. Valid estimates of disease occurrence in children are required.

Available data demonstrate that up till now, both the FDA and EMA programs have been successful in meeting their stated goals. According to a report to the US Congress in July 2016, implementation of the BPCA and PREA have resulted in more than 600 pediatric labelling changes[31]. Based on a five-year evaluation (August 2007-December 2012), the EMA and its PDCO approved more than 600 PIPs with 30% including neonates. There were 221 labelling changes pertaining to safety and efficacy in children and 89 additions of dosing information about children (a direct consequence of studies from PIPs)[32]. Out of 152 authorizations that were granted, 31 (34%) included a pediatric indication with 10 linked to a PIP. Some PIPs were completed but the information did not support the use of the drugs in children. However, this information can be included in the product label, indicating that the PIP process can lead to decisions not to use medicines in children.

Despite the achievements, major concerns about insufficient capacity for pediatric drug research (especially pharmacoepidemiology), and the scarcity of human (including trained

pediatric investigators) and economic resources were discovered[33]. The increase in research activity has highlighted the complexity of conducting drug research in children. Even if enough pediatric clinical trials are conducted, RCTs may be inadequate to answer some questions regarding drug effects in children. Typically, RCTs include few (and carefully selected) persons who are followed up for short periods. Therefore, when approved drugs are administered to heterogeneous populations during routine clinical practice, the drugs may not be as effective. Due to small sample size especially in studies including neonates and infants, RCTs are not well suited to studying effects of rare exposures and/or outcomes. Because of short follow-up, long-term effects of drug use cannot be investigated. Yet long-term drug effects especially safety issues have become an important issue, as evidenced by the public workshop organized by the US FDA in April 2016, aimed at stimulating discussion among stakeholders[34].

Pharmacoepidemiological studies exhibit characteristics that can help to overcome the aforementioned challenges. Drug prescription and health outcomes data (pertaining to the general population including children) from routine healthcare can generate enough sample size for studies, even of rare exposures and outcomes. By linking databases while maintaining anonymity, studies of neonates and infants, investigating rare exposures and/or outcomes in particular can be conducted. However, pharmacoepidemiological methods that are well suited to children specifically are lacking.

Data sources for studying disease occurrence and effects of drugs in children: focusing on the WHO

Being the United Nations' organ that is concerned with maintaining public health globally, the WHO invests considerable effort and resources to study disease occurrence and the effects of drugs in the general population, including children. The WHO utilizes data from vital registrations and verbal autopsy to measure the occurrence of diseases that result in death. Vital registration data implies data pertaining to live births, deaths, fetal deaths, marriages and divorces[35]. In developed countries where there are good civil registration systems, vital statistics are easily available and therefore a good source for assessing cause of death. Complete or incomplete death registration systems provide information about cause of death

for almost all high income countries, as well as many countries in Eastern Europe, Central Asia, Latin America and the Caribbean[36,37]. Although to a much less extent, such information is also available in other regions. In contrast, many low-and-middle-income (LMIC) countries lack well developed record-keeping systems, many deaths are undocumented and therefore, verbal autopsy (VA) is a good method for assessing cause of death[38-40]. VA is a method of gathering health information about a deceased individual to determine his or her cause of death and has been widely used in children[40]. Health information and a description of events prior to death are acquired from conversations or interviews with a person or persons familiar with the deceased. To assign a probable cause of death, health professionals or computer algorithms then analyze the information. In order to estimate the occurrence of non-fatal diseases or injuries, the WHO and other stakeholders commonly conduct surveys to collect the required data[36].

Regarding drug effects, the WHO focuses on monitoring the safety of medicines. The WHO Collaborating Center for International Drug Monitoring (Uppsala, Sweden) monitors the safety of medicines that are used globally. Usually, countries submit individual case safety reports (ICSRs) into a global database called VigiBase[41]. As at December 2015, 122 WHO member countries had submitted about 11 million ICSRs to VigiBase, with about 1 million coming from LMICs. From 2017, VigiBase will receive ICSRs transferred by the EMA on a daily basis[41]. The data submitted to VigiBase is usually routinely screened for new-suspected adverse drug reactions. While methods for screening of data pertaining to adults have been extensively researched, the same cannot be said of children.

The efforts of the WHO can be complemented by using active surveillance. Electronic health records (EHR), including medical and claims data, contain vast amounts of information pertaining to diagnosis, referrals, laboratory tests and results as well as drug prescriptions. Such data can be used for population-based studies of disease occurrence and drug effects including both safety and effectiveness. Data pertaining to children specifically (especially underrepresented age categories like neonates) are not readily available especially for studies of rare diseases, drugs and outcomes. Such data should be identified and characterized. Researchers that can analyze pediatric data specifically, to generate pediatric-specific evidence are required.

Aims and outline of this thesis

The Global Research in Pediatrics (GRIP) (http://www.grip-network.org/index.php/cms/en/home) was set up to provide a progressive and durable integration of the research capacity of the major European (and other) countries and the US. To achieve this objective, various required approaches were identified. First, implementing pediatric studies requires well–trained researchers, investigators and other experts in number and capacity that do not currently exist. Therefore providing a joint clinical pharmacology training programme was outlined as the main objective of GRIP.

Secondly, GRIP was set up to promote sharing of best practices in research, including methodologies and research tools that can be used globally. Central to this is the evaluation of methodologies and research tools that meet the needs of researchers and patients. Therefore GRIP was aimed at focusing on knowledge translation, exploitation and mobilization. Attaining these objectives require close collaboration between pediatric health professionals, academics and representatives of the pharmaceutical industries, ethics bodies and regulatory authorities.

Thirdly, GRIP was aimed at building upon existing European and US excellence and therefore included partners with direct and strong links in training and pediatric research networks. Therefore GRIP mobilized 17 partners from Europe, the National Institutes of Child Health and Development-National Institutes of Health (NICHD-NIH) representing a network of US institutions and the FDA, the National Center for Child Health and Development (NCCHD) in Japan, the Hospital for Sick Children in Toronto, Canada, and the WHO. Ultimately, a total of more than 1000 institutions worldwide, linked to the aforementioned partners and their affiliates and networks were identified.

As specific objectives, GRIP aimed to: increase the number of internationally trained pediatric clinical pharmacologists, researchers and formulation scientists; develop an integrated electronic infrastructure for epidemiological, pharmacovigilance and post marketing research; develop pediatric research tools to facilitate interoperability in pediatric research thereby improving efficiency in clinical research and enabling comparison of study results; develop and evaluate models for information sharing for Human Research Subject Protection among ethics committees and Institutional Review Boards to facilitate review and support consistency in

review practice; explore and validate the use of new protocol designs, procedures and methodologies for clinical trials in children; create and maintain an international platform to share knowledge and educate professionals on pediatric drug formulation to support clinical trials worldwide; set up an international initiative for implementation of clinical trials in neonates; create a durable collaboration between participating partners and expand network activities to other countries and settings including LMICs; and base dissemination and implementation of GRIP outputs on well-planned activities relating to knowledge translation, exploitation and mobilization.

The work resulting in this thesis was conducted as part of the second specific objective of GRIP i.e. develop an integrated electronic infrastructure for epidemiological, pharmacovigilance and post marketing research. In defining this objective, GRIP aimed to exploit the information that is compiled in real life, and captured in spontaneous reporting and EHR databases. By applying pharmacoepidemiological methods, disease occurrence can be estimated from EHR data. Also, drug and vaccine utilization, safety of drug and vaccine use in pediatrics, and effectiveness of drugs can be evaluated. To allow the combination of large-scale research databases from various countries in the European Union (EU) and the US, a common data model was planned with mapping of diagnosis and drug terminologies. Also, GRIP planned to create thesauri for disease coding systems used throughout the world, and define procedures for data mining and data pooling. Further, GRIP planned to develop common methodologies for: measuring disease incidence and prevalence; assessing drug utilization; performing drug safety signal detection; and evaluating drug safety and effectiveness.

In chapter 1, we provide a general introduction to the thesis, highlighting: the difficulties associated with accurately measuring occurrence of disease, the lack of evidence regarding safe and effective use of drugs, the attempts that have been made to generate better evidence of drug use and persisting problems.

Table 1: Overview of topics that are described in this thesis

Chapter	Research topic	Design	Setting/Data source(s)	Countries (number and/or specific countries)	Exposure(s)	Outcome(s)
2.1	Impact of different assumptions on estimates of disease in children: A retrospective cohort study	Cohort study	IPCI	1 (Netherlands)	NA	AOM, APN, Asthma, Type 1 DM
3.1	Pediatric Drug Safety Signal Detection: A new Drug-Event Reference Set for Performance Testing of Data-Mining Methods and Systems	Review	eMC, Dailymed, Micromedex, peer-reviewed literature (medline and embase)	NA	Drugs (16)	16
3.2	Drug safety monitoring in children: Performance of signal detection algorithms and impact of age stratification	Spontaneous reporting analyses	FAERS	1 (USA)	Drugs (16)	16
4.1	Pharmacoepidemiological safety studies in children: a systematic review	Review	Medline and embase	28	Drugs and vaccines (291)	212
4.2	Quality of published pediatric pharmacoepidemiological safety studies: Implications for evidence-based drug prescribing in pediatrics	Review	Medline and embase	24	NA	NA
5.1	Comparing drug effectiveness in children: a systematic review	Review	Medline and embase	33	NA	NA
5.2	Comparing drug effectiveness in children using propensity scores based on different durations of patient history: A retrospective cohort study	Cohort study	IPCI	1 (Netherlands)	Drug (ICS+LABA, fixed)	asthma exacerbation

6.1	Reference set for performance testing of pediatric vaccine safety signal detection methods and systems	Review	Medline, embase and cochrane	NA	Vaccines (13)	14
6.2	Current needs in pediatric pharmacoepidemiology	Survey	ISPE members	USA, Canada, The Netherlands, Taiwan	NA	NA

IPCI - Integrated Primary Care Information; NA – Not applicable; AOM – Acute Otitis media; APN - Acute Pyelonephritis; DM - Diabetes mellitus; Emc - Electronic Medicnes Compendium; FAERS – US FDA Adverse Event Reporting System; ICS+LABA – Inhalational Corticosteroids and Long-acting Beta-2-agonists

In chapter 2, we investigate the impact of the peculiar characteristics of diseases affecting children on accurate measurement of their incidence and prevalence by testing different assumptions.

In chapter 3, we test different methods for detecting safety signals resulting from the use of drugs. According to the Council for International Organizations of Medical Sciences (CIOMS)[42]; a signal can be defined as 'information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention (i.e. administration of a medicine) and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.' We explain the need for creating a pediatric-specific reference set of drug-adverse event combinations. Also, we describe how we used this reference set for testing the performance of published signal detection algorithms (SDAs) when these SDAs are applied to pediatric data specifically.

In chapter 4, we describe published pharmacoepidemiological safety studies that included children with the aim of identifying gaps in study conduct and reporting of published results. Also, we evaluated the quality of the studies with the aim to identify study characteristics related to the quality. Consequently, critical appraisal of published studies may become easier for clinicians and other persons with limited knowledge of epidemiology.

In chapter 5, we investigate the methods that have been applied to conduct comparative (pharmacoepidemiological) drug effectiveness studies in children, aiming to identify areas that can be improved upon. Also, we test the impact of propensity scores adjustment to control confounding by indication, a common type of confounding in comparative drug effectiveness studies. As an example, we investigate the effectiveness of asthma treatment in children on the prevention of asthma exacerbations. Asthma was chosen as it is a common and chronic condition in children.

In chapter 6, we present other issues that are also important for a complete understanding of the problems we highlighted in the introduction of this thesis. We emphasize the need to monitor vaccine safety in children since they represent the drugs that are most frequently used in children worldwide. Monitoring of vaccine safety requires the creation of a specific adverse event reference set. Also, we present results of a survey that was conducted to identify the most pressing needs in the field of pediatric pharmacoepidemiology.

In chapter 7, the main findings of the thesis are summarized and discussed.

Chapter 2 Estimating the occurrence of childhood diseases

Chapter 2.1 Impact of different assumptions on estimates of pediatric disease occurrence from health care data: A retrospective cohort study

Abstract

Purpose: Pediatric-specific drug legislations have been introduced and require estimates of disease incidence in children to support the pediatric investigation plans. Automated population-based electronic healthcare records (EHR) provide a potential data source but methods for calculation of disease occurrence have not been specified for children. We aimed to understand the impact of assumptions regarding duration of disease episode and length of run-in period on incidence estimates from EHRs.

Methods: Children aged 0-17 years (5-17 years for asthma) registered in the Integrated Primary Care Information (IPCI) database between 2002 and 2014, were studied. We tested impact of assumptions on incidence estimates. These were firstly, maximum duration of disease episode (namely 0, 14, 30, 60 and 90 days) for recurrent diseases (acute otitis media (AOM) (common) and acute pyelonephritis (APN) (rare)). Secondly we tested the impact of database run-in period when applied to chronic diseases: asthma (common) and type 1 diabetes (DM) (rare). We calculated incidence rate ratios (IRR) with 95% confidence intervals (CI) and stratified by age using 1-year categories.

Results: In the IPCI database, 503,495 children were registered during the study period. The incidence of AOM was highest in < 2 year old children. Using 30 days episode length as reference, the rate increased with 8% if the duration was 14 days and it decreased with 8% when it was extended to 60 days. Episode duration had no impact on the rate of APN (rare disease). Lack of a naïve period (to exclude prevalent cases) as compared to a 24 months naïve period overestimated the incidence rate for asthma as well as for DM by a factor of two.

Conclusions: Use of electronic health care records of which IPCI is a representative example, allows for estimation of disease incidence but the assumptions on episode length and run-in period impact on the incidence estimates, and this differs for common/rare recurrent and chronic diseases. We recommend that disease incidence estimation for children based on dynamic electronic health care databases carefully explore assumptions around episode length and naïve period.

Introduction

Globally, legislations have been introduced to stimulate development of drugs for children specifically[26,43,44.] Regulatory authorities now require pharmaceutical companies to include pediatric investigation plans (PIPs) when submitting proposals for drug development in adults. PIPs may be waived if the target indication affects only adults. For PIPs that are considered for approval, the potential therapeutic benefits for children should be explained in the document. Such explanation may include data regarding the background occurrence of the indication in the pediatric population[30].

Population based electronic health care records (EHR) provide an excellent datasource for calculation of disease occurrence[45], however there are specific methodological challenges that should be considered based on the fact that these data are not collected for research but for every day care.

Firstly since EHR were introduced only in the last decades, software systems may change, and patients may also move between physicians/health care plans. Therefore the data often captures only a specific (limited) part of an individual's life-time. In order to distinguish incident from prevalent disease, researchers usually apply a look-back (run-in) period which is often arbitrarily chosen and the impact of the choice is not investigated or reported[46]. In addition, parents visit a physician usually at the start of the disease of their child but not anymore once the condition is over, which hampers calculation of the duration of transient diseases.

Secondly, the characteristics of childhood diseases present additional challenges, children suffer mostly from common transient infection related disease such as acute otitis media (AOM). On the other end of the spectrum of recurrent diseases there may be rare conditions such as acute pyelonephritis (APN)[9 10]. Diseases that affect children may also be chronic and differ in frequency: asthma is common and chronic unlike type 1 diabetes (DM) which is also chronic but less common[12,13]. It would be important to understand the impact of different assumptions on estimation of disease occurrence.

As part of the Global Research in Paediatrics - Network of Excellence (http://www.grip-network.org/), we aimed to understand how different assumptions regarding duration of a disease episode (for transient and recurrent diseases) and run-in period (for chronic diseases) may impact incidence and prevalence

estimates. As examples, we investigated AOM and APN (both transient and recurrent), and asthma and type 1 diabetes (both chronic conditions).

Methods

Setting

This retrospective cohort study was performed using the Integrated Primary Care Information (IPCI) database as an example for other electronic health care databases. IPCI is a longitudinal, observational, primary care database with records of approximately 1,500,000 patients from about 450 general practitioners in the Netherlands. The records comprise information on patient demographics, symptoms and diagnoses, referrals, laboratory test and results, drug prescriptions, hospitalizations and discharge letters. Details of the data source have been published elsewhere[47]. Diagnoses are coded according to the International Classification for Primary Care (ICPC)[48]. Drug names are coded following the World Health Organization-Anatomic Therapeutic Chemical (WHO-ATC) classification system. The database has been proven to be valid for conducting pharmacoepidemiological studies[49]. The study and the access to the database were approved by the IPCI governance board (number 05/2015)

Study population

All children aged 0-17 years that were registered for at least one day between January 1 2002 and December 31 2014 could be included in the study. For the investigation of asthma, the minimum age for inclusion was 5 years since the diagnosis of asthma in children under 5 years old is prone to misclassification due to the high incidence of viral infections associated with wheezing[50,51]. Patients entered the study population at the latest of the following dates: start of the study period, date of birth or date of registration in IPCI, age of 5 years (asthma only). Exit from the study population occurred at the earliest of the following events: leaving the GP practice, death, subject turned 18 years old or end of the study period. Since some chronic diseases require run-in periods to exclude prevalent cases, start of follow-up was dependent on the length of the run-in period, which was added to the criteria listed above.

Outcome definition and identification

Four outcomes of interest were studied based on different frequencies (common or rare) and durations (transient or chronic). The outcomes were identified based on diagnosis and prescription codes. See appendix 1.

Acute otitis media (AOM) is a transient disease, the systemic and local features of AOM usually resolve within 24-72 hours[52,53]. One patient can experience more than one episode of AOM[54]. Children with AOM were identified through a search on the International Classification of Primary Care (ICPC) AOM disease code H74.

Acute pyelonephritis (APN) is also a transient disease. According to the Dutch classification, ICPC disease code U70 implies that APN was diagnosed by urine testing[55]. APN may be recurrent [56]

Asthma is a chronic and rather common condition in children[13]. Cases were identified by combining the ICPC disease code (R96) with at least 2 prescriptions for asthma medication (ATC code R03) in the year following the initial diagnosis[13,57].

Type 1 diabetes (DM) is a chronic and rare disease in children. Cases were identified by combining ICPC disease code (T90) and at least 1 prescription for insulin (A10A) in the year following the initial diagnosis[58].

Statistical analyses

Overall and age-specific incidence rates (IR) were calculated by dividing the events/outcomes by the total number of person-years (PY) accumulated in the study population. The IR was expressed per 100,000 PY. Age stratification was done in 1-year categories. For the transient outcomes (AOM and APN), recurrent episodes were considered as new events based on a duration of episodes of 0,14,30,60 and 90 days. Person-time was not censored at diagnosis. For the chronic outcomes, person-time was censored at the date of first diagnosis. The run-in period was altered from 24 to 12 and 6 months to assess the impact on the incidence rate. Further, the impact of not applying a run-in period was tested. The 95% confidence intervals (CI) around the incidence rates were estimated based on the negative binomial distribution[59]. For the transient outcomes (AOM and APN), age-specific incidence rate ratios (IRR) were calculated by comparing the IRs based on clinically plausible episode durations - 14 days vs 30 days. For

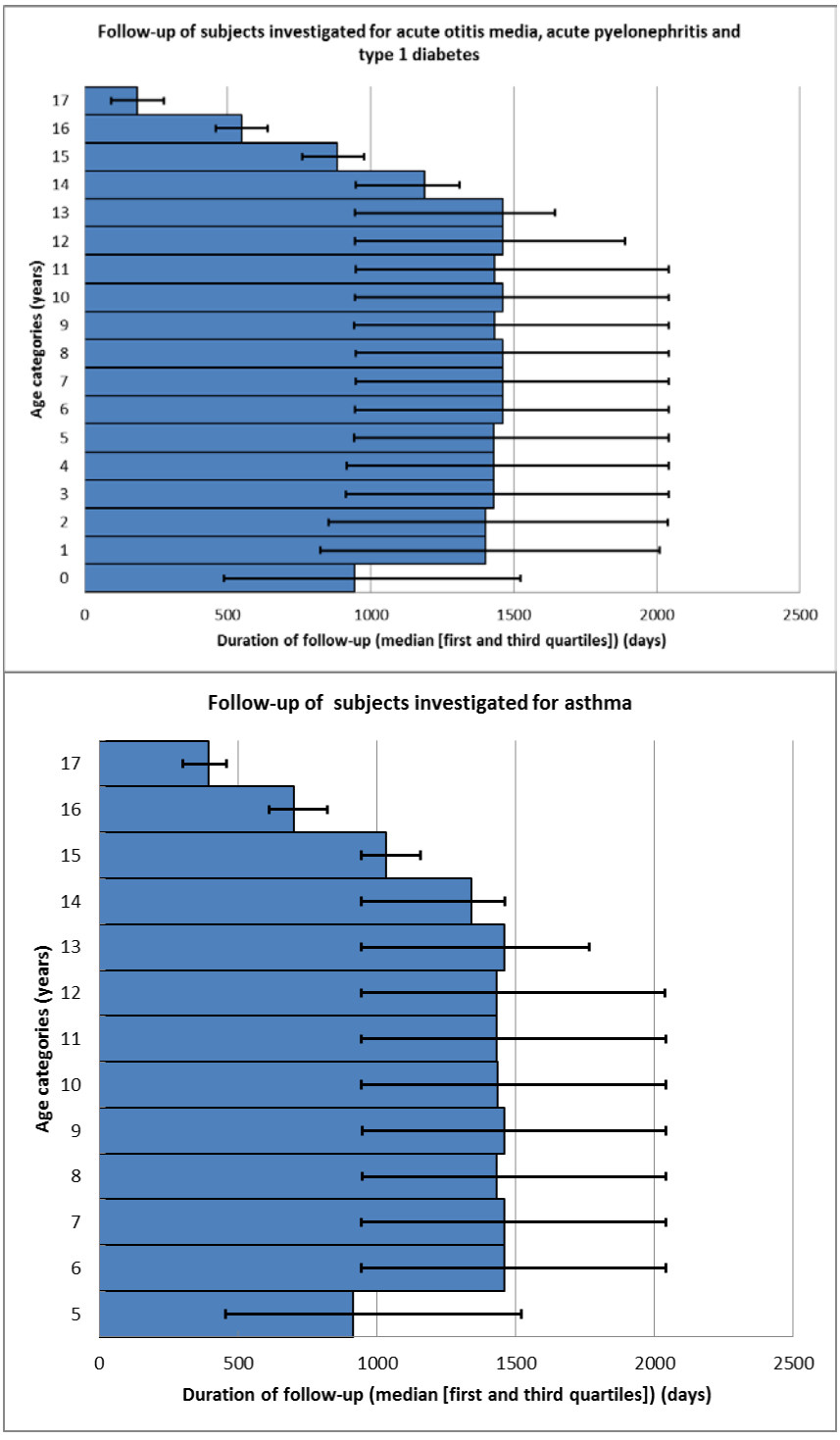
the chronic outcomes (asthma and DM), age-specific IRRs were calculated by dividing the IR resulting from not applying run-in vs 24 months' run-in.

Point prevalence was calculated on July 1 2010 by dividing the number of children with the outcome on that date by the total number of children in the study population on that date. 95% CIs were calculated based on the Wilson score interval [60]. To calculate the age-specific prevalence rate ratio (PRR) for the transient outcomes (AOM and APN), we assumed an event to be new if it occurred ≥30 days after the preceding event and we divided the resulting point prevalence by the estimate that was based on 14 days duration. Regarding the chronic outcomes (asthma and DM), age-specific PRRs were calculated by dividing the point prevalence resulting from 24 months' run-in vs no run-in. The 95% CIs around the IRRs and PRRs were calculated following the negative binomial distribution [61].

Analyses were conducted using a custom built Java application called Jerboa Reloaded (Erasmus University Medical Center, Rotterdam), and IBM SPSS Statistics for windows version 21.0, Armonk, NY: IBM Corp.

Results

To investigate AOM and APN, the study population comprised 503,495 children. For asthma (studied in children 5 years or older) and DM we studied 304856 and 405600 children respectively; the total PYs of follow-up were 710,980 PY and 1,042,067 PY . Figure 1 shows the distribution of age (at start of follow-up (no run in)) and duration of follow-up of the population base, without censoring.



Note: Run-in was not applied and subjects were not censored

Figure 1: Median follow-up time according to the age categories of the studied populations

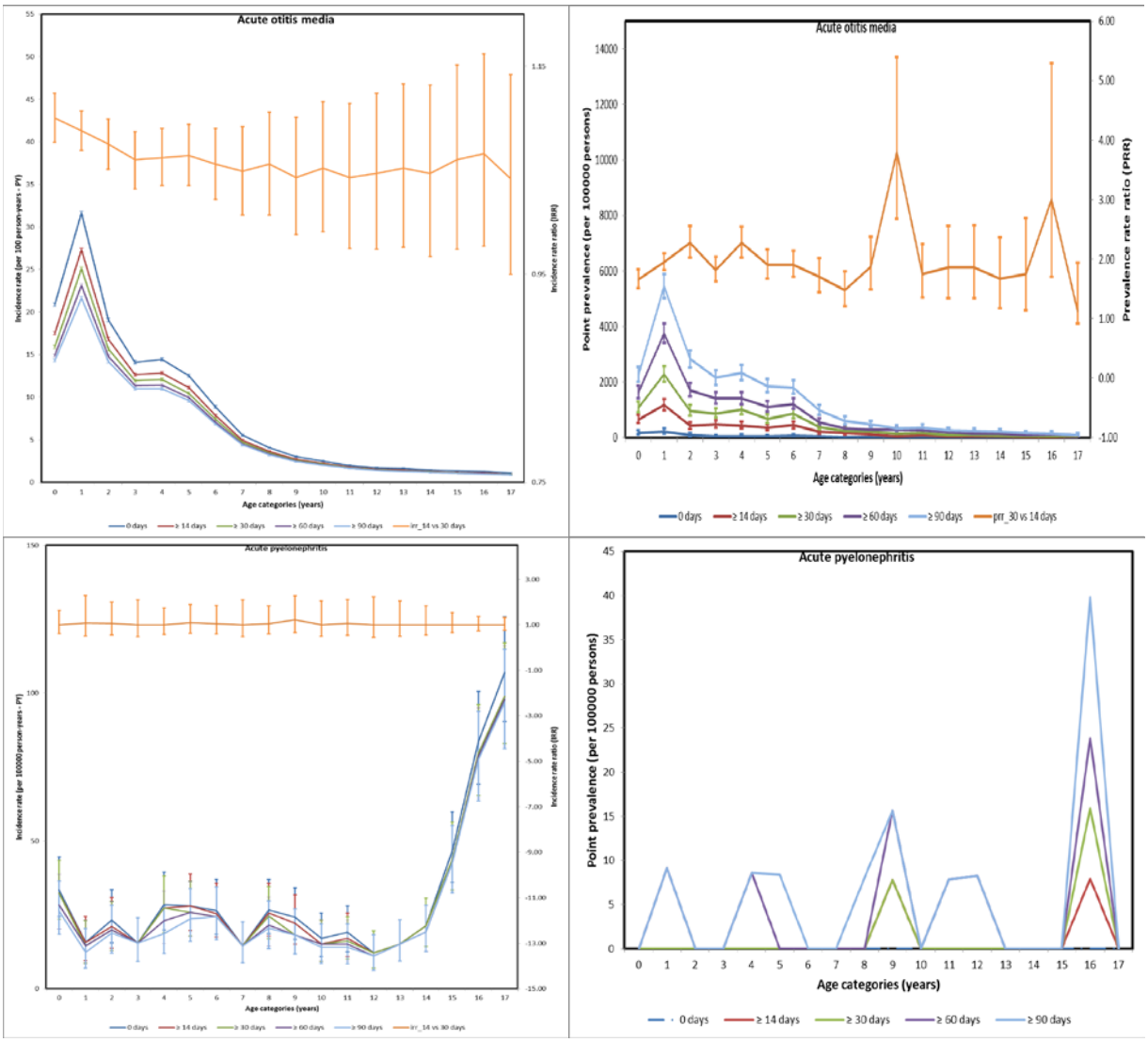
Recurrent diseases and impact of episode duration

Based on the assumptions that a new event can only re-occur 0, ≥14, ≥30, ≥60, or ≥90 days after the preceding event, overall IRs for AOM decreased from 8.2, 7.1, 6.6, 6.2 to 5.9 per 100 PY respectively (table 1). The estimates resulting from the shortest assumed duration were the highest, decreasing with increasing length of an episode in all age categories (figure 2). Incidence was highest in the youngest children although this did not affect the impact of episode duration on the IRR: comparing 14 vs 30 days: IRR=1.10 (95% CI: 1.08; 1.12) for subjects aged <1 year and 1.09 (95% CI: 1.07; 1.11) for subjects aged 1-2 years; overall IRR= 1.08 (95% CI: 1.07; 1.09). The incidence rates for APN were much lower than for AOM. Assuming 0, ≥14, ≥30, ≥60 or ≥90 days between new events, the overall IRs reduced relatively little from 31.1, 29.6, 28.9, 27.9 to 27.0 per 100,000 PY, respectively. The age-specific IRRs to test assumptions on duration of episodes comparing 14 vs 30 days were all around 1, showing no age specific effect modification of the impact of episode duration.

Table 1: Total number of studied children, total person-years (PY) of follow-up, total number of incident events (transient and recurrent outcomes) or cases (chronic outcomes), and overall incidence rates according to the investigated outcomes

Outcome	Assumption [a]	Total number of subjects [b]	Total person-years (PY)	Total number of events/cases	Incidence rate (per 100,000 PY)
Acute otitis media	0 days	503,495	1,781,625	146,391	8,216.7
	≥14 days	503,495	1,761,172	124,749	7,083.3
	≥30 days	503,495	1,752,235	115,107	6,564.0
	≥60 days	503,495	1,746,245	107,860	6,176.7
	≥90 days	503,495	1,742,821	103,089	5,915.1
Acute pyelonephritis	0 days	503,495	1,734,774	540	31.1
	≥14 days	503,495	1,734,750	513	29.6
	≥30 days	503,495	1,734,740	502	28.9
	≥60 days	503,495	1,734,724	484	27.9
	≥90 days	503,495	1,734,713	468	27.0
Asthma[b]	No run-in	304,856	710,980	4,238	596.1
	6-months run-in	304,856	710,980	3,385	476.1
	12 months run-in	304,856	710,980	2,786	391.9
	24 months run-in	304,856	710,980	1,881	264.6
Type 1 diabetes	No run-in	405,600	1,042,067	256	24.6
	6-months run-in	405,600	1,042,067	212	20.3
	12 months run-in	405,600	1,042,067	172	16.5
	24 months run-in	405,600	1,042,067	115	11.0

[a] For the transient outcomes, this refers to the time between new episodes; for the chronic outcomes, it refers to the length of the run-in period; [b] For asthma and type 1 diabetes, subjects that had a minimum 24 months'run-in were studied to know the impact of decreasing the run-in period on the incidence rate



Note: The confidence intervals for the point prevalence of Acute pyelonephritis are not presented because they are too wide

Figure 2: Incidence rate, Incidence rate ratio, point prevalence and prevalence rate ratio for the transient outcomes

The impact of episode duration length had quite an opposite effect on the point prevalence with increasing duration of episodes the point prevalence increased. The overall PRR that compared an episode duration of 30 days to 14 days duration for AOM was 1.92 (95% CI: 1.73; 2.12), which was higher than for APN: 1.50 (95% CI: 0.25; 8.98). In APN the impact was less pronounced due to a very low prevalence overall.

Chronic diseases and impact of run-in period

By applying a 0, 6, 12, or 24 months' naïve period, overall IRs for asthma (age 5-17 years) lowered from 5.96, 4.76, 3.92 to 2.65 per 1,000 PY respectively. The impact of a 0 vs 24 months' run-in was a more than two fold increase in incidence rate across all ages (figure 3), IRR overall=2.25 (95%CI: 2.13; 2.38).

By applying a 0, 6, 12, or 24 months' naïve period, overall IRs for DM were 2.46, 2.03, 1.65 and 1.10 per 10,000 PY respectively. Again, the highest IRs were observed when no run-in was applied and they were lowest with 24-months' run-in. The impact of applying 0 vs 24 months' run-in leads to a twofold increase in incidence rate in most age categories, IRR overall=2.22 (95%CI: 1.79; 2.77).

The impact of an increase in the run-in period, during which prevalent cases would be identified and excluded, was a lowering of the rate of asthma as well as DM. The impact of applying a 24 months' run-in vs no run-in on the age specific point prevalence rate was negligible for both asthma (overall PRR: 1.10 (95% CI: 1.06; 1.14)) as well as DM (overall PRR: 0.82 (95% CI: 0.64; 1.04)).

The results are summarized in figure 4.

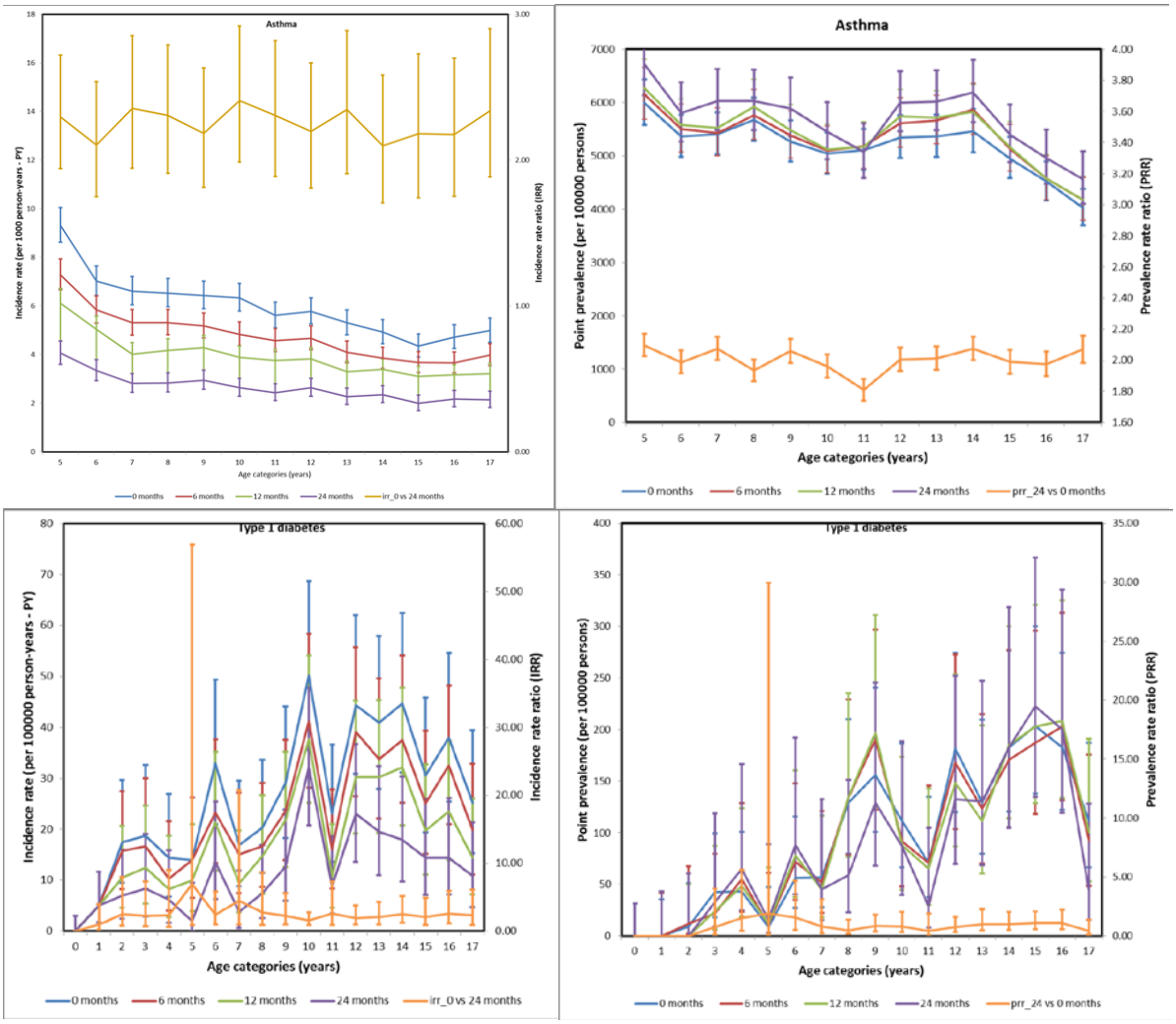


Figure 3: Incidence rate, Incidence rate ratio, point prevalence and prevalence rate ratio for the chronic outcome

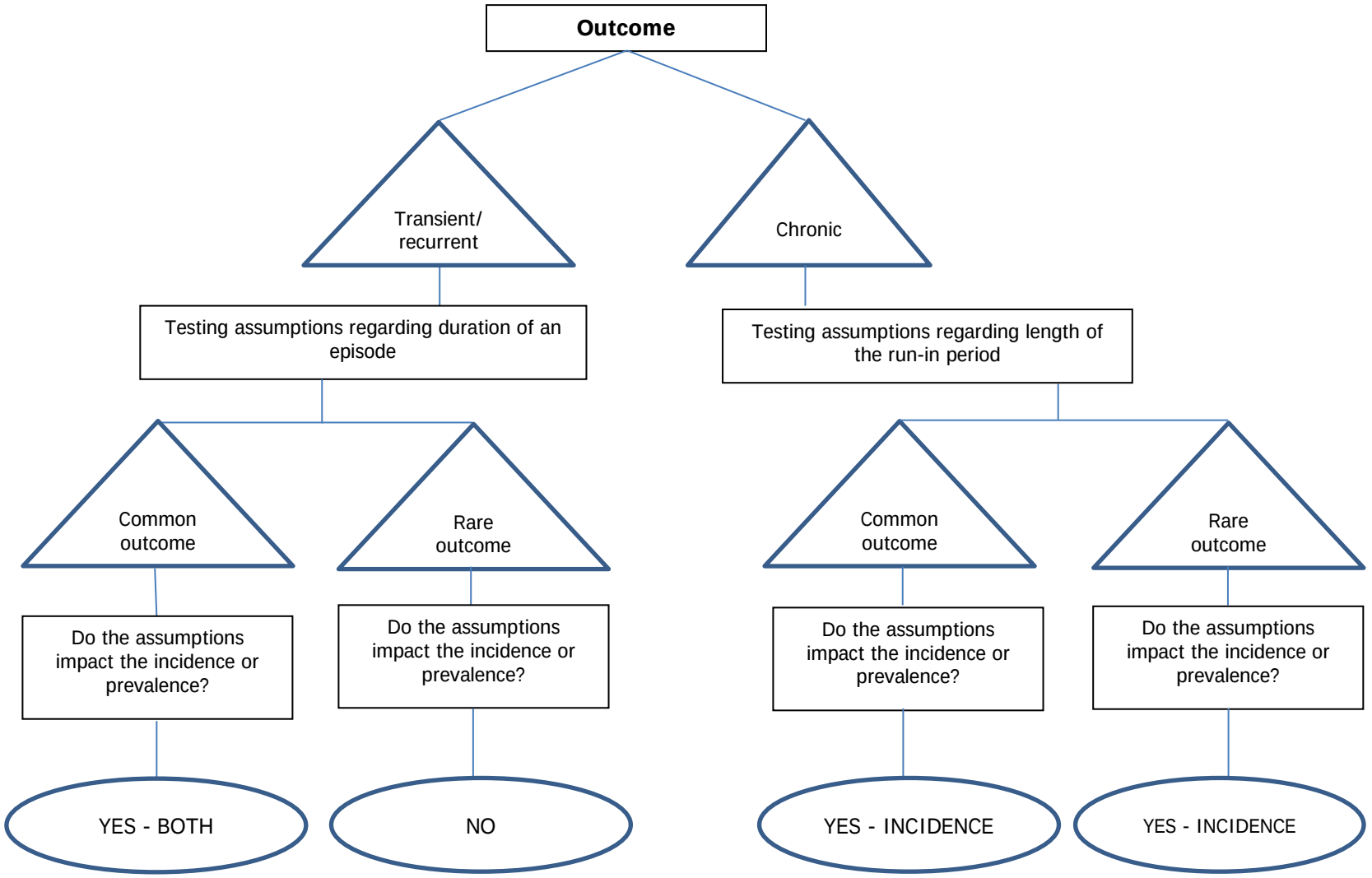


Figure 4: Summary of the impact of assumptions on the investigated outcomes

Discussion

This study showed that incidence and point prevalence of disease in childhood can be estimated well using a population-based dynamic electronic health care record database. The lack of complete follow-up from birth till 17 years of age, and the fact that only the visit for a disease and not the ending of a disease is recorded in the electronic medical record has an impact on disease occurrence estimation. Usually epidemiologists apply assumptions to deal with these limitations, such as 'assuming a standard disease episode duration' and use of a run-in period prior to start of follow-up that can be used to exclude prevalent disease. In this paper we wanted to investigate the impact of these assumptions on the different occurrence measures in children, and we witnessed relatively great impact. General rules can be obtained from this exercise: for common recurrent diseases the impact of the choice of episode duration is relatively high, assuming longer disease episodes leads to lower incidence. The impact of a change in episode duration on the incidence is negligible in a rare recurrent disease. This is understandable since the probability of having another event of a rare disease is low and this will not likely occur close together. The impact of an increasing episode duration on the prevalence of a common recurrent disease is opposite, with increasing duration the point prevalence increases. The impact is negligible on the point prevalence for a rare recurrent disease. We recommend that studies aiming to estimate incidence and prevalence of common recurrent diseases better explore the impact of the episode length since the true length cannot be observed in medical record databases. Patients do not return to tell the general practitioner (GP) that disease is cured. For rare diseases the impact of different episode durations may be ignored both for incidence and prevalence estimations. For chronic diseases, varying the run-in impacts the incidence with negligible impact on the prevalence. We recommend that studies investigating chronic diseases apply the longest possible run-in to avoid misclassifying prevalent cases as incident.

Regarding AOM, there was no difference in incidence when we compared two clinically plausible episode durations: 14 versus 30 days; 30 days has been applied in a previous study[9]. Based on the natural history of AOM, the actual duration of an episode is not clear[62]. Therefore we also compared the incidence rates (results not presented) we derived from the shortest (0 days) versus longest (90 days) assumptions, the

estimates were significantly different. When we performed the same comparisons for APN, the result was not significant, further confirming that the episode duration is important for estimating the occurrence of only the common outcomes. We observed that assuming episode duration of 30 vs 14 days significantly impacted the prevalence of AOM. We recommend further research to know the most appropriate assumptions to apply when estimating the occurrence of AOM and other common and recurrent childhood diseases. Prevalence might be a good measure.

Regarding both asthma and DM, increasing the run-in period considerably decreased the incidence. This finding is important given that people can be observed for only a part of their lifetime; despite conducting the current study over a 12-year calendar period, the median duration of follow-up for the studied population was 1500 days, showing the incomplete follow-up (figure 1). Therefore we recommend that the longest feasible run-in period be applied when estimating the incidence of chronic diseases.

This study has strengths and limitations. As strengths, we tested assumptions that are plausible from both an epidemiological and clinical point of view and we demonstrated the ability to estimate the impact of different assumptions.Limitations are the fact that we looked only at 4 different conditions and try to draw general conclusions. We do feel however that the conclusions hold, but cannot provide thresholds when something is considered rare or common. This will be a continuum, with the specific demonstrators we try to show that assumptions should be considered and the impact may be considerable. A second limitation is that we applied the assumption to one database only, a highly dynamic general practitioners' database. The impact of the episode length is generalizable across all databases, but the impact of the run in period may be less pronounced in more stable regional or national databases where persons are registered from birth.

Conclusions

Population based electronic health care records provide a rich and readily available source of data for estimation of disease occurrence in children which can be used in pediatric investigation plans. Trial planning as well as potential market implications usually require estimates of occurrence in children.

Assumptions on the episode length and run in period may impact a lot on the absolute measures of occurrence and should be explored, especially in more common childhood diseases.

Appendix 1: Characteristics and event (transient and recurrent outcomes) or case (chronic outcomes) definitions for the investigated outcomes

Outcome	Duration	Frequency	Prevalence/ Incidence in general population	Clinical definition	Case definition	Alternative assumptions
Acute otitis media:	Transient	Common	107 episodes/1000 PY[63]	'Acute otitis media is understood to be an inflammation of the middle ear with a maximum duration of three weeks. Acute otitis media is generally associated with earache, symptoms of general illness, fever and sometimes purulent discharge (otorrhoea), and is characterised by a bulging tympanic membrane with change in colour (red or opaque)' [64] the systemic and local features of AOM usually resolve within 24-72 hours [52,53].	ICPC code H71 [54]	Varying the time between new events [a] 0 days ≥14 days ≥30 days ≥60 days and ≥90 days
Acute pyelonephritis	Transient	Rare	15.7/100000 persons[65]	Symptoms of Urinary Tract Infection (UTI) in children may include fever, vomiting, screaming, anorexia, and irritability. Acute pyelonephritis is a component of UTI [55]	ICPC code U70[b] AND prescription of any antibiotic (J01) on the same date of diagnosis[c] [55]	Varying the time between new events [b] 0 days ≥14 days ≥30 days ≥60 days ≥90 days
Asthma	Chronic	Common	6.7/1000 PY[13]	Asthma is a syndrome with a highly variable clinical spectrum, characterised by airway inflammation [66]	ICPC code R96 AND at least two prescriptions for asthma medications (R03) in the first year following the initial diagnosis [13].	Varying the run-in period[d] No run-in (prevalent cases included) 6 months 12 months 24 months

Type 1 diabetes	Chronic	Rare	23.2/100000 children [12]	'Type 1 diabetes is an autoimmune – mediated disease associated with several complications and decrease in quality of life' [67]	ICPC code T90 AND at least one prescription of insulin (A10A) in the first year following the initial diagnosis [58].	Varying the run-in period[d] No run-in (prevalent cases included) 6 months 12 months 24 months

[a] For '0 days', this implies that every record is considered as a new episode and for the other assumptions, all records within the stated time window (<14 , <30 , <60, and <90 days) are considered as the same episode.

[b] According to the Dutch classification, ICPC code U70 implies that APN was diagnosed by urine testing [55]

[c] In the Netherlands, physicians are encouraged to administer antibiotics for every case of AP because of the risk of renal scarring.

[d] This applies only to prevalence calculation; run in period will not be applied to patients with age< run-in period

Chapter 3 Detecting drug safety signals

Chapter 3.1 Pediatric Drug Safety Signal Detection: A new Drug-Event Reference Set for Performance Testing of Data-Mining Methods and Systems

Abstract

Background: Better evidence regarding drug safety in the pediatric population might be generated from existing data sources like spontaneous reporting systems and electronic health care records. The Global Research in Paediatrics (GRiP) – Network of Excellence aims to develop pediatric-specific methods that can be applied to these data sources. A reference set of positive and negative drug-event associations is required.

Objective: To develop a pediatric-specific reference set of positive and negative drug-event associations.

Methods: Considering user patterns and expert opinion, sixteen drugs that are used in individuals aged 0-18 years were selected; and evaluated against sixteen events, regarded as important safety outcomes. A cross-table of unique drug-event pairs was created. Each pair was classified as potential positive or negative control based on information from the drug's Summary of Product Characteristics and Micromedex. If both information sources consistently listed the event as adverse event, the combination was reviewed as potential positive control. If both did not, it was evaluated as potential negative control. Further evaluation was based on published literature.

Results: Some selected drugs are ibuprofen, flucloxacillin, domperidone, methylphenidate, montelukast, quinine, and cyproterone/ethinylestradiol. Some selected events are bullous eruption, aplastic anemia, ventricular arrhythmia, sudden death, acute kidney injury, psychosis and seizure. Altogether, 256 unique combinations were reviewed, yielding 37 positive (17 with evidence in children and 20 with evidence in adults only) and 90 negative control pairs, the remainder being unclassifiable.

Conclusion: We propose a drug-event reference set that can be used to compare different signal detection methods in the pediatric population.

Introduction

In the last 50 years, drug safety monitoring has developed rapidly in terms of increasing interest, broadening capacity, innovation of methods and availability of data [68-70]. This evolution has focused more on the adult population than the pediatric age group (individuals aged 0 -18 years). However, drug safety monitoring in pediatrics is of particular importance, because we continue to observe that many drugs are prescribed unlicensed and there is lack of adequate information on safety issues affecting this age group. This is of particular concern as the impact of adverse events during growth and maturation may be more serious and longer term as compared to adults [17,71-74].

Globally, specific regulations are being implemented to generate better evidence on safety and efficacy in the pediatric population but mostly by clinical trials [24,75]. Although useful for efficacy, such trials are usually too small and with too short follow-up to yield adequate information on rare adverse drug reactions (ADR) and long-term safety [76]. Therefore, other and preferably existing data sources should be utilized to provide information on safety of drugs in pediatrics [77]. Existing sources with lots of data comprise spontaneous reporting systems (SRS) and electronic health care record (EHR) databases.

Although analysis of spontaneous reports is currently the most commonly used method for identifying safety signals, specific approaches to surveillance of the pediatric population are limited. The Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII recently advocated for an increased pediatric focus in signal detection [42]. CIOMS also suggested methods to control for confounding in vaccines safety assessment, an issue specific to the pediatric population, and de Bie et. al proposed further refinement of these methods [78].

Safety signal detection using SRS databases may be complemented by mining longitudinal data in EHRs as described by the European Adverse Drug Reaction (EU-ADR) project - 'Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge' and the 'Observational Medical Outcomes Partnership' (OMOP) project [79-81]. Although newly developed methods i.e. Longitudinal Gamma Poisson Shrinker (LGPS) show promising results on pediatric data [82], more extensive and systematic testing is needed.

The Global Research in Paediatrics (GRiP) - Network of excellence (http://www.grip-network.org/) was set up with the general objective of facilitating the development, and safe use of medicines in the pediatric population; a specific objective being to apply innovative approaches, standardized methodologies, as well as better utilization of existing healthcare and spontaneous reporting databases. GRiP aims to tailor existing signal detection methods to pediatric safety data. Comparison of the performance of existing methods within and across SRS and EHR databases is the first step in defining suitable methods to be implemented. For this purpose, creation of a reference set comprising pediatric drug-event pairs serving as positive and negative control, is required to calculate baseline performance statistics. Coloma et al. recently described the methodology for creating a reference set used to test methods in the EU-ADR project [83]. Similarly, Ryan et. al. established a reference set for testing methods in the OMOP project [84]. However, both were not specific to the pediatric population and comprise many drugs infrequently prescribed within this age group, and events that rarely (or never) affect them.

In this paper we describe how we created a proposed reference set for comparing the performance of different methods in detecting drug safety signals in the pediatric population. This may be used for spontaneous reporting databases as well as electronic health care record databases

Methods

The first step in creating the reference set was to select a list of eligible drugs to be utilized. Based on four criteria, four (primary) lists of drugs were created: we compiled drugs that are frequently prescribed in pediatrics (including off-label use), on outpatient basis in high income countries (as per papers and reports of use) [85,86]; to allow for inpatient databases to be assessed, we included drugs that are administered to hospitalized persons aged 0-18 years (or administered by specialists) [86]; to allow for databases from low-and-middle-income countries (LMICs) to be assessed, we included drugs that are used in such countries (as per World Health Organization – WHO list of essential medicines for children)[87]; and to allow for testing signal detection performance by different age groups, we included drugs that are used in specific pediatric age groups (for example - adolescents) [86].

To obtain a final drug list, a stepwise procedure was implemented. First, if 2 or more drugs (5th level chemical substances, World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Classification System) belonged to the same class ('WHO-ATC, 4th level'), and were listed in an equal number of primary lists (>1), we preferentially selected only the drug that had the oldest initial marketing authorization worldwide. This was done to have most evidence available. For example, doxycycline (WHO-ATC code J01AA02) would be selected instead of minocycline (WHO-ATC code J01AA08) because although they both belong to the same class - 'WHO-ATC, 4th level' (tetracyclines), doxycycline was first marketed in 1967 [88], and minocycline in 1972 [89]. Secondly, we preferentially selected drugs that appeared in most of the lists, for example a drug appearing on 3 of 4 primary lists would be retained instead of another drug appearing on only 2 lists. The final list comprised more than 30 drugs which was beyond our capacity and resources and was reduced to 16 for pragmatic reasons.

Events were chosen (independent of the drugs) with the aim of generating a set which may be used for methods' development on spontaneous reporting as well as electronic health care records. Both rare and common events were included to allow for investigation of effect modification. Starting with common adverse events observed in pediatrics as reported by Star et al. 2011[90], we selected only events that were deemed serious (as per WHO definition-[91]); and specific (to avoid misclassification). For example *aplastic anemia* was selected rather than *anemia*; as the former connotes a more serious and specific medical condition. Some events (i.e. psychosis and seizure) were included by consensus in the research team because they were considered relevant for the pediatric population from a pharmacovigilance and public health point of view. Fifteen drugs and events were considered as the minimum required for generating enough positive and negative associations. Finally, the total number of drugs and events was set at 16 for pragmatic reasons.

Four researchers -MS, IW, JB and GWJ- with a range of expertise spanning pediatrics, pharmacology, and pharmacoepidemiology, determined the final list of selected drugs and events. MS and IW are pharmacists/pharmacoepidemiologists; JB is a pediatrician; while GWJ is a pediatrician/clinical pharmacologist/pharmacoepidemiologist.

All events of interest were defined using standard resources (i.e. medical textbooks, uptodate.com and scientific societies such as CIOMS) to increase the likelihood of comprehensive literature searches. The final reference set was generated by cross tabulating the final lists of drugs and events which led to a matrix of 256 unique drug-event pairs. In order to classify each unique drug-event pair as a 'positive', 'negative' or 'unclassifiable' association, evidence was reviewed in 2 sequential steps:

Review of Summary of Product Characteristics (SPC) and Micromedex

First, 2 researchers (OO and CF) with expertise in general medicine, pharmacy and pharmacoepidemiology reviewed each drug's SPC to ascertain that a specific event (for example aplastic anemia) was listed as a possible adverse event under the appropriate section(s): 'Undesirable effects' (section 4.8) and/or 'Special warnings and precautions for use' (section 4.4) from the electronic Medicines Compendium (eMC) [92]. DailyMed (the 'Contraindications, Warnings, Precautions' and/or 'Adverse Reactions' section(s)) was consulted only if a drug was not listed in eMC [93]. The eMC contains >9000, up-to-date, freely accessible documents containing information about medicines licensed for use in the United Kingdom (UK). Prior to publishing, these documents are usually checked and approved by either the UK Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA). DailyMed, published by the National Library of Medicine (NLM) in the US, contains up-to-date information about drugs licensed for use in the US. Both eMC and DailyMed are freely accessible online.

Secondly, OO and CF reviewed Micromedex to check if the event was listed under the section: 'Adverse Reactions' within the Drugdex component. Micromedex is an online drug information system that contains referenced information from various sources needed for clinical decision-making including adverse effects of drugs (http://www.micromedex.com/).

After reviewing the SPC and Micromedex, drug-event pairs were classified as: (1) 'potential positive control' (event was mentioned in both SPC and Micromedex); or (2) 'potential negative control' (event was mentioned in neither SPC nor Micromedex); or (3) unclassifiable (discordant information between

SPC and Micromedex). 'Potential positive control' and 'potential negative control' pairs were retained and the relationship of each drug-event pair was further evaluated using published literature (**figure 1).**

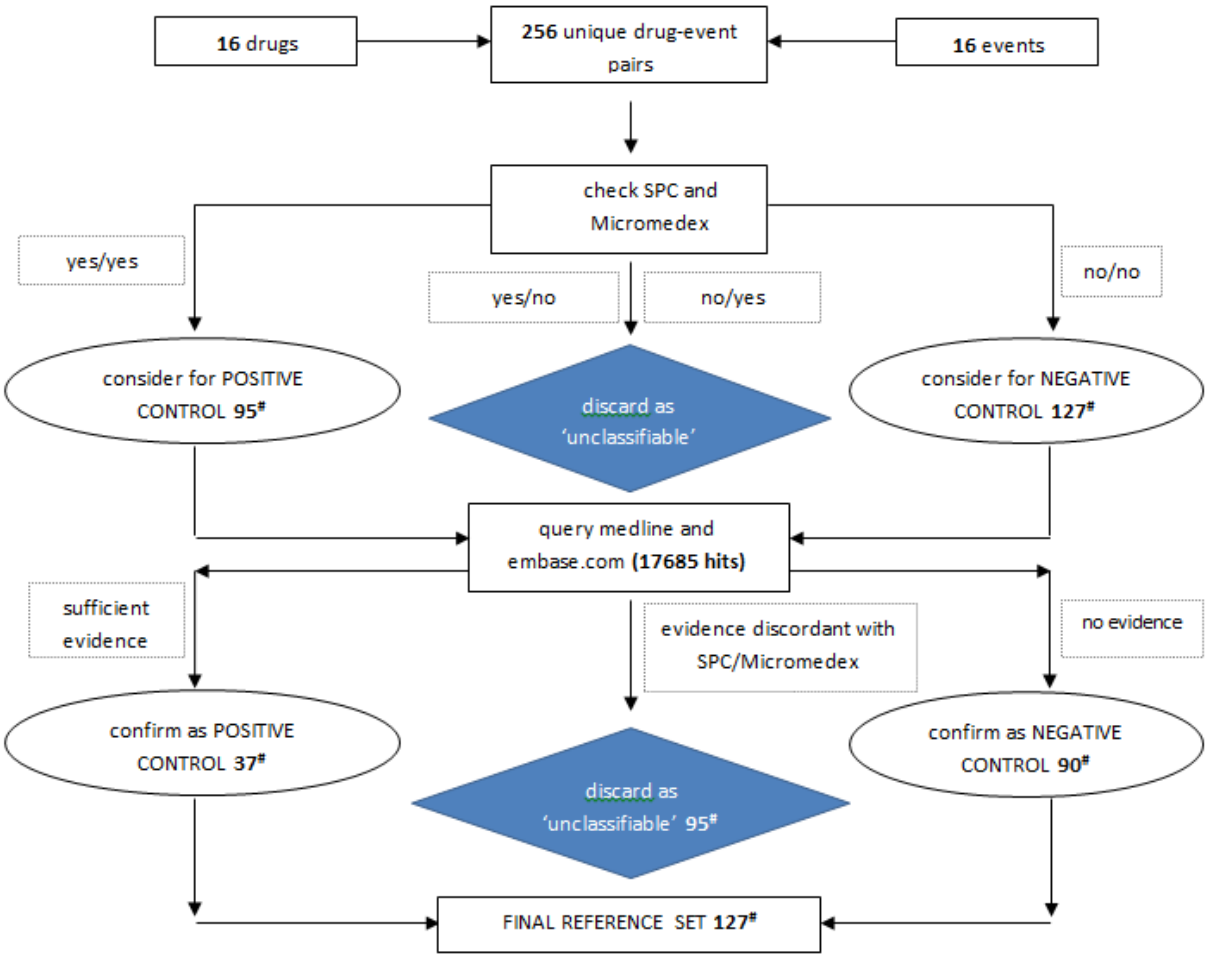


Fig. 1 Procedure adopted for the construction of the reference set (adapted from Coloma et al. 2013). *SPC* Summary of Product Characteristics, # drug-event pairs

Review of published literature

For each drug-event pair that was classified as a **'potential negative control',** a systematic literature search was conducted in Embase.com and Medline (via OvidSP). The sensitive search algorithm applied to both title and abstract, comprised controlled vocabulary plus free text for each of 2 concepts: event of interest and drug.

For each **'potential positive control'**, the search algorithm was more specific (to avoid large numbers of papers) than for the potential negative controls and included only controlled vocabulary for the drug name. However, the event was searched by using both controlled vocabulary and free text. In addition, controlled vocabulary was included for the concept: 'general adverse drug reaction', this was done to increase the probability of retrieving only those articles where adverse event and drug co-occurred in the context of drug safety [83].

For potential negative and positive control pairs we only considered articles published in English. Publications could be biological and/or epidemiological studies. Epidemiological studies could be case reports, observational studies (i.e. cohort, case-control), reviews, meta-analysis and clinical trials. As examples, the search strings for the negative control *sudden death-cyproterone/ethinylestradiol,* and positive control *sudden death-clarithromycin are presented in* **appendix 1***.*

One of 5 researchers (OO, CF, FF, MC, and YH) reviewed retrieved publications pertaining to a unique drug-event pair. All 5 researchers have received medical, biological and/or pharmacology training. Based on data extracted from relevant publications, unique drug-event pairs were classified according to the criteria outlined in **table 1**. For example, a pair was assigned as **level I** evidence if there was evidence from at least one randomized controlled trial or meta-analysis, while 'positive control – grade 1' (PC1) meant that in addition, there was 'proven biological mechanism for causal association'. **Level V** evidence - (not mentioned in SPC/Micromedex) AND (published evidence against causal association; OR no published evidence supporting causal association) - qualified a specific drug-event pair as a negative control, while 'negative control – grade 1' (NC1) meant that in addition, there was 'proven biological

mechanism against causal association'. 'Proven biological mechanism' meant that there was at least 1 publication providing relevant biological evidence regarding a unique drug-event pair. Two researchers - MS and FK (a pediatrician, clinical pharmacologist and pharmacoepidemiologist) - reviewed all associations that were classified as positive or negative control.

Whereas confirmation of negative control pairs required lack of association for either adults or the pediatric age group, positive control pairs were specifically assessed for availability of evidence pertaining to persons aged 0-18years. However, such evidence was not mandatory for classification as positive control, due to the acknowledged lack of pediatric-specific studies [94]. Those with lack of evidence in pediatrics are listed separately.

To further illustrate the process of reviewing the published literature, 126 unique references were retrieved following database search for articles supporting the potential positive control *sudden death-clarithromycin.* Of these, 103 articles were excluded following title/abstract screening; while 13 articles were excluded following full-text screening. Full text copies of 6 articles could not be obtained. Finally, 4 articles-*1 clinical trial, 2 case control studies and 1 case report*-presented sufficient evidence to support the association.

Table 1: Evaluation and grading of unique drug-event pairs based on SPC/Micromedex and literature evidence

Classification	Level of evidence	Description	Biological mechanism	Description	Grade
Positive Control (PC)	**I**	(Included in SPC/Micromedex) AND (Evidence from at least one randomized controlled trial or meta-analysis)	Proven for causal association	Evidence from at least one publication explaining mechanistic pathway	**PC1**
			Plausible for causal association	No published evidence	**PC2**
	II	(Included in SPC/Micromedex) AND (Evidence from at least one observational study [e.g. cohort, case-control, case-crossover, self-controlled case series] OR review of spontaneous reports OR systematic review OR [at least three published case reports from different sources and concerning different patients with causality evaluation of definite or probable])	Proven for causal association	Evidence from at least one publication explaining mechanistic pathway	**PC1**
			Plausible for causal association	No published evidence	**PC2**
Indeterminate	**III**	(Included in SPC/Micromedex) AND (Evidence from less than three published case reports and no further substantiation in the literature)			
	IV	Included in SPC/Micromedex BUT no published case reports or studies			
Negative Control (NC)	**V**	(Not mentioned in SPC/Micromedex) AND (published evidence against causal association OR no published evidence supporting causal association)	Proven against causal association	Evidence from at least one publication explaining mechanistic pathway	**NC1**
			Plausible against causal association	No published evidence	**NC2**

SPC - summary of product characteristics

Results

As presented in **table 2**, 16 drugs (unique WHO-ATC codes, 5th level chemical substance) were selected for the reference set. They comprise 8 anti-infectives: flucloxacillin, clarithromycin, doxycycline, lopinavir (which is always administered in fixed-dose combination with ritonavir), isoniazid, praziquantel, mebendazole and quinine. The remaining are respiratory drugs (fluticasone, administered as inhalant, and montelukast), gastrointestinal drugs (loperamide and domperidone), antipyretic/analgesic (ibuprofen), a drug for attention-deficit hyperactivity disorder (methylphenidate), anti-acne (isotretinoin), and a hormonal oral contraceptive (cyproterone/ethinylestradiol).

We selected 16 events for the reference set. They are bullous eruption (comprising fixed drug eruption [FDE], erythema multiforme [EM], Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]), aplastic anemia, agranulocytosis, thrombocytopenia, psychosis, suicide, ventricular arrhythmia, sudden death, QT prolongation, venous thromboembolism, anaphylaxis, seizure, acute kidney injury, acute liver injury, sepsis and sudden infant death syndrome (SIDS) (**table 2**). Medical definitions for all the events and their proposed (unvalidated) MedDRA codes are presented in **appendix 2.**

From the total number of combinations (256), we discontinued assessment of 34 unclassifiable drug-event pairs since we found discrepant information between the SPC and Micromedex. For the remaining 222 pairs the literature search generated 17,685 hits. Based on review of these hits 127 pairs were confirmed as 'positive control' (37 pairs) or 'negative control' (90 pairs) (**tables 2 and 3**); for 95 'unclassifiable' pairs there was discrepant information between the published literature on one hand, and the SPC and Micromedex on the other hand.

Table 2: Classification of each drug-event pair as positive control or negative control

		Selected Adverse Events															
		Bullous eruption	Aplastic anemia	Agranulo-cytosis	Thrombo-cytopenia	Psycho-Sis	Sui-cide	Vent. arrhyth-mia	Sudden death	QT prolon-gation	Venous thrombo-embolism	Anaphy-laxis	Seizure	Acute kidney injury	Acute liver injury	Sepsis	SIDS
Selected Drugs	flucloxa-cillin																
	clarithro-mycin																
	doxycy-cline																
	lopina-vir																
	isonia-zid																
	prazi-quantel																
	meben-dazole																
	quinine																
	flutica-sone																
	monte-lukast																
	isotreti-noin																
	lopera-mide																
	dompe-ridone																
	methyl-phenidate																
	ibupro-fen																
	cyproteron e/eth.est.																

Abbreviations: Vent.- ventricular; SIDS - Sudden Infant Death Syndrome; Eth.est.- Ethinylestradiol;

	Positive control
	Negative control

Table 3: Level of epidemiological and biological evidence; population in which association was found (adults, 'children'[a] or both) and grading of positive drug-event associations.

Event	Positive associations					
	ATC code	Drug name	Level of epidemiological evidence[b]	Population (A / B / C)[c]	Biological evidence (Pr/Pl)[d]	Grade
Bullous eruption[e]	J01FA09	clarithromycin	II	B	Pl	PC2
	J01CF05	doxicycline	II	B	Pl	PC2
	J04AC01	isoniazid	II	B	Pl	PC2
	P01BC01	quinine	II	A	Pl	PC2
	M01AE01	ibuprofen	II	B	Pl	PC2
Aplastic anemia	P01BC01	quinine	II	A	Pr	PC1
Agranulocytosis	P02CA01	mebendazole	II	A	Pl	PC2
	P01BC01	quinine	II	A	Pr	PC1
Thrombocytopenia	J01FA09	clarithromycin	II	C	Pl	PC2
	J01CF05	doxicycline	I	A	Pl	PC2
	P01BC01	quinine	II	A	Pr	PC1
	M01AE01	ibuprofen	I	A	Pl	PC2
Psychosis	J01FA09	clarithromycin	II	A	Pl	PC2
	J04AC01	isoniazid	II	A	Pl	PC2
	R03DC03	montelukast	II	C	Pl	PC2
	D10BA01	isotretinoin	II	B	Pr	PC1
	N06BA04	methylphenidate	I	C	Pr	PC1
Suicide	R03DC03	montelukast	II	C	Pl	PC2
	D10BA01	isotretinoin	II	B	Pr	PC1
Ventricular arrhythmia	J01FA09	clarithromycin	II	A	Pl	PC2
	P01BC01	quinine	II	A	Pl	PC2
	A03FA03	domperidone	II	A	Pr	PC1
Sudden death	J01FA09	clarithromycin	I	A	Pl	PC2
	A03FA03	domperidone	II	A	Pr	PC1
QT prolongation	J01FA09	clarithromycin	II	A	Pr	PC1
	P01BC01	quinine	I	B	Pr	PC1

Anaphylaxis	M01AE01	ibuprofen	II	B	Pr	PC1
Seizure	J04AC01	isoniazid	II	B	Pr	PC1
Acute kidney injury	P01BC01	quinine	II	A	Pl	PC2
	M01AE01	ibuprofen	II	B	Pr	PC1
Acute liver injury	J01CF05	flucloxacillin	II	A	Pl	PC2
	J01FA09	clarithromycin	II	B	Pl	PC2
	J05AE06	lopinavir	I	A	Pl	PC2
	J04AC01	isoniazid	I	B	Pl	PC2
	P02CA01	mebendazole	I	B	Pl	PC2
	P01BC01	quinine	II	A	Pl	PC2
	M01AE01	ibuprofen	II	A	Pl	PC2

ATC Anatomical Therapeutic Chemical, Pr proven biological evidence, Pl plausible biological evidence, PC positive control

[a] In this context, 'Children' refers to individuals aged 0-18 years

[b] Epidemiological evidence levels I and II are defined in Table 1

[c] Population in which epidemiological evidence was found: A-adults; B-both adults and 'children'; C-'children'.

[d] As defined in table 1

[e] Bullous eruption includes: fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

In confirming the 37 positive control pairs, evidence was used from 171 relevant publications, comprising 14 biological studies, 10 clinical trials, 23 observational studies, 34 reviews, and 90 case reports/series. The association between quinine and thrombocytopenia had the highest number of supporting publications i.e. 20 (out of 171): eight publications pertained to biological evidence while 12 reported on epidemiologic evidence. **Table 4** shows how the positive associations: *quinine-thrombocytopenia* and *clarithromycin-sudden death* were established. For the complete evaluation of all positive drug-event associations, please refer to **appendix 3.**

Table 4: Examples of evaluation of a positive drug-event association: 1) quinine-thrombocytopenia and 2) clarithromycin-sudden death

ATC Code	Drug Name	Event Type	Labelled as AE in SPC(Yes/No)	Type/No. of Supporting Literature Citations
P01BC01	**Quinine**	**Thrombocytopenia**	Yes	Total number of supporting citations = 20
			*eMC (Special warnings and precautions for use; Undesirable effects)	Biological studies = 8 Review of biological studies = 4 Systematic review = 1
			#Micromedex (Summary): Blackbox warning;(Contraindications/Warnings→Contraindications; precautions); (Adverse effects→serious)	Case series = 1 Case reports = 4 Review of Spontaneous reports = 2
J01FA09	**Clarithromycin**	**Sudden death**	Yes	Total number of supporting citations = 4
			*eMC (Undesirable effects)	Clinical trial = 1
			# Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Case-control = 2 Case report = 1

ATC Anatomical Therapeutic Chemical, AE Adverse effect, *SPC* Summary of Product Characteristics, *eMC* Electronic Medicines Compendium; * https://www.medicines.org.uk/emc/; # http://micromedex.com/

As presented in **table 3**, we generated 37 positive associations; of these, level I evidence was available for only 8 (22%) and 13 (35%) were supported by both biological and epidemiological evidence. Only 4 associations (clarithromycin-thrombocytopenia, montelukast-psychosis, montelukast-suicide AND methylphenidate-psychosis) were supported by evidence generated exclusively from the pediatric age group, while 13 associations were supported by evidence from both adults and the pediatric population. Overall, 17 (46%) of all positive associations were based on evidence from the pediatric population. Twenty associations were supported by evidence from only adults.

In **appendix 4**, we compare the reference set we have created with the reference sets that were created within EU-ADR and OMOP. Out of the 16 drugs that were selected for GRiP, 4 were also included in EU-ADR and/or OMOP: fluticasone, ibuprofen, isoniazid and mebendazole. Ibuprofen was classified to be a positive control for acute kidney injury (AKI) in each of the 3 reference sets; while the same drug was classified to be associated with acute liver injury (ALI) only within GRiP and EU-ADR. Isoniazid was classified as positive control for ALI, both in GRiP and OMOP. OMOP nor EU-ADR labelled mebendazole with AKI, nor fluticasone with ALI.

Discussion

We describe a pediatric focused reference set of drug-event associations that may be used for testing the performance of different signal detection methods and databases. To our knowledge, this is the first structured approach to creating a reference set that is specific to pediatric safety outcomes. This approach yielded 37 positive and 90 negative drug-event associations, 17 positive associations were supported by evidence in children, and 20 were based on adult information only.

Projects such as OMOP and EU-ADR have also created reference sets, but none of them was targeted to pediatrics, in addition the construct of these reference sets was different [83,95-97]. In the current project, drugs and events were selected independently, unlike EU-ADR and OMOP [83,84]. In addition the EU-ADR network restricted the list of drugs based on the amount of drug exposure that would be required to identify associations with selected adverse events at pre-specified relative risk (RR) values. This was done so that such drug-event associations could actually be identified if indeed they occurred within the network. Similar calculations were not done for the current project although most of the selected drugs are frequently administered in the pediatric population (based on reported evidence in the literature). Further, the reference set resulting from the current project will be applied to SRS databases (in addition to EHRs) and therefore should preferably be unbiased to one or the other.

The GRiP reference set focused on diversity of drugs and events which may allow us to stratify by outpatient/inpatient care, frequent and rare events. Sets with drugs for inpatient use may favour performance of data mining on SRS databases, while sets utilizing drugs prescribed for outpatient treatments may favour mining performance on EHR databases [98]. In order to have enough power for both, we focused on drugs with longer license status.

In selecting adverse events, we considered both frequent and rare events. Thus, the resulting reference set can be tested in a wide variety of databases with unique adverse event profiles, such as spontaneous reporting systems, hospital based and general practice health care databases. Previous reference sets focused mostly on rare and well known drug-induced events

which may favour SRS [83]. Such events may be reported more often than common, multifactorial events because they are easier to identify as being caused by drugs. Given that the composition of the lists of drugs and adverse events to be tested may have an extensive impact on performance assessment [99], we tried to ensure that the criteria and data sources that were utilized to create the reference set were independent of the data on which they will eventually be tested.

We conducted extensive reviews to list evidence for both positive and negative controls. Fewer publications were retrieved for the potential positive control pairs (7745 hits), compared to the potential negative control pairs (9940 hits), possibly because the search algorithm for the former was more specific. However, this was considered necessary to increase the probability of retrieving relevant publications (i.e. publications that reported on adverse event and drug in the context of drug safety), an approach similar to that adopted by the EU-ADR project[83].

To validate potential negative controls, terms that were related to the actual event term were considered. For example suicide-isoniazid was initially classified as potential negative control because suicide was not mentioned (in relation to isoniazid), both in SPC (DailyMed) and Micromedex. However a case report described the occurrence of suicide attempt following ingestion of isoniazid[100]. Therefore this association could not be confirmed as negative control. Whereas the negative drug-event associations required lack of association for adults or the pediatric population, the positive drug-event associations were specifically (or primarily) assessed for availability of evidence pertaining to the pediatric age group. However, due to the general lack of pediatric pharmacoepidemiological data only 4 associations (clarithromycin-thrombocytopenia, montelukast-psychosis, montelukast-suicide AND methylphenidate-psychosis) were supported by evidence generated exclusively from this age group: a case-control study for clarithromycin-thrombocytopenia [101]; case reports (more than 3) for montelukast-psychosis [102]; review of spontaneous reports for montelukast-suicide [103]; and clinical trial as well as case series for methylphenidate-psychosis[104]. The scarcity and quality of pediatric-specific data further highlight the difficulties in generating safety evidence in the pediatric population, thereby underlining the importance of developing a tool to define

appropriate signal detection methods in this population. We recommend that the 20 positive associations that come from adult evidence only, be treated separately in the performance testing in pediatric data.

We chose to classify all pairs with inconsistent evidence as unclassifiable, to avoid misclassification. We searched for biological (in addition to epidemiological) evidence to further strenghthen retrieved evidence for positive controls. However we were able to find such evidence for only 13 out of 37 positive associations: quinine-aplastic anemia[105]; quinine-agranulocytosis[106]; quinine-thrombocytopenia[107]; isotretinoin-psychosis[108,109]; methylphenidate-psychosis [110,111]; isotretinion-suicide[108,109]; domperidone-ventricular arrhythmia[112]; domperidone-sudden death[113]; clarithromycin-QT prolongation[114]; quinine-QT prolongation[115,116]; ibuprofen-anaphylaxis[117]; isoniazid-seizure[118]; and ibuprofen-acute kidney injury[119]. Of these, quinine-thrombocytopenia had the highest number of supporting publications i.e. 8 regarding biological evidence (besides 12 others pertaining to epidemiological evidence). This is possibly because quinine has been in use for a long time, both as over-the-counter (OTC) and prescription drug[120]; therefore its safety profile has been well investigated. Otherwise, the limited biological evidence for most of the other positive associations may reflect the current gap of knowledge and understanding of adverse drug reactions.

Comparing our reference set to others, we found little overlap in the choice of drugs, possibly because we aimed to be pediatric-specific in our selection while also including drugs used in specific sub-populations (i.e. adolescents) and context (LMICs). Out of 16 drugs considered in GRiP, only 4 were considered also in EU-ADR and/or OMOP: isoniazid, ibuprofen, mebendazole and fluticasone. Perhaps this, as well as differences in adverse event selection explains the few similarities we found across the 3 reference sets. Nevertheless, ibuprofen was found to be associated with acute kidney injury in all the sets.

There are several limitations in the use of a reference set and the creation of it. Some potential positive associations that are well known (i.e. *domperidone-QT prolongation* and *cyproterone/ethinylestradiol-venous thromboembolism* both of which have been well

investigated) could not be validated. The search query we used to retrieve the publications may have been too specific. For other unconfirmed potential positive control pairs, events mentioned in the SPC and Micromedex may have been reported through means other than peer-reviewed literature (for example US Federal Drug Administration - FDA - reports).

Time is an important limiting aspect in building a reference set, both for the positive as well as negative controls. We labelled drug-event associations as negative if there is lack of evidence, which in itself is something that may rapidly change over time, checking of the absence of evidence should always be done prior to using the reference set. For the positive controls it is important to know at which point in time the association was 'known' as this may lead to changes in reporting behaviour to spontaneous reporting databases and to changes in clinical care. Those changes may have an impact on the ability to detect associations (e.g. in spontaneous reporting databases it may increase the association whereas it may decrease in electronic health care databases) [121-123]. Time stamping of the 'known' associations would be important. This was however impossible for this reference set since we chose drugs that are available for a long time and have been registered nationally. Inclusion of information in an SPC may vary from country to country. We recommend investigators that will use this set, to assess in their reality when associations were 'known' in order to evaluate the impact of that on performance.

In order to use the reference set, the events need to be translated into codes. This is an important step and may impact on the performance testing. In appendix 2 we have provided initial MedDRA codes as most of the events have SMQs. These codes should be reviewed and the impact of choices should be carefully evaluated, they may differ between spontaneous reporting databases and electronic health care records. Within the GRiP project we aim to perform this work for MeDDRA, ICD-9, 10, READ and ICPC and a full code list with the impact of choice on performance will become available later.

Conclusion

We have generated a pediatric focused reference set that can be applied for testing performance of methods and databases for drug safety signal detection in the pediatric population. This reference set may be viewed as dynamic. The status of drug-event associations may change over time, particularly as more evidence derived specifically from the pediatric population becomes available in the future. Therefore periodic review and checking against the local situation is advisable.

Appendix 1: Medline search algorithms for sudden death- cyproterone/ethinyl estradiol (negative control) and sudden death-clarithromycin (positive control)

Association	Concept	Algorithm
sudden death- cyproterone/ethinyl estradiol	sudden death	(exp Death, Sudden/ OR (((sudden* OR unexpect* OR instant*) adj3 (death OR dead OR died OR dying)) OR mors subita).ab,ti.)
		AND
	cyproterone/ ethinylestradiol	(Estradiol/aa and Cyproterone Acetate/) or ((cyproterone acetate adj3 (ethinyl estradiol or ethinyloestradiol)) or co cyprindiol or cocyprindiol or climen or diane or dianette).ab,ti.
sudden death- clarithromycin	sudden death	(exp Death, Sudden/ OR (((sudden* OR unexpect* OR instant*) adj3 (death OR dead OR died OR dying)) OR mors subita).ab,ti.)
		AND
	general adverse drug reaction	drug toxicity/
		AND
	clarithromycin	clarithromycin/

Note: For each association, the search results were limited to articles published in English

Appendix 2: Medical definitions of selected adverse events; and corresponding proposed but unvalidated Medical Definition for Regulatory Activities (MedDRA) codes (SMQ-standardized MedDRA query; PT-preferred term; LT-lower level term; HT-high level term; HG- high level group term; OL-noncurrent lower level term)

S/N	Event	Medical (case) definition	References	MedDRA codes
1	**bullous eruptions**	**fixed drug eruption** These are reactions characterized by: (1) One or more sharply demarcated, erythematous lesions, sometimes leading to a blister. (2) Hyperpigmentation which often results after resolution of the acute inflammation. (3) With rechallenge, the lesion recurs in the same (i.e., fixed) location. (4) Lesions often involve the lips, hands, legs, face, genitalia, and oral mucosa and cause a burning sensation. (5) Most patients have multiple lesions. **See references for further details** **erythema multiforme** Characteristics include: (1) Acute self-limited, usually mild and often relapsing muco-cutaneous syndrome. (2) Usually benign but with frequent recurrences (3) The skin lesions are usually target-shaped plaques with or without central blisters, predominant on the face and extremities. **sub-types** (1) Erythema multiforme minor: Skin lesions without involvement of mucous membranes (2) Erythema multiforme major: Skin	(1) Shinkai K, Roujeau J, Stern RS, Wintroub BU. Chapter 55. Cutaneous Drug Reactions. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9098524. Accessed October 1, 2012 (2) Stern RS, Shear NH. Cutaneous reactions to drugs and biological modifiers. In: Cutaneous Medicine and Surgery, Arndt KA, LeBoit PE, Robinson JK, Wintroub BU (Eds), WB Saunders, Philadelphia 1996. Vol 1, p.412. (3) Yawalkar N. Drug-induced exanthems. Toxicology. 2005;209:131–134. doi: 10.1016/j.tox.2004.12.023 (1) Roujeau J. Chapter 39. Erythema Multiforme. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Dallas NA, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56032944. Accessed October 2, 2012.	(LT/10016740), (LT/10048796) (LT/10015217), (LT/10015218),(LT/10015221), (LT/10015222), (LT/10015223), (LT/10015223), (LT/10015224), (LT/10033726), (LT/10033730), (LT/10037876), (LT/10040843), (LT/10044259), (LT/10057783), (LT/10057866), (LT/10057970), (LT/10057971), (LT/10068560), (PT/10015218), (PT/10037876), (PT/10057970)

		lesions with involvement of mucous membranes (3) Mucosal erythema multiforme (Fuchs syndrome, ectodermosis pluriorificialis): Mucous membrane lesions without cutaneous involvement **See references for further details** **epidermal necrolysis (Stevens-Johnsons Syndrome and toxic epidermal necrolysis)** Characteristics include: (1) They are "rare and life-threatening, mainly drug induced". (2) There is "widespread apoptosis of keratinocytes provoked by the activation of a cell-mediated cytotoxic reaction and amplified by cytokines, mainly granulysin" (3) "Confluent purpuric and erythematous macules evolving to flaccid blisters and epidermal detachment predominating on the trunk and upper limbs and associated with mucous membrane involvement". (4) Pathologic analysis shows full-thickness necrosis of epidermis associated with mild mononuclear cell infiltrate **See references for further details**	(1) Valeyrie-Allanore L, Roujeau J. Chapter 40. Epidermal Necrolysis (Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis). In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Dallas NA, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56033128. Accessed October 2, 2012.	(LT/10006561), (LT/10015156), (LT/10015209), (LT/10015210), (LT/10015211), (LT/10015219), (LT/10015220), (LT/10015222), (LT/10028077), (LT/10030068), (LT/10030081), (LT/10042029), (LT/10042030), (LT/10042033), (LT/10042849), (LT/10047376), (OL/10042032), (PT/10030081), (PT/10042033), (LT/10014986), (LT/10025166), (LT/10025167), (LT/10025168), (LT/10028848), (LT/10028849), (LT/10043221), (LT/10044223), (OL/10025165), (OL/10042821), (OL/10044222), (PT/10044223)

S/N	Event	Medical (case) definition	References	MedDRA codes
2	**aplastic anemia**	Aplastic anemia is characterized by the suppression of all bone marrow lines – erythroid, granulocytic and megakaryocytic ultimately	(1) Primack BA, Mahaniah KJ. Chapter 31. Anemia. In: South-Paul JE, Matheny SC, Lewis EL, eds. *CURRENT Diagnosis & Treatment in Family*	(LT/10049494), (LT/10002037),(LT/10002038), (LT/10002061), (LT/10002274), (LT/10002274), (LT/10002275), (LT/10002294), (LT/10002962),

	leading to pancytopenia **Characteristics** (1) Pancytopenia (2) Hypocellular bone marrow (3) Normal hematopoetic cells **See references for further details**		*Medicine*. 3rd ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=8153552. Accessed October 2, 2012 (2) Neal S. Young; Acquired Aplastic Anemia. Annals of Internal Medicine. 2002 Apr;136(7):534-546 (3) Guinan EC. Diagnosis and management of aplastic anemia. Hematology Am Soc Hematol Educ Program. 2011;2011:76–81	(LT/10002967), (LT/10002968), (LT/10002969), (LT/10002970), (LT/10002971), (LT/10003506), (LT/10004738), (LT/10005980), (LT/10005984), (LT/10005986), (LT/10005987), (LT/10010776), (LT/10010777), (LT/10012381), (LT/10020954), (LT/10021069), (LT/10021074), (LT/10021075), (LT/10021077), (LT/10026846), (LT/10026848), (LT/10026853), (LT/10033661), (LT/10036699), (LT/10048580), (LT/10051779), (LT/10053138), (LT/10053213), (LT/10053504), (LT/10054329), (LT/10054361), (LT/10054580), (LT/10057528), (LT/10064566), (LT/10065553), (LT/10068061), (LT/10068063), (LT/10071576), (LT/10071584), (PT/10002967), (PT/10003506), (PT/10004738), (PT/10021074), (PT/10033661), (PT/10051779), (PT/10053138), (PT/10053213), (PT/10053504), (PT/10057528), (PT/10065553), (PT/10071576)

S/N	Event	Medical (case) definition	References	MedDRA codes
3	**Agranulocytosis**	**agranulocytosis** means the absence of granulocytes (i.e. Absolute Neutrophil count of zero). However, **"agranulocytosis or acute neutropenia** currently refers to a profound decrease or an absolute lack of circulating granulocytes, classically resulting in a neutrophil count of ***<0.5 × 10^9/l"*** In the majority of patients, the neutrophil count is ***< 0.1 × 10^9/l*** **See references for further details**	(1) Andres E., Zimmer J., Mecili M., Weitten T., Alt M., Maloisel F. Clinical presentation and management of drug-induced agranulocytosis. Expert Rev. Hematol. 2011; 4 (2): 143- 151 (2) Frank Andersohn, Christine Konzen, Edeltraut Garbe; Systematic Review: Agranulocytosis Induced by Nonchemotherapy Drugs. Annals of Internal Medicine. 2007 May;146(9):657-665	(LT/10001507), (LT/10003506), (LT/10004738), (LT/10005984), (LT/10018687), (LT/10029366), (LT/10029369), (LT/10029382), (LT/10050443), (LT/10051645), (LT/10057528), (LT/10066542), (PT/10001507), (PT/10003506),(PT/10004738), (PT/10018687), (PT/10029366),(PT/10050443), (PT/10051645), (PT/10057528), (SMQ/20000023)

S/N	Event	Medical (case) definition	References	MedDRA codes
4	**Thrombocytopenia**	Thrombocytopenia can be defined as follows: **(1) Level 1 of diagnostic certainty (confirmed TP):** Platelet count less than ***150×109 L−1*** **AND** confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding. **(2) Level 2 of diagnostic certainty (unconfirmed TP):** Platelet count less than 150×109 L−1 ***Drug-induced thrombocytopenia (DITP)*** *should be suspected in a patient who presents with new onset of thrombocytopenia without an obvious cause other than drug ingestion. A patient with recurrent episodes of acute thrombocytopenia should be suspected of having a drug-induced etiology. A detailed history, including all of the medications being taken by the patient, is essential. This should include all prescribed drugs, over-the-counter medications, herbal preparations, folk remedies, quinine-containing beverages, and recent vaccinations.* **See references for further details**	(1) Wise RP*,* Bonhoeffer J*,* Beeler J*, et al.* Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data*.* Vaccine 2007*;* 25*:* 5717–5724 (2) Royer, D. J., George, J. N. and Terrell, D. R. (2010), Thrombocytopenia as an adverse effect of complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. European Journal of Haematology, 84: 421–429	(HG/10035534), (HT/10035533), (HT/10043555), (LT/10012530), (LT/10024922), (LT/10035524), (LT/10035526), (LT/10035527), (LT/10035528), (LT/10035529), (LT/10035531), (LT/10035532), (LT/10035540), (LT/10035545), (LT/10036735), (LT/10037557), (LT/10037561), (LT/10038213), (LT/10039884), (LT/10043545), (LT/10043546), (LT/10043552), (LT/10043553), (LT/10043554), (LT/10043556), (LT/10043557), (LT/10043558), (LT/10043559), (LT/10043560), (LT/10043561), (LT/10043569), (LT/10044394), (LT/10048672), (LT/10050245), (LT/10051057), (LT/10051601), (LT/10058336), (LT/10062506), (LT/10063129), (LT/10066667), (LT/10070664), (LT/10072326), (LT/10072332), (MTH_SMQ/20000031), (OL/10013258), (OL/10043551), (PT/10035526), (PT/10035528), (PT/10035531), (PT/10035532), (PT/10035540), (PT/10037557), (PT/10043554), (PT/10043557), (PT/10043561), (PT/10050245), (PT/10062506), (PT/10070664), (PT/10072326), (SMQ/20000031)

S/N	Event	Medical (case) definition	References	MedDRA codes
5	**psychosis**	**'psychosis** is a disturbance in the perception of reality, evidenced by hallucinations, delusions, or thought disorganization. Psychotic states are periods of high risk for agitation, aggression, impulsivity, and other forms of behavioral dysfunction' **'*hallucinations*** are false sensory perceptions occurring in any of the five sensory modalities. Auditory hallucinations are the most common, followed by visual, tactile, olfactory, and gustatory' **'*delusions*** are false beliefs that are firmly held despite obvious evidence to the contrary, and not typical of the patient's culture, faith, or family. Persecutory, grandiose, religious, somatic, and other delusions are all common and cut across diagnostic boundaries' **'*thought disorganization*** - disruption of the logical process of thought may be represented by loose associations, nonsensical speech, or bizarre behavior. These symptoms are typically accompanied by a high level of functional impairment and high risk for agitated and aggressive behavior' **See references for further details**	(1) Shelton RC. Chapter 17. Other Psychotic Disorders. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. *CURRENT Diagnosis & Treatment: Psychiatry*. 2nd ed. New York: McGraw-Hill; 2008. http://www.accessmedicine.com/content.aspx?aID=3284695. Accessed October 2, 2012. (2) UpToDate. *Overview of psychosis*. 2013 [cited 2014 19th June]; Available from: http://www.uptodate.com/contents/overview-of-psychosis?source=search_result&search=overview+of+psychosis&selectedTitle=1~150.	(HT/10004938), (HT/10006360), (HT/10012259), (LT/10000958), (LT/10001022), (LT/10001443), (LT/10001444), (LT/10001445), (LT/10001449), (LT/10001450), (LT/10001451), (LT/10004908), (LT/10004935), (LT/10008522), (LT/10008524), (LT/10009080), (LT/10011717), (LT/10012239), (LT/10012240), (LT/10012241), (LT/10012242), (LT/10012243), (LT/10012244), (LT/10012245), (LT/10012246), (LT/10012247), (LT/10012247), (LT/10012248), (LT/10012257), (LT/10012260), (LT/10012261), (LT/10012262), (LT/10012287), (LT/10012393), (LT/10012408), (LT/10013143), (LT/10013144), (LT/10013145), (LT/10013708), (LT/10013741), (LT/10013758), (LT/10013759), (LT/10013761), (LT/10015134), (LT/10015626), (LT/10016894), (LT/10018669), (LT/10018671), (LT/10019379), (LT/10021031), (LT/10021166), (LT/10021720), (LT/10023164), (LT/10026754), (LT/10026755), (LT/10026756), (LT/10026757), (LT/10026758), (LT/10026780), (LT/10026781), (LT/10026784), (LT/10026785), (LT/10026786), (LT/10026787), (LT/10026789), (LT/10026790), (LT/10026791), (LT/10027740), (LT/10027945), (LT/10033864), (LT/10033867), (LT/10033870), (LT/10034702), (LT/10037200), (LT/10037234), (LT/10037235), (LT/10037237), (LT/10037238), (LT/10037239), (LT/10037240), (LT/10037241), (LT/10037242), (LT/10037243), (LT/10037245), (LT/10037248), (LT/10037250), (LT/10037253), (LT/10037953), (LT/10037954), (LT/10039612), (LT/10039613), (LT/10039621), (LT/10039622), (LT/10039635), (LT/10039987), (LT/10040534), (LT/10040535), (LT/10041317), (LT/10041317), (LT/10044395), (LT/10045620), (LT/10045654), (LT/10045655), (LT/10045656), (LT/10045855), (LT/10045856), (LT/10046122), (LT/10046160), (LT/10048343), (LT/10053415), (LT/10053632),

				(LT/10056309), (LT/10056326), (LT/10057667), (LT/10059232), (LT/10059419), (LT/10061040), (LT/10061920), (LT/10062645), (LT/10063033), (LT/10065617), (LT/10066731), (LT/10068305), (LT/10070669), (LT/10072389), (LT/10072392), (OL/10001437), (OL/10001448), (OL/10004918), (OL/10013739), (OL/10025459), (OL/10025460), (OL/10026788), (OL/10031481), (OL/10031518), (OL/10031602), (OL/10031619), (OL/10032253), (OL/10032711), (OL/10032712), (OL/10032889), (OL/10033866), (OL/10037221), (PT/10001022), (PT/10001443), (PT/10008522), (PT/10012239), (PT/10012241), (PT/10012244), (PT/10012245), (PT/10015134), (PT/10018671), (PT/10023164), (PT/10033864), (PT/10034702), (PT/10039621), (PT/10039987), (PT/10040535), (PT/10041317), (PT/10041317), (PT/10053632), (PT/10056326), (PT/10057667), (PT/10059232), (PT/10061040), (PT/10061920), (PT/10062645), (PT/10063033), (PT/10065617), (PT/10070669), (SMQ/20000117)

S/N	Event	Medical (case) definition	References	MedDRA codes
6	**suicide**	**Two concepts** will be considered: (1) completed suicide (2) suicide attempt **completed suicide** Death caused by self-directed injurious behavior with any intent to die as a result of the behavior. **suicide attempt** A non-fatal self-directed potentially injurious behavior with any intent to die as a result of the behavior. A suicide attempt may or may not result in injury.	(1) Crosby AE, Ortega L, Melanson C. Self-directed Violence Surveillance: Uniform Definitions and Recommended Data Elements, Version 1.0. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2011	(LT/10000394), (LT/10003728), (LT/10010144), (LT/10013738), (LT/10033298), (LT/10033927), (LT/10036001), (LT/10042462), (LT/10042463), (LT/10042464), (LT/10042465), (LT/10042466), (LT/10067875), (OL/10057354), (PT/10010144), (PT/10042464), (SMQ/20000035), (SMQ/20000037)

		See references for further details		

S/N	Event	Medical (case) definition	References	MedDRA codes
7	**ventricular arrhythmia**	**Three concepts** will be considered: (1) Ventricular Tachycardia (2) Ventricular Fibrillation (3) Bradycardia **ventricular tachycardia** This can be defined on the basis of heart rate and ECG findings. **On the basis of heart rate:** • >180 beats/minute (regular) in infants and young children • > 120 beats/minute (regular) in older children/adolescents (indicate tachycardia generally) **On the basis of ECG, the following features apply:** • Ventricular rate is >120 beats per minute and regular • P waves are often not identifiable, may have AV dissociation, or may have retrograde depolarization • QRS is typically wide (>0.09 sec) • T waves are often opposite in polarity from the QRS complex **ventricular fibrillation (VF)** It is characterized by rapid***, chaotic, and asynchronous contraction of the left ventricle.*** The surface electrogram of VF reveals a ***rapid, irregular, dysmorphic pattern with no clearly defined QRS complex.***	(1) UpToDate. *Causes of wide QRS complex tachycardia in children*. 2014 [cited 2014 19th June]; Available from: http://www.uptodate.com/contents/causes-of-wide-qrs-complex-tachycardia-in-children?source=machineLearning&search=causes+of+wide+qrs+tachycardia+in+children&selectedTitle=1~150&sectionRank=1&anchor=H3#H3. (2) Rho RW, Page RL. Chapter 42. Ventricular Arrhythmias. In: Fuster V, Walsh RA, Harrington RA, eds. *Hurst's The Heart*. 13th ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=7814365. Accessed October 4, 2012 (3) Michaelson M, Engle MA. Congenital complete heart block: An international study of the natural history. In: Cardiovascular Clinics, Brest AN, Engle MA (Eds), FA Davis, Philadelphia 1972. p.85 (4) Kugler JD. Sinus node dysfunction. In: Pediatric Arrhythmias: Electrophysiology and Pacing, Gillette PC, Garson AG Jr (Eds), WB Saunders, Philadelphia 1990. p.250.	(LT/10003131), (LT/10003132), (LT/10016571), (LT/10016573), (LT/10034048), (LT/10034049), (LT/10034050), (LT/10043082), (LT/10047281), (LT/10047282), (LT/10047290), (LT/10047292), (LT/10047293), (LT/10049447), (LT/10051363), (LT/10060730), (LT/10066663), (LT/10066685), (LT/10066686), (LT/10073034), (OL/10047395), (PT/10047281), (PT/10047290), (PT/10049447)

bradycardia

Normally, the value for average heart rates varies with age. Younger patients usually have higher heart rates which decrease to adult values by the late teenage years. Bradycardia can be established by either using 12-lead electrocardiogram (ECG) or by 24-hour ambulatory monitoring.

On the basis of 12-lead electrocardiogram (ECG):

- **Newborn to 3 years**: < 100 beats/minute
- **3 - 9 years:** < 60 beats/ minute
- **9 – 16 years**: < 50 beats per minute

On the basis of 24-hour ambulatory monitoring:

- **Newborns – 2 years:** < 60 beats/minute while asleep and < 80 beats/ minute while awake
- **2 – 6 years:** < 60 beats per minute
- **6 – 11 years:** < 45 beats/ minute
- **> 11 years (adolescents):** < 40 beats/minute
- **> 11 years who are well-trained athletes:** < 30 beats per minute

N.B The 24-hour ambulatory guidelines vary from the ECG guidelines as they include the slower heart rates that occur normally at rest and sleep

See references for further details

S/N	Event	Medical (case) definition	References	MedDRA codes
8	**sudden death**	**Two concepts** will be considered: (1) Sudden death (2) Sudden cardiac death **Sudden death** **Two definitions** will be considered for sudden death: (1) Unwitnessed death occurring within 24hrs of being seen alive and functioning normally. (2) Natural, unexpected death within 1 hour of the onset of symptoms. Four temporal elements have to be considered in the use of this definition: prodromes, onset of the terminal event, cardiac arrest, and biological death. The 1-hour definition refers to the period between onset of the terminal event, that is, acute changes in cardiovascular status, and cardiac arrest. The biological legal death can occur days or weeks after the cardiac arrest, as patients can survive with irreversible brain damage and life support **Sudden cardiac death (SCD)** **Sudden cardiac death (SCD)** is said to have occurred when there is sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation, thereby leading to death (**if corrective measures are not taken rapidly)**	(1) C. van der Werf, I. van Langen, A.A. Wilde. Sudden death in the young: what do we know about it and how to prevent? Circ Arrhythm Electrophysiol, 3 (2010), pp. 96–104 (2) UpToDate. *Overview of sudden cardiac arrest and sudden cardiac death*. 2013 [cited 2014 19th June]; Available from: http://www.uptodate.com/contents/overview-of-sudden-cardiac-arrest-and-sudden-cardiac-death?source=search_result&search=overview+of+sudden+cardiac+arrest+and+sudden+cardiac+death&selectedTitle=1~150.	(HT/10011907), (LT/10042434), (LT/10042435), (LT/10042436), (LT/10042437), (LT/10046269), (LT/10049418), (LT/10052810), (LT/10063894), (LT/10063895), (LT/10069409), (OL/10011915), (OL/10011938), (PT/10042434), (PT/10049418), (PT/10063894)

		Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. ***Sudden cardiac death should not be used to describe events that are not fatal."*** **See references for further details**		

S/N	Event	Medical (case) definition	References	MedDRA codes
9	**QT prolongation.**	**Torsades de pointes (TdP)** will be included in this definition **QT prolongation** It refers to prolongation of heart rate-corrected QT (QTc) interval from a 12-lead electrocardiogram (ECG). For ***children aged 1 – 15 years***, prolonged QTc is defined as: • **> 460 milliseconds** Bazett formula ($QTc=QT/RR^{0.5}$) is most often used for heart rate correction **Long QT syndrome (LQTS)** This is characterized by prolonged QT with clinical manifestations/sequelae like palpitations, syncope, seizures, and sudden cardiac death (SCD). **Torsades de pointes (TdP)** Torsades de pointes (TdP) is a form of polymorphic ventricular tachycardia (VT) that occurs in the setting of acquired or	(1) ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non Antiarrhythmic Drugs; CPMP/986/96. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. London: Committee for proprietary medicinal products. 1997 (2) UpToDate. *Definition of normal, borderline, and prolonged corrected QT interval (QTc) in seconds according to age and gender*. [cited 2012 18th October]; Available from: http://www.uptodate.com/contents/image?imageKey=CARD/78934&topicKey=CARD%2F1053&source=preview&rank=undefined. (3) El-Sherif N, Turitto G. Torsade de pointes. Curr Opin Cardiol 2003;18(1):6–13 (4) Passman R, Kadish A. Polymorphic ventricular tachycardia, long Q-T	(LT/10014383), (LT/10014387), (LT/10024802), (LT/10024803), (LT/10036887), (LT/10037094), (LT/10037700), (LT/10037703), (LT/10037705), (LT/10044066), (LT/10044067), (LT/10053604), (LT/10053698), (LT/10054581), (PT/10014387), (PT/10024803), (PT/10044066), (SMQ/20000001)

		congenital QT interval prolongation. It is usually found on ECG. **Polymorphic VT** is defined as a ventricular rhythm faster than 100 beats per min with frequent variations of the QRS axis, morphology, or both. ***In the specific case of TdP, these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis. The peaks of the QRS complexes appear to "twist" around the isoelectric line of the recording; hence the name torsades de pointes or "twisting of the points."*** **See references for further details**	syndrome, and torsades de pointes. *Med Clin North Am*. 2001;85: 321–341.	

S/N	Event	Medical (case) definition	References	MedDRA codes
10	**venous thromboembolism**	**Two manifestations** of venous thromboembolism will be considered: (1) Deep venous thrombosis (DVT) (2) Pulmonary thromboembolism (PE) **deep venous thrombosis (DVT)** This is characterized by: • Leg pain • Inguinal or abdominal pain • Swelling, and reddish or purple discoloration of the legs • Palpable cord (reflecting a thrombosed vein), • Ipsilateral edema • Warmth, and/or superficial venous dilation • "Positive" result on **compression**	(1) UpToDate. *Pathogenesis and clinical manifestations of venous thrombosis and thromboembolism in infants and children*. 2013 [cited 2014 19th June]; Available from: http://www.uptodate.com/contents/pathogenesis-and-clinical-manifestations-of-venous-thrombosis-and-thromboembolism-in-infants-and-children?source=search_result&search=pathogenesis+and+clinical+manifestation+of+thrombosis+and+thromboembolism+in+children&selectedTitle=1~150. (2) Lensing AWA, Prandoni P, Prins HR, Büller HR. Deep-vein thrombosis.	(HT/10037379), (HT/10037379), (HT/10047197), (LT/10000853), (LT/10012098), (LT/10012107), (LT/10013877), (LT/10013879), (LT/10014521), (LT/10014537), (LT/10034272), (LT/10037377), (LT/10037380), (LT/10037436), (LT/10038547), (LT/10043566), (LT/10043567), (LT/10043578), (LT/10043630), (LT/10043642), (LT/10047251), (LT/10047252), (LT/10049915), (LT/10049916), (LT/10049917), (LT/10049918), (LT/10050071), (LT/10051055), (LT/10054751), (LT/10056966), (LT/10064602), (LT/10065052), (LT/10066529), (LT/10066738), (LT/10066899), (LT/10073531), (OL/10014511), (OL/10034191), (OL/10037378), (PT/10034272), (PT/10037377), (PT/10038547), (PT/10051055), (PT/10064602)

ultrasonography

- "Positive" result on **impedance plethysmography**
- "Positive" result on **contrast venography** (**reference test**).

pulmonary thromboembolism (PE)

This is characterized by:

- Pleuritic chest pain
- Tachypnea
- Cough
- Tachycardia
- Acute dyspnea
- Sudden collapse
- Leukocytosis
- Increased erythrocyte sedimentation rate (ESR)
- Elevated serum LDH or AST (SGOT) with a normal serum bilirubin
- **Arterial blood gases**: hypoxemia, hypocapnia, and respiratory alkalosis

See references for further details

Lancet. 1999;353:479-485.

(3) Hirsh J, Hull RD, Raskob GE. Clinical features and diagnosis of venous thrombosis. J Am Coll Cardiol 1986;8:114B-27B

(4) Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis . Lancet . 1995;;345:1326-1330.

(5) Kahn SR, Joseph L, Abenhaim L, Leclerc JR. Clinical prediction of deep vein thrombosis in patients with leg symptoms. Thromb Haemost. 1999;81:353-7

(6) Donnelly R, Emslie-Smith AM, Gardner ID, Morris AD. ABC of arterial and venous disease. Non-invasive methods of arterial and venous assessment. Br Med J 2000;320:698–701.

(7) Hull R, Taylor DW, Hirsh J, Sackett DL, Powers P, Turpie AGG, Walker ID: Impedance plethysmography: The relationship between venous filling and sensitivity and specificity for proximal vein thrombosis. Circulation 58:898, 1978

(8) Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M: Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981; 64(3):622.

(9) Lensing AW, Büller HR, Prandoni P, Batchelor D, Molenaar AH, Cogo A, Vigo M, Huisman PM, ten Cate JW. Contrast venography, the gold

			standard for the diagnosis of deep-vein thrombosis: improvement in observer agreement. Thromb Haemost. 1992;67(1):8. (10) Buck JR, Connors RH, Coon WW, Weintraub WH, Wesley JR, Coran AG. Pulmonary embolism in children. J Pediatr Surg. 1981;16(3):385. (11) Byard RW, Cutz E. Sudden and unexpected death in infancy and childhood due to pulmonary thromboembolism. An autopsy study. Arch Pathol Lab Med. 1990;114(2):142. (12)Matthew DJ, Levin M. Pulmonary thromboembolism in children. Intensive Care Med. 1986;12(6):404.	

S/N	Event	Case definition	References	MedDRA codes
11	**anaphylaxis**	See Brighton Collaboration case definition	(1) Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. (2) Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, de Souza Brito G, Heininger U, Imoukhuede B, Khamesipour A, Erlewyn-Lajeunesse M, Martin S, Mäkelä M, Nell P, Pool V, Simpson N; Brighton Collaboration Anaphylaxis Working Group. (3) Vaccine. 2007 Aug 1;25(31):5675-84. Epub 2007 Mar 12.	(SMQ/20000071)

S/N	Event	Medical (case) definition	References	MedDRA codes
12	**seizure**	This is defined in 3 levels with respect to diagnostic certainty. All levels are acceptable. **Level 1 of diagnostic certainty** (1) witnessed sudden loss of consciousness ***AND*** (2) generalized, tonic, clonic, tonic–clonic, or or atonic motor manifestations. **Level 2 of diagnostic certainty** history of unconsciousness ***AND*** (1) generalized, tonic, clonic, tonic–clonic, or atonic motor manifestations. **Level 3 of diagnostic certainty** (1) history of unconsciousness ***AND*** (2) other generalized motor manifestations **See references for further details**	(1) Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher M, et al. (2004) Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 22 (5–6): 557–562	(SMQ/20000212)

S/N	Event	Medical (case) definition	References	MedDRA codes
13	**acute kidney injury (AKI)**	**'acute kidney injury (AKI)** is defined as a decrease in glomerular filtration rate (GFR), which traditionally is manifested by an elevated or a rise in serum creatinine. However, serum creatinine is often a delayed and imprecise test as it reflects GFR in individuals at steady state with stable kidney function, and does not accurately estimate the GFR in a patient whose renal function is changing'	(1) Nephrology TA. The American Society of Nephrology Renal Research Report. J Am Soc Nephrol. 2005;16:1886–1903 (2) Devarajan P. Update on mechanisms of ischemic acute kidney injury. J Am Soc Nephrol 2006; 17: 1503–1520 (3) Devarajan P. Emerging urinary biomarkers in the diagnosis of acute kidney injury. Expert Opin Med Diagn. 2008;2:387–398 (4) Zappitelli M. Epidemiology and diagnosis of acute kidney	(HT/10038443), (LT/10000821), (LT/10000952), (LT/10001041), (LT/10001049), (LT/10001051), (LT/10001099), (LT/10005481), (LT/10005483), (LT/10009254), (LT/10009255), (LT/10011361), (LT/10011363), (LT/10011372), (LT/10011373), (LT/10011375), (LT/10016150), (LT/10021678), (LT/10022436), (LT/10022865), (LT/10022870), (LT/10022872), (LT/10023414), (LT/10023419), (LT/10024963), (LT/10028864), (LT/10028865),

		'The term AKI has largely replaced acute renal failure (ARF) as it more clearly defines renal dysfunction as a continuum rather than a discrete finding of failed kidney function' **pediatric AKI** presents as a wide range of clinical manifestations from a minimal elevation in serum creatinine to anuric renal failure, arises from multiple causes, and occurs in a variety of clinical settings. Below are the normal range of values of serum creatinine for different pediatric age groups: • **Newborn** – 0.3 to 1.0 mg/dL (27 to 88 micromol/L) • **Infant** – 0.2 to 0.4 mg/dL (18 to 35 micromol/L) • **Child** – 0.3 to 0.7 mg/dL (27 to 62 micromol/L) • **Adolescent** – 0.5 to 1.0 mg/dL (44 to 88 micromol/L) **See references for further details**	injury. *Semin Nephrol* 28: 436–446, 2008 (5) Andreoli SP: Acute kidney injury in children. *Pediatr Nephrol* 2009; 24:253–263 (6) Askenazi D. Evaluation and Management of Critically Ill Children with Acute Kidney Injury. Curr Opin Pediatr. 2011 April ; 23(2): 201–207. doi:10.1097/MOP.0b013e328342ff37. (7) Devarajan P (2011) Biomarkers for the early detection of acute kidney injury. Curr Opin Pediatr 23: 194–200. 10.1097/MOP.0b013e328343f4dd [doi] (8) The Harriet Lane Handbook, 19th ed, Tschudy KM, Arcara KM (Eds), Mosby, St. Louis 2012. p.642.	(LT/10028876), (LT/10029162), (LT/10033695), (LT/10033699), (LT/10033711), (LT/10035276), (LT/10035278), (LT/10037825), (LT/10038422), (LT/10038436), (LT/10038437), (LT/10038438), (LT/10038439), (LT/10038440), (LT/10038441), (LT/10038479), (LT/10038491), (LT/10038493), (LT/10038494), (LT/10038526), (LT/10038541), (LT/10040233), (LT/10055003), (LT/10056221), (LT/10061436), (LT/10068447), (LT/10068736), (LT/10069339), (OL/10001047), (OL/10001048), (OL/10001048), (OL/10001050), (PT/10005481), (PT/10005483), (PT/10011372), (PT/10022870), (PT/10038422), (PT/10038436), (PT/10038491), (PT/10055003), (PT/10068447), (SMQ/20000003)

S/N	Event	Medical (case) definition	References	MedDRA codes
14	**acute liver injury (ALI)**	Only potential cases of drug-induced liver injury (DILI) are of interest; an important requirement will be the availability or otherwise of histological data. The following manifestations will be considered: - Hepatic necrosis - Liver cirrhosis - Other cases of DILI in which there is no histological data available	(1) Bénichou C. 1990 *Criteria of drug-induced liver disorders. Report of an international consensus meeting.* J Hepatol. 11:272–*276* (2) UpToDate. *Drug-induced liver injury*. 2014 [cited 2014 19th June]; Available from: http://www.uptodate.com/c	(HT/10019669), (HT/10019833), (LT/10001544), (LT/10001547), (LT/10001548), (LT/10001550), (LT/10001551), (LT/10001669), (LT/10001675), (LT/10001677), (LT/10001679), (LT/10001771), (LT/10001845), (LT/10004659), (LT/10004660), (LT/10004685), (LT/10004697), (LT/10005308), (LT/10005313), (LT/10008639), (LT/10008641), (LT/10009210), (LT/10009211), (LT/10009213), (LT/10009214), (LT/10010689), (LT/10010690),

(A) **On the basis of *availability of histological data:***

(1) hepatic necrosis: characterized by

- Death of hepatic parenchyma: single cell (necrobiosis), or multicell in piecemeal, focal, periacinar, midzonal, periportal or paracentral locations.
- Massive necrosis: refers to events in individual acini in which all hepatocytes are dead.

(2) liver cirrhosis: Features include

- Necrosis of liver cells, slowly progressive over a long period and ultimately causing chronic liver failure and death
- Fibrosis, involving both central veins and portal areas
- Regenerative nodules, the result of hyperplasia of surviving liver cells
- Distortion of normal hepatic lobular architecture
- Diffuse involvement of the whole liver

Note: A regenerative nodule is an abnormal mass of liver cells without a normal cord pattern or central venule and surrounded completely by fibrosis

(B) In the *absence of histological data,* only liver tests (NOT liver function tests) can be used in diagnosis as follows:

(1) liver injury:

- Increase of over 2N (2 times N; where N is the upper limit of normal range) in Alanine Aminotransferase (ALT) or Conjugated Bilirubin (CB)
  OR
- A combined increase in Aspartate Aminotransferase (AST), Alkaline Phosphatase (AP) and Total Bilirubin (TB), provided one of them is above 2N

Various forms of drug-induced liver injury

- **hepatocellular:** increase of over 2N in ALT alone, or R≥5 [where R (ratio) is the serum acti**v**ity of ALT/serum activit**y** of AP. Each activity is measured as a multiple of N. Both

ontents/drug-induced-liver-injury?source=search_result&search=drugs+and+the+liver+patterns+of+druinduced+liver+injury&selectedTitle=6~150.

(3) Chandrasoma P., Taylor C.R. (1998). Chapter 43. The Liver: II. Toxic & Metabolic Diseases; Neoplasms. In P. Chandrasoma, C.R. Taylor (Eds), *Concise Pathology*, 3e. Retrieved September 18, 2012 from http://www.accessmedicine.com/content.aspx?aID=189816.

(LT/10011853), (LT/10013705), (LT/10013762), (LT/10018455), (LT/10018457), (LT/10018644), (LT/10019641), (LT/10019642), (LT/10019648), (LT/10019649), (LT/10019684), (LT/10019684), (LT/10019692), (LT/10019693), (LT/10019693), (LT/10019710), (LT/10019754), (LT/10019766) , (LT/10019796), (LT/10019831), (LT/10019832), (LT/10019834), (LT/10019835), (LT/10019837), (LT/10022224), (LT/10022227), (LT/10024665), (LT/10024666), (LT/10024667), (LT/10024668), (LT/10024701), (LT/10028859), (LT/10028867), (LT/10034513), (LT/10034927), (LT/10040133), (LT/10040275), (LT/10040526), (LT/10044345), (LT/10045974), (LT/10049199), (LT/10049228), (LT/10050279), (LT/10056502), (LT/10056806), (LT/10058473), (LT/10059570), (LT/10059571), (LT/10066503), (LT/10066756), (LT/10066756), (LT/10066758), (LT/10067125), (LT/10067718), (LT/10067969), (LT/10067969), (LT/10067970), (LT/10067971), (LT/10070815), (LT/10071561), (LT/10072032), (LT/10072268), (LT/10072734), (LT/10072937), (OL/10000670), (OL/10001673), (OL/10001678),(OL/10003695), (OL/10004708), (OL/10009209),(OL/10018456), (OL/10018643), (OL/10032161),(OL/10039482), (OL/10040274), (PT/10001547),(PT/10001551), (PT/10004659), (PT/10004685), (PT/10019641), (PT/10019692), (PT/10019754), (PT/10019834), (PT/10019837), (PT/10059570), (PT/10059571), (PT/10066758), (PT/10067125), (PT/10067718), (PT/10067969), (PT/10067969), (PT/10070815), (PT/10072268), (SMQ/20000013)

		should have been measured together at the time of recognition of liver injury]. - **cholestatic:** Liver injury is designated cholestatic when there is increase of over 2N in AP alone, or R≤2 - **mixed:** occurs when there is a combination of the following: increase in ALT (over 2N) and AP as well as 2<R<5. R ismost useful in patients with jaundice and may vary during the course of liver injury.		

S/N	Event	Medical (case) definition	References	MedDRA codes
15	**sepsis**	**'Sepsis** refers to Systemic Inflammatory Response Syndrome (SIRS) in the presence of or as a result of suspected or proven infection' **'Systemic Inflammatory Response Syndrome (SIRS)** is a widespread inflammatory response that may or may not be associated with infection. ***The presence of two or more of the following criteria (one of which must be abnormal temperature or leukocyte count)*** defines SIRS': • Core temperature (measured by rectal, bladder, oral, or central probe) of >38.5ºC or <36ºC • Tachycardia, defined as a mean heart rate >2 standard deviations above normal for age, or for children <1 year of age, bradycardia defined as a mean heart rate <10th percentile for age • Mean respiratory rate >2 standard deviations above normal for age • Leukocyte count elevated or depressed for age, or >10 percent immature neutrophils	(1) Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005:2–8	(HT/10040054), (LT/10002714), (LT/10002715), (LT/10011213), (LT/10014824), (LT/10015296), (LT/10027268), (LT/10027280), (LT/10027281), (LT/10028912), (LT/10034110), (LT/10034111), (LT/10034511), (LT/10034690), (LT/10035650), (LT/10035651), (LT/10039444), (LT/10039445), (LT/10040047), (LT/10040048), (LT/10040049), (LT/10040050), (LT/10040051), (LT/10040053), (LT/10040070), (LT/10040070), (LT/10040072), (LT/10040073), (LT/10040078), (LT/10040079), (LT/10040081), (LT/10040082), (LT/10040083), (LT/10040084), (LT/10040085), (LT/10040086), (LT/10040087), (LT/10040088), (LT/10040089), (LT/10040092), (LT/10040095), (LT/10040096), (LT/10040097), (LT/10040580), (LT/10040580), (LT/10041930), (LT/10041931), (LT/10042184), (LT/10042185), (LT/10042197), (LT/10045470), (LT/10045471), (LT/10046161), (LT/10046231), (LT/10046237), (LT/10047431), (LT/10047434), (LT/10048960), (LT/10049151), (LT/10049253), (LT/10049665), (LT/10051017), (LT/10051018), (LT/10051080), (LT/10051379), (LT/10051379), (LT/10051739), (LT/10053022), (LT/10053166),

See references for further details	(LT/10053588), (LT/10053596), (LT/10053597), (LT/10053598), (LT/10053599), (LT/10053600), (LT/10053840), (LT/10053879), (LT/10053879), (LT/10054047), (LT/10054137), (LT/10054160), (LT/10054162), (LT/10054167), (LT/10054168), (LT/10054169), (LT/10054170), (LT/10054177), (LT/10054188), (LT/10054189), (LT/10054210), (LT/10054213), (LT/10054219), (LT/10054221), (LT/10054249), (LT/10054250), (LT/10054252), (LT/10054253), (LT/10054254), (LT/10054255), (LT/10054256), (LT/10054257), (LT/10054264), (LT/10054284), (LT/10054608), (LT/10054611), (LT/10054612), (LT/10054613), (LT/10054615), (LT/10054616), (LT/10054617), (LT/10054618), (LT/10054619), (LT/10054620), (LT/10054637), (LT/10054641), (LT/10054642), (LT/10054688), (LT/10054691), (LT/10055078), (LT/10056430), (LT/10057767), (LT/10057847), (LT/10058040), (LT/10058041), (LT/10058867), (LT/10058872), (LT/10058873), (LT/10058874), (LT/10058875), (LT/10058876), (LT/10058877), (LT/10058878), (LT/10058879), (LT/10058888), (LT/10058889), (LT/10058973), (LT/10059070), (LT/10060410), (LT/10060411), (LT/10060413), (LT/10060437), (LT/10062357), (LT/10062357), (LT/10063085), (LT/10064952), (LT/10066745), (LT/10069141), (LT/10069141), (LT/10069684), (LT/10070681), (LT/10071362),(MTH_HT/10040054), (MTH_LT/10040078), (MTH_LT/10040082), (MTH_LT/10047431), (OL/10021867), (OL/10021901), (PT/10014824), (PT/10015296), (PT/10027280), (PT/10040047), (PT/10040049), (PT/10040051), (PT/10040070), (PT/10040070), (PT/10045470), (PT/10048960), (PT/10049151), (PT/10051017), (PT/10051018), (PT/10051379), (PT/10051379), (PT/10051739), (PT/10053166), (PT/10053588), (PT/10053840), (PT/10053879), (PT/10053879), (PT/10054047), (PT/10054137),

				(PT/10054160), (PT/10054162), (PT/10054177), (PT/10054210), (PT/10054213), (PT/10054219), (PT/10054221), (PT/10054264), (PT/10056430), (PT/10057767), (PT/10057847), (PT/10058040), (PT/10058041), (PT/10058872), (PT/10058873), (PT/10058874), (PT/10058875), (PT/10058876), (PT/10058877), (PT/10058878), (PT/10058879), (PT/10058889), (PT/10058973), (PT/10059070), (PT/10063085), (PT/10064952), (PT/10069141), (PT/10069141), (PT/10069684), (PT/10070681), (PT/10071362), (SMQ/20000070)

S/N	Event	Medical (case) definition	References	MedDRA codes
16	**sudden infant death syndrome (SIDS)**	**'sudden infant death syndrome (SIDS)** is defined as the sudden death of an infant younger than one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history'. 'This definition emphasizes the necessity of autopsy, death scene investigation, and review of the clinical history when making the diagnosis of SIDS, to exclude other explanations for the sudden unexpected infant death that can mimic SIDS'. **See references for further details**	(1) CDC(1996) Sudden infant death syndrome—United States, 1983–94. MMWR Morb Mortal Wkly Rep 45:859–863 (2) Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. Pediatr Pathol.1991;11 :677– 684	(LT/10011220), (LT/10011910), (LT/10040666),(LT/10040667), (LT/10042439), (LT/10042440), (LT/10055089), (LT/10055090), (LT/10055091), (LT/10055092), (LT/10069606), (OL/10011939), (OL/10021733), (PT/10042440)

Appendix 3: Evaluation of all positive drug-event associations.

ATC Code	Drug Name	Adverse Event (AE) Type	Labelled as AE in SPC [Yes/No]	Type/No. of Supporting Literature Citations
J01FA09	clarithromycin	bullous eruption	Yes #eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 7 Cohort study = 2 Case report = 5
J01CF05	doxycycline	bullous eruption	Yes #eMC (Undesirable effects) Micromedex (Summary): Adverse effects→serious	Total number of supporting citations = 5 Case report = 3 Case series = 2
J04AC01	isoniazid	bullous eruption	Yes #eMC (Undesirable effects) Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 6 Clinical Trial = 1 Cohort study = 1 Case report = 4
P01BC01	Quinine	bullous eruption	Yes Dailymed (Adverse reactions) Micromedex (Summary): Contraindications/Warnings→ precautions	Total number of supporting citations = 2 Case report = 1 Case series = 1
M01AE01	Ibuprofen	bullous eruption	Yes #eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 10 Case report = 5 Case series = 5
P01BC01	Quinine	aplastic anaemia	Yes #eMC (Undesirable effects) Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 4 Biological study = 1 Case report = 3
P02CA01	mebendazole	agranulocytosis	Yes	Total number of supporting citations = 1

			[#]eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Drugdex): Cautions → Adverse Reactions	Cohort study = 1
P01BC01	Quinine	agranulocytosis	Yes [#]eMC (Undesirable effects) Micromedex (Summary): Adverse effects→serious	Total number of supporting citations = 4 Review of biological mechanism = 2 Case report = 2 Note: this was considered a 'positive control – grade 1' despite the fact that they were only 2 case reports, because of the availability of biological evidence.
J01FA09	Clarithromycin	thrombocytopenia	Yes [#]eMC (Undesirable effects) Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 1 Case control= 1
J01CF05	Doxycycline	thrombocytopenia	Yes [#]eMC (Undesirable effects) Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 1 Systematic literature review = 1
P01BC01	Quinine	thrombocytopenia	Yes [#]eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ contraindications); (Adverse effects→serious)	Total number of supporting citations = 20 Biological studies = 8 Review of biological studies = 4 Systematic literature review = 1 Review of spontaneous reports = 2 Case report = 4 Case series = 1
M01AE01	Ibuprofen	thrombocytopenia	Yes [#]eMC (Undesirable effects) Micromedex (Summary): Adverse effects→serious	Total number of supporting citations = 3 Clinical trial = 1 Case control =1 Case series = 1
J01FA09	Clarithromycin	psychosis	Yes [#]eMC (Undesirable effects) Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 4 Case report = 4
J04AC01	Isoniazid	psychosis	Yes [#]eMC (Special warnings and precautions for use)	Total number of supporting citations = 4 Cohort study = 2

			Micromedex (Drugdex): Cautions → Adverse Reactions	Case report = 2
R03DC03	montelukast	psychosis	Yes #eMC (Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 1 Case series = 1
D10BA01	Isotretinoin	psychosis	Yes #eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 2 Systematic literature review = 1 Case report = 1
N06BA04	methylphenidate	psychosis	Yes #eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 4 Biological study = 2 Cross over clinical trial = 1 Case series = 1
D10BA01	isotretinoin	suicide	Yes #eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 3 Systematic literature review = 1 Review of spontaneous reports = 1 Review of spontaneous reports and case series = 1
R03DC03	montelukast	suicide	Yes #eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 1 Review of spontaneous reports = 1
J01FA09	clarithromycin	ventricular arrhythmia	Yes #eMC (Undesirable effects) Micromedex (Summary): Contraindications/Warnings→ Contraindications; precautions	Total number of supporting citations = 1 Review of spontaneous reports = 1

P01BC01	quinine	ventricular arrhythmia	Yes Dailymed (Contraindications; Warnings and Precautions; Adverse reactions) Micromedex (Summary): (Contraindications/Warnings→ contraindications; precautions); (Adverse effects→serious)	Total number of supporting citations = 1 Case series = 1
A03FA03	domperidone	ventricular arrhythmia	Yes #eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 3 Biological study = 1 Cohort study = 1 Case control = 1
J01FA09	clarithromycin	sudden death	Yes #eMC (Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 4 Clinical trial = 1 Case-control = 2 Case report = 1
A03FA03	domperidone	sudden death	Yes #eMC (Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 7 Experimental study = 1 Nested case control = 1 Case control = 5
J01FA09	clarithromycin	QT prolongation	Yes #eMC (Contraindications; Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ contraindications); (Adverse effects→serious)	Total number of supporting citations = 2 Basic science = 1 Review of spontaneous reports = 1
P01BC01	quinine	QT prolongation	Yes #eMC (Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ contraindications; precautions); (Adverse effects→serious)	Total number of supporting citations = 7 Clinical trial = 1 Systematic literature review = 4 Review of spontaneous reports = 1 Case report = 1
M01AE01	ibuprofen	anaphylaxis	Yes #eMC (Undesirable effects) Micromedex (Summary):	Total number of supporting citations = 5 Review of pharmacology = 1 Review of spontaneous reports = 1

				(Contraindications/Warnings→ precautions); (Adverse effects→serious)	Case report = 2 Case series = 1
J04AC01	isoniazid	seizure	Yes	#eMC (Special warnings and precautions for use) Micromedex (Summary): Adverse effects→serious	Total number of supporting citations = 8 Review of biological mechanism = 1 Clinical trial = 1 Case report = 5 Case series = 1
P01BC01	quinine	acute kidney injury	Yes	#eMC (Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious)	Total number of supporting citations = 5 Case report with systematic literature review = 1 Case report = 4
M01AE01	ibuprofen	acute kidney injury	Yes	#eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious)	Total number of supporting citations = 10 Review of clinical trials = 1 Case control = 1 Case report = 5 Case series = 2 Review of spontaneous reports = 1
J01CF05	flucloxacillin	acute liver injury	Yes	#eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 11 Cohort study = 2 Literature review = 4 Review of spontaneous reports = 1 Case reports = 3 Case series = 1
J01FA09	clarithromycin	acute liver injury	Yes	#eMC (Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→ contraindications; precautions); (Adverse effects→serious)	Total number of supporting citations = 3 Cohort study = 1 Case report = 1 Review of spontaneous reports = 1
J05AE06	lopinavir	acute liver injury	Yes	#eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious)	Total number of supporting citations = 4 Clinical trial = 2 Cohort study = 1 Case report = 1
J04AC01	isoniazid	acute liver injury	Yes		Total number of supporting citations = 7

				[#]eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious)	Clinical trial = 1 Case report = 4 Case series = 2
P02CA01	mebendazole	acute liver injury	Yes	Dailymed (Warnings and precautions; Adverse Reactions) Micromedex (Summary): Adverse effects→serious	Total number of supporting citations = 2 Clinical trial = 1 Case report = 1
P01BC01	quinine	acute liver injury	Yes	Dailymed (Adverse Reactions) Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious)	Total number of supporting citations = 3 Case reports = 3
M01AE01	ibuprofen	acute liver injury	Yes	[#]eMC (Special warnings and precautions for use; Undesirable effects) Micromedex (Summary): (Contraindications/Warnings→precautions); (Adverse effects→serious)	Total number of supporting citations = 5 Review of spontaneous reports = 1 Case report = 3 Case series = 1

[#]Electronic Medicines Compendium

Appendix 4: Comparison of GRiP, EU-ADR and OMOP reference sets

	PROJECT	bullous eruption	aplastic anemia	agranulo cytosis	thrombo cytopena	psychosis	suicide	ventricular arrhythmia	sudden death	QT prolong ation	thrombo embolism	anaphy laxis	seizure	AKI	ALI	sepsis	SIDS
isoniazid	GRiP																
	EU-ADR																
	OMOP																
m'dazole	GRiP																
	EU-ADR																
	OMOP																
fluticaso	GRiP																
	EU-ADR																
	OMOP																
ibuprofe	GRiP																
	EU-ADR																
	OMOP																

Abbreviations: m'dazole – mebendazole; AKI – acute kidney injury; ALI – acute liver injury; SIDS – sudden infant death syndrome;

	Positive control
	Negative control

Chapter 3.2 Drug safety monitoring in children: Performance of signal detection algorithms and impact of age stratification

Abstract

Introduction: Spontaneous reports of suspected adverse drug reactions (ADRs) can be analysed to yield additional drug safety evidence for the pediatric population. Signal detection algorithms (SDAs) are required however the performance of SDAs in the pediatric population specifically is unknown. We tested the performance of two SDAs on pediatric data from the US FDA Adverse Event Reporting System (FAERS) and investigated the impact of age stratification and age adjustment on SDAs' performance.

Methods: We tested the performance of two established SDAs: Proportional Reporting Ratio (PRR) and Empirical Bayes Geometric Mean (EBGM) on a pediatric dataset from FAERS (2004 to 2012). We compared SDAs' performance to a published pediatric-specific reference set, by calculating diagnostic-test related statistics including the area under the Receiver Operating Characteristics curve (AUC). Impact of age stratification and age-adjustment SDAs' performance was assessed. Age adjustment was performed by pooling (Mantel-Hanszel) stratum-specific estimates.

Results: A total of 115,674 pediatric reports (patients aged 0-18 years) comprising 893,587 drug-event combinations (DECs) were analysed. Crude values of the AUC were similar for both SDAs: 0.731 (PRR) and 0.745 (EBGM). Stratification unmasked four DECs, for example 'ibuprofen and thrombocytopenia'. Age-adjustment did not improve performance.

Conclusion: The performance of the two tested SDAs was similar in the pediatric population. Age adjustment does not improve performance and is therefore not recommended to be performed routinely. Stratification can reveal new associations, therefore is recommended when either drug use is age-specific or when an age-specific risk is suspected.

Introduction

Spontaneous reports of suspected adverse drug reactions (ADRs) can yield important information regarding the safety of drugs [124]. Usually, such reports are screened for emerging safety issues by applying statistical methods called signal detection algorithms (SDAs). Current SDAs compare the reporting rate of a drug-event combination (DEC) of interest with the expected count calculated from the overall reporting rate of that reaction in the entire database [124,125]. Although SDAs are routinely applied to reports pertaining to the general population, the performance of SDAs in the pediatric population specifically has not been investigated to date. Compared to adults, the pattern of drug use and occurrence of ADRs in pediatrics may differ [126-128] since the latter population comprises a heterogeneous group of subjects at various stages of development with age-dependent organ maturation and hormonal changes [129]. Several studies investigating ADR reporting in children identified different reporting patterns in this population compared to adults [126,128,130,131]. Since ADRs may be age–specific, adjustment for age seems to be a logical step when investigating pediatric ADRs and has been advocated by some researchers [127]. The major aim of stratification is verification of confounding and effect modification which otherwise may mask true signals [132]. Confounding by age can be dealt with by stratifying for age categories and pooling stratum-specific estimates. However if age specific estimates differ (in case of effect modification) pooling/adjustment should not be done, but instead, a verification of each individual stratum. While stratification has been investigated by some researchers [133], adjustment is routinely implemented in some Bayesian but not in frequentist SDAs [134-136] Few studies have systematically addressed the impact of age stratification or adjustment and the results are contradictory [132,137,138].

Within the context of the Global Research in Pediatrics (GRiP) – Network of excellence [139], we aimed to evaluate the performance of two well-established SDAs in the pediatric population and determine if age stratification or adjustment impacts signal detection in this population.

Methods

Data source

Data was retrieved from the publicly available version of the US FDA Adverse Event Reporting System (FAERS), which comprises spontaneous reports of suspected ADRs submitted by manufacturers, healthcare professionals and patients. FAERS is one of the largest repositories of spontaneous reports in the world [140,141]. In this study, we analyzed reports received from the first quarter of 2004 through the third quarter of 2012.

For performance analysis, only reports of ADRs occurring in children and adolescents (<18 years of age) were retained. The ADRs in FAERS are coded according to the Medical Dictionary for Regulatory Activities (MedDRA®)[142].

To improve the quality of the dataset, we excluded reports with missing age, the main variable in our study. Also, reports with reported age equal to zero and with a MedDRA® preferred term indicating prenatal exposure were removed, as these imply *in-utero* drug exposure and were therefore not relevant for our study. We minimized the number of duplicates (i.e. the same report submitted by different reporters) by applying an algorithm based on case identifier, report identifier, drug and event names. For multiple reports (i.e. the same report is reported at a later time, with additional and updated information) [143], the most recent (and most updated) report was retained for analysis.

As drug names included in FAERS are not standardized, a harmonization procedure was implemented. Briefly, this consisted of removing superfluous characters and applying a generalized edit distance matching algorithm [144] to map free text drug names to synonyms and finally to the corresponding active substance and World Health Organization-Anatomic Therapeutic Chemical (WHO-ATC) code.

In this study, only those drugs reported as primary or secondary suspect in the FAERS database were retained for analysis. Analysis was performed at Drug-Event Combination (DEC) level, meaning that within each report, every suspect drug was combined with all reported ADRs. Thus, one report may comprise more than one DEC.

Signal Detection Algorithms (SDAs)

We tested two well established SDAs which are routinely used by various national and international regulatory and/or research institutions for signal detection: the proportional reporting ratio (PRR) [125] and the empirical Bayes geometric mean (EBGM) [136] (see Table 1).

We also tested count of reports, as a positive control. In order to define a signal of disproportionate reporting (SDR) [145,146], we selected thresholds that are currently applied in routine practice. We applied the SDAs at the end of the study period, when the maximum number of reports had accrued.

Table 1: Signal detection algorithms and corresponding thresholds applied

Signal Detection Algorithm	Applied Threshold[a]	Institution where the method and the respective threshold is currently used
Number of reports	n ≥5	*NA*
PRR	PRR lower bound 95% CI ≥ 1 & n ≥ 5 reports	European Medicines Agency
EBGM	EB05 CI≥ 1.8 and n≥ 3 reports & EBGM ≥2.5	Medicines and Healthcare products Regulatory Agency (MHRA)

PRR= Proportional reporting ratio; EBGM= Empirical Bayes Geometric Mean; CI=confidence interval; NA= Not available; EB05= Lower bound of the 95% confidence interval
[a] Thresholds were obtained from Candore et al [146]

Performance assessment measures

The performance of the SDAs was assessed by calculating diagnostic-test related statistics, namely specificity and sensitivity, positive predictive value (PPV), and negative predictive value (NPV) [147][25]. Sensitivity is the ability of the method to correctly identify true signals while specificity is the ability to correctly exclude false signals. PPV and NPV are posterior probabilities, describing how many of the signals classified as positive or negative are indeed correctly classified [147,148].

Since diagnostic-test related statistics are dependent on the threshold choice, their individual comparison has only limited, albeit practical value. Therefore, we also estimated the area under the curve (AUC) of receiver operating characteristics (ROC) in order to compare the performance of the SDAs [32]; the AUC incorporates both sensitivity and specificity across all the possible values for a certain SDA. Calculation of AUCs was conducted by varying only the point estimate of each SDA and did not take into account the other components of the SDA.

For the purpose of performance evaluation, a previously constructed pediatric-specific GRIP reference set of positive and negative drug-event associations was used. It consists of 37 positive and 90 negative DECs and includes drugs that are administered to children and events

that are regarded as important for this population. The positive DECs are those that were confirmed to occur based on evidence from Summary of Product Characteristics (SmPC) and the published literature, while the negative DECs are those that could not be confirmed at the time of literature review by neither the SmPC nor the published literature. For a full description of the reference set, see Osokogu et al [149].

Stratification and adjustment for age

The impact of age stratification and adjustment on the performance of the SDAs was investigated. First, we checked for possible effect modification across age strata, by stratifying the data according to age categories defined by the International Conference on Harmonization (ICH) [150] and calculating stratum-specific measures for each SDA.

Secondly, we calculated age-adjusted estimates for PRR and EBGM by combining the stratum-specific estimates in an overall measure [151]. The performance of each SDA was reassessed after adjustment.

Statistical analysis

Differences in the performance (AUC) of each SDA, crude versus age-adjusted and crude versus count of reports (positive control) were tested using paired chi-squared tests. Stratum-specific contingency tables were tested for homogeneity using the Breslow Day Tarone test [152]. The Mantel-Haenszel approach was used for pooling and calculating age-adjusted estimates [28]. The lower bound of the EBGM 95% confidence interval (EBGM05) was calculated using the EB05 for each stratum and then computing a Mantel-Haenszel average based upon Zeinoun [153]. Statistical significance was defined by p value < 0.05.

Analysis was performed using SAS software version 9.2. Graphs were made in SAS software version 9.2 and R version 3.1.3.

Results

Descriptive analysis

For the study period (first quarter of 2004 through the third quarter of 2012), a total of 4,285,088 reports were retrieved from FAERS. After eliminating duplicates (n=43,125), removal of adult reports (n=2,686,530) and reports with missing age (n=1,419,524) or age equal to zero with a MedDRA® preferred term indicating prenatal exposure (n=20,235), 115,674 reports

corresponding to 893,587 individual DECs were retained for analysis of pediatric spontaneous reports (see Table 2).

Table 2 Description of pediatric reports by age categories

Age group	Number of reports, n (%)
Neonates: 0-27 days	5,091 (4.40%)
Infants: 28 days-23 months	12,566 (10.86%)
Children: 2-11 years	49,982 (43.21%)
Adolescents: 12-17 years	48,035 (41.53 %)
Total	**115,674 (100%)**

The total number of pediatric reports that included the investigated drugs and ADRs from the reference set can be observed in Fig. 1, which also shows data regarding adults (for comparison purposes). The number of children exposed to the drugs of interest, for whom any of the investigated ADRs was reported, varied from 26 patients (for praziquantel) to 7,535 patients (for ibuprofen) with a median of 781 patients exposed across all drugs. The number of events of interest in FAERS ranged from 164 reports (ventricular arrhythmia) to 14,777 (anaphylaxis), with a median of 1,004 reports across all events. For a more detailed description of reports counts please refer to *Electronic Supplementary material Table 1.*

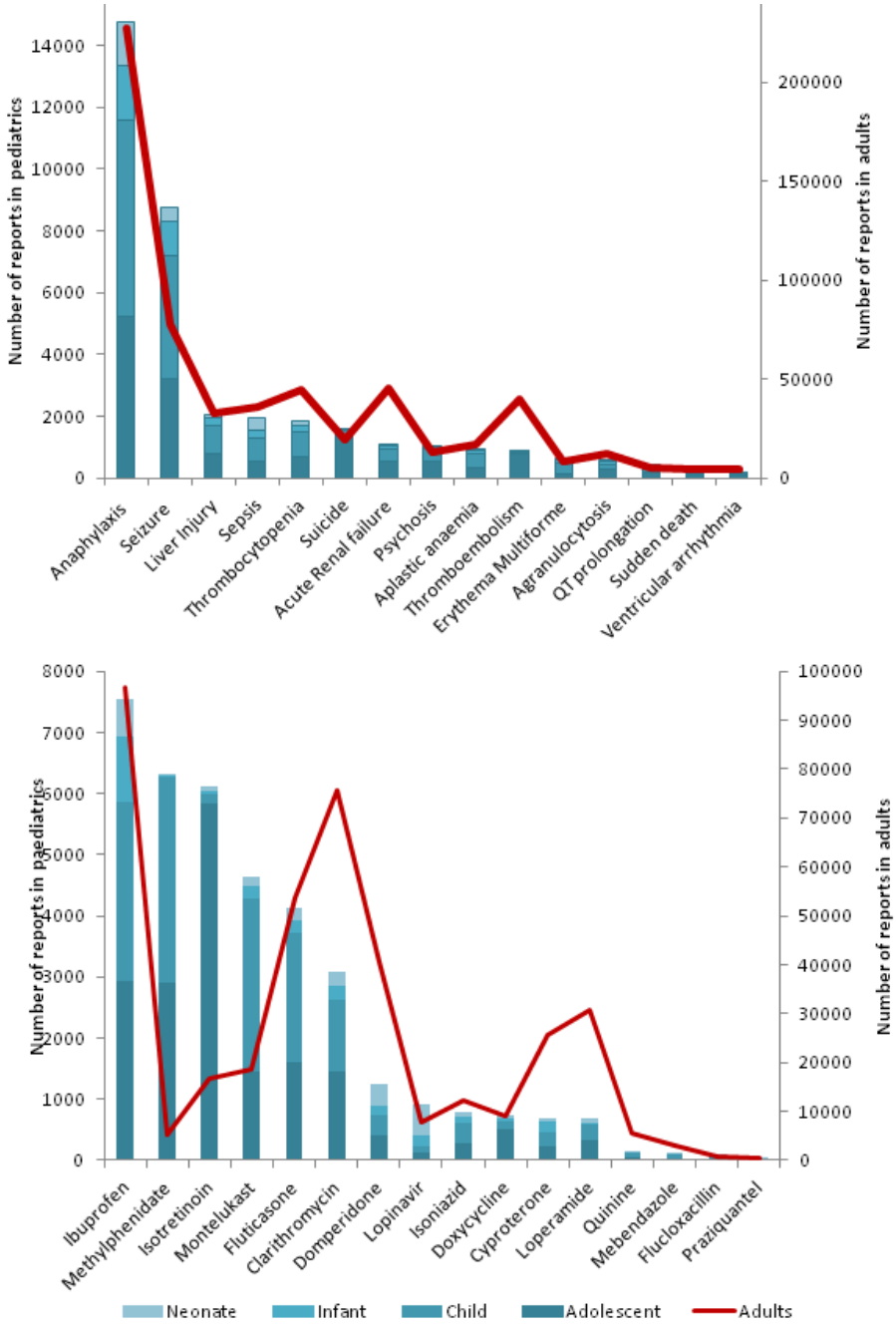


Fig. 1 Count of reports in pediatric and adult population for the investigated ADRs and drugs, cumulatively for the period Q1 2004 -Q3 2012[a]

[a] -Number of reports in children is represented by bars and plotted on the left axis, while the number of reports in adults is represented by the red line and plotted on the right axis; Reports with missing age or age=0 were excluded. Only reports mentioning any of the drugs or events in the reference set were considered.

Overall performance of SDAs

Both SDAs showed high specificity and low sensitivity. They both had similar specificity values (PRR:83.8% and EBGM:91.9%), while sensitivity was lower for EBGM than for PRR (17.2% vs. 37.9%). The NPV and PPV were similar for both SDAs. When we applied the threshold-

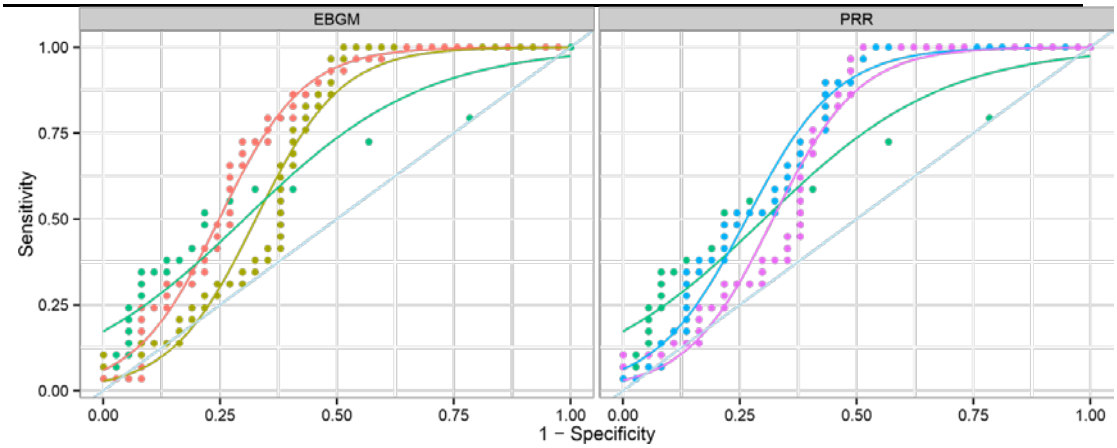
independent (AUC-based) approach, the tested SDAs showed similar performance in the pediatric population although the AUC value for EBGM (0.745) was slightly higher than for PRR (0.731). None of the SDAs performed better than the simple report count (AUC=0.634, *p-values: PRR=0.27 and EBGM=0.14)*

Stratification and adjustment for age and its impact on performance

Upon calculating SDA values per age stratum and testing for heterogeneity across strata, we observed effect modification for some associations. Some false negatives (positive DECs which failed to be highlighted as signals when analyzing data pertaining to the entire pediatric population) were unmasked in some strata. Four DECs were unmasked in total: ibuprofen-thrombocytopenia and isoniazid-seizure (by PRR) and clarithromycin-erythema multiforme and ibuprofen-erythema multiforme (by EBGM). Conversely, 'ibuprofen-acute liver injury', also a positive DEC, was highlighted when we analyzed data pertaining to the entire pediatric population but after stratifying, it became clear that this DEC was highlighted only in older children (adolescents), and not highlighted in younger children (see Fig. 3). For an overview of SDA values across age strata and results of heterogeneity tests please refer to the *Electronic Supplementary material figures 1A and 1B.*

Fig. 2: Performance of signal detection algorithms within the entire pediatric population

SDA	Sensitivity	Specificity	PPV	NPV	AUC	p-value[b]
Number of reports	58.62	67.57	58.62	67.57	0.634	*reference*
PRR	37.93	83.78	64.71	63.27	0.731	0.266
EBGM	17.24	91.89	62.50	58.62	0.745	0.144
After age adjustment [a]						*(reference-crude PRR/EBGM)*
PRR	34.48	86.49	66.67	62.75	0.688	0.267
EBGM	10.34	97.30	75.00	58.06	0.683	0.216



We evaluated the performance of the methods within individual age strata (see Table 3). On average, performance of the SDAs was lower within age strata compared to the entire pediatric population and performance improved with increasing stratum size. For infants and neonates, the performance was very low, not better than chance (*p-value* > 0.5 for both SDAs). The adolescent group exhibited the best performance which was similar to the overall performance.

Table 3 Performance of signal detection algorithms across age strata

Age groups	Signal Detection Algorithms	Size of the age stratum (number of reports)	AUC
Neonates		5,091	
	Number of Reports		0.625
	EBGM		0.600
	PRR		0.65
Infants		12,566	
	Number of Reports		0.667

	EBGM		0.548
	PRR		0.554
Children		49,982	
	Number of Reports		0.654
	EBGM		0.698
	PRR		0.649
Adolescents		48,035	
	Number of Reports		0.698
	EBGM		0.771
	PRR		0.718
Entire pediatric population	Number of Reports	115,674	0.634
	EBGM		0.746
	PRR		0.733

PRR= Proportional reporting ratio; EBGM= Empirical Bayes Geometric Mean; AUC=area under the curve

After adjusting for age by pooling the stratum-specific estimates, the performance of the SDAs decreased, although not significantly (see Fig. 2; crude vs. adjusted AUC for PRR 0.731 vs. 0.688, *p-value = 0.267;* crude vs. adjusted AUC for EBGM 0.745 vs. 0.683, *p-value = 0.216*).

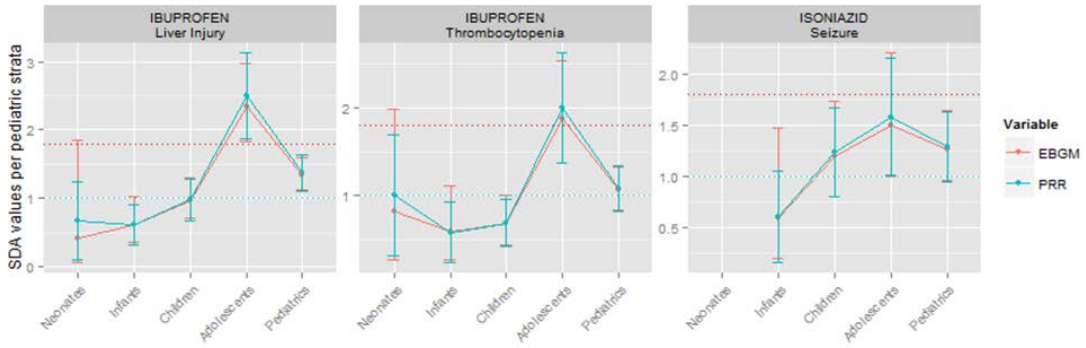


Fig. 3: Variation of PRR and EBGM estimates across pediatric specific strata – selected examples

p-values were calculated with Breslow Day Tarone test for homogeneity

Discussion

In this study, we have demonstrated that age stratification for detection of drug safety signals in children may unmask some signals that do not appear in neither crude nor adjusted analysis. Adjustment for age does not improve performance of the PRR and EBGM.

For the investigated events, similar reporting patterns were observed for children and adults while the investigated drugs appeared to have different reporting patterns (see Figure 1).

Different drug-related reporting patterns in children vs adults were previously reported [128].Consequently, reported drug-event associations for children may differ from adults [126,128], underlining the need for pediatric-specific approaches to signal detection especially when we consider that even within the pediatric population, reported drugs may vary by age group [126,154].

Overall, the PRR and EBGM showed good performance although results were slightly lower than results reported on other (not pediatric-specific) reference sets [155,156]. The similarity in performance between PRR and EBGM is in accordance with recent results from the PROTECT project [146]. The fact that the performance (based on AUC) of PRR and EBGM was not statistically significantly better than simple report count may be due to the lack of power. Within age strata, performance seemed to correlate with stratum size: the poorest results were observed for infants and neonates (the smaller groups), slightly improving for children while the best performance was observed for adolescents, the age stratum with the highest number of tested DECs. Decrease in power due to fewer reports and therefore DECs may account for this observation. The fact that we used lower bounds of confidence intervals for signaling instead of point estimates might have exacerbated the influence of sample size on the results, since smaller strata will have higher variability. In neonates and infants for whom expected counts were difficult to calculate because of few reports, we observed that simple report counts performed similar or even better than the SDAs and might be an alternative to commonly used SDAs. The fact that simple report count performed better than SDAs may have been because the reference set comprised known DECs (which in turn may have influenced reporting) rather than emerging safety issues, a hypothesis proposed by Noren et al [157].

Inspection of SDA values across child specific strata (age-stratification) revealed some heterogeneity in estimates pointing to some effect modification. For example, 'ibuprofen-thrombocytopenia', was found as a signal in the adolescents' group but not detected in the entire pediatric population or the younger age categories. This suggests that age-specific SDA calculations are sometimes needed, rather than age-adjusted SDA estimates. The age-adjusted estimates did not improve performance; in fact even PPV unexpectedly decreased. Simulation studies have shown that when adjusted for strata, Bayesian methods such as EBGM tend to be

underestimated when there are sparse strata [138]; this was also the case in our study. Previous studies in adults show contradictory results, with some showing a beneficial effect [132] while others did not [138]. The reason for our finding is not entirely clear; a possible explanation is that age is not a strong confounder for the investigated DECs. Also, the method of weighting (Mantel-Haenszel approach) may have played a role since more weight was assigned to age groups with more reports (adolescents and children). This may have masked signals occurring in age groups with fewer reports.

The limitations of data mining in FAERS include those inherent to spontaneous reporting databases: underreporting, lack of denominator data and control group, biases in reporting, as well as missing and poor quality data [158]. Missing information regarding age substantially reduced the study sample size since we could not determine whether these reports described patients aged less than 18 years old. While these biases are well acknowledged and have a definite impact, they cannot be completely avoided. Compared to adults, there are fewer reports and different reporting patterns for children [126,159,160] which may complicate signal detection in the pediatric population.

Evaluating performance of SDAs is a constant challenge due to lack of standard methodologies, imperfect reference standards and uncertainty regarding the best thresholds (See supplementary material for measures of performance using alternative thresholds). Some of the drugs and events in the reference set are specific to one age group within pediatrics and this is obvious in Fig. 1, even though the reference set was designed to be relevant for the entire pediatric population. We acknowledge that the reference set used, although specifically constructed for this purpose, does not include all the ADRs that are highly specific for pediatrics. This highlights the need for pediatric-specific approaches to signal detection; accounting for not just the entire pediatric population but also the different age strata within pediatrics. Still, the reference set captures various drug use and ADRs patterns [161] and is currently the only available pediatric-specific reference set. The thresholds applied to define a signal were obtained from previous publications and other cut-off points may generate better results; further research on pediatric-specific thresholds should be encouraged.

Conclusion

Our study revealed that age adjustment did not improve performance of the SDAs. However, stratification revealed some variation in SDAs' values across strata (effect modification) and inspection of stratum-specific estimates might sometimes yield useful information during routine surveillance.

Supplementary Material

Supplementary Table 1 Counts of reports DECs from reference set in pediatrics

True Positive Associations [a]

Drug	Event	A	B	C	D[b]
Clarithromycin	Erythema Multiforme	11	778	540	113446
Clarithromycin	Liver Injury	18	771	2216	111770
Clarithromycin	Psychosis	9	780	1323	112663
Clarithromycin	QT prolongation	6	783	511	113475
Clarithromycin	Sudden death	1	788	276	113710
Clarithromycin	Thrombocytopenia comb	11	778	1689	112297
Clarithromycin	Ventricular arrhythmia	3	786	243	113743
Domperidone	Sudden death	1	78	276	114420
Doxycycline	Erythema Multiforme	1	208	550	114016
Doxycycline	Thrombocytopenia comb	3	206	1697	112869
Flucloxacillin	Liver Injury	3	14	2231	112527
Ibuprofen	Acute Renal failure	247	3015	1262	110251
Ibuprofen	Anaphylaxis combined	547	2715	14296	97217
Ibuprofen	Erythema Multiforme	36	3226	515	110998
Ibuprofen	Liver Injury	86	3176	2148	109365
Ibuprofen	Thrombocytopenia comb	52	3210	1648	109865
Isoniazid	Liver Injury	13	344	2221	112197
Isoniazid	Psychosis	3	354	1329	113089
Isoniazid	Seizure combined	37	320	9198	105220
Isotretinoin	Psychosis	99	3130	1233	110313
Isotretinoin	Suicide	197	3032	2023	109523
Lopinavir	Liver Injury	5	202	2229	112339

Mebendazole	Liver Injury	2	56	2232	112485
Montelukast	Psychosis	95	2316	1237	111127
Montelukast	Suicide	130	2281	2090	110274
Quinine	Agranulocytosis	1	96	528	114150
Quinine	Liver Injury	2	95	2232	112446
Quinine	Thrombocytopenia comb	1	96	1699	112979
Quinine	Ventricular arrhythmia	1	96	245	114433

True Negative Associations [a]

Drug	Event	A	B	C	D[b]
Clarithromycin	Suicide	3	786	2217	111769
Clarithromycin	Thromboembolism	1	788	697	113289
Cyproterone	Anaphylaxis combined	2	17	14841	99915
Domperidone	Acute Renal failure	2	77	1507	113189
Domperidone	Agranulocytosis	2	77	527	114169
Domperidone	Anaphylaxis combined	5	74	14838	99858
Domperidone	Aplastic anaemia	1	78	994	113702
Domperidone	Liver Injury	2	77	2232	112464
Domperidone	Sepsis	2	77	2012	112684
Domperidone	Suicide	3	76	2217	112479
Domperidone	Thrombocytopenia comb	4	75	1696	113000
Doxycycline	QT prolongation	1	208	516	114050
Doxycycline	Suicide	5	204	2215	112351
Doxycycline	Thromboembolism	3	206	695	113871
Fluticasone	Acute Renal failure	2	1703	1507	111563
Fluticasone	Liver Injury	3	1702	2231	110839

Fluticasone	QT prolongation	1	1704	516	112554
Fluticasone	Sepsis	3	1702	2011	111059
Fluticasone	Thrombocytopenia comb	6	1699	1694	111376
Ibuprofen	Sepsis	79	3183	1935	109578
Isoniazid	Sepsis	1	356	2013	112405
Isoniazid	Ventricular arrhythmi	6	351	240	114178
Isotretinoin	Anaphylaxis combined	230	2999	14613	96933
Isotretinoin	QT prolongation	2	3227	515	111031
Isotretinoin	Sepsis	28	3201	1986	109560
Loperamide	Acute Renal failure	2	166	1507	113100
Loperamide	Liver Injury	1	167	2233	112374
Loperamide	Sepsis	3	165	2011	112596
Loperamide	Suicide	21	147	2199	112408
Loperamide	Thrombocytopenia comb	11	157	1689	112918
Mebendazole	Anaphylaxis combined	13	45	14830	99887
Montelukast	Anaphylaxis combined	142	2269	14701	97663
Montelukast	Aplastic anaemia	4	2407	991	111373
Montelukast	QT prolongation	1	2410	516	111848
Montelukast	Sepsis	4	2407	2010	110354
Montelukast	Thrombocytopenia comb	15	2396	1685	110679
Montelukast	Thromboembolism	1	2410	697	111667

[a] Reference set associations with no reports in pediatrics not presented

[b] A, B, C, and D represent the following cell counts:

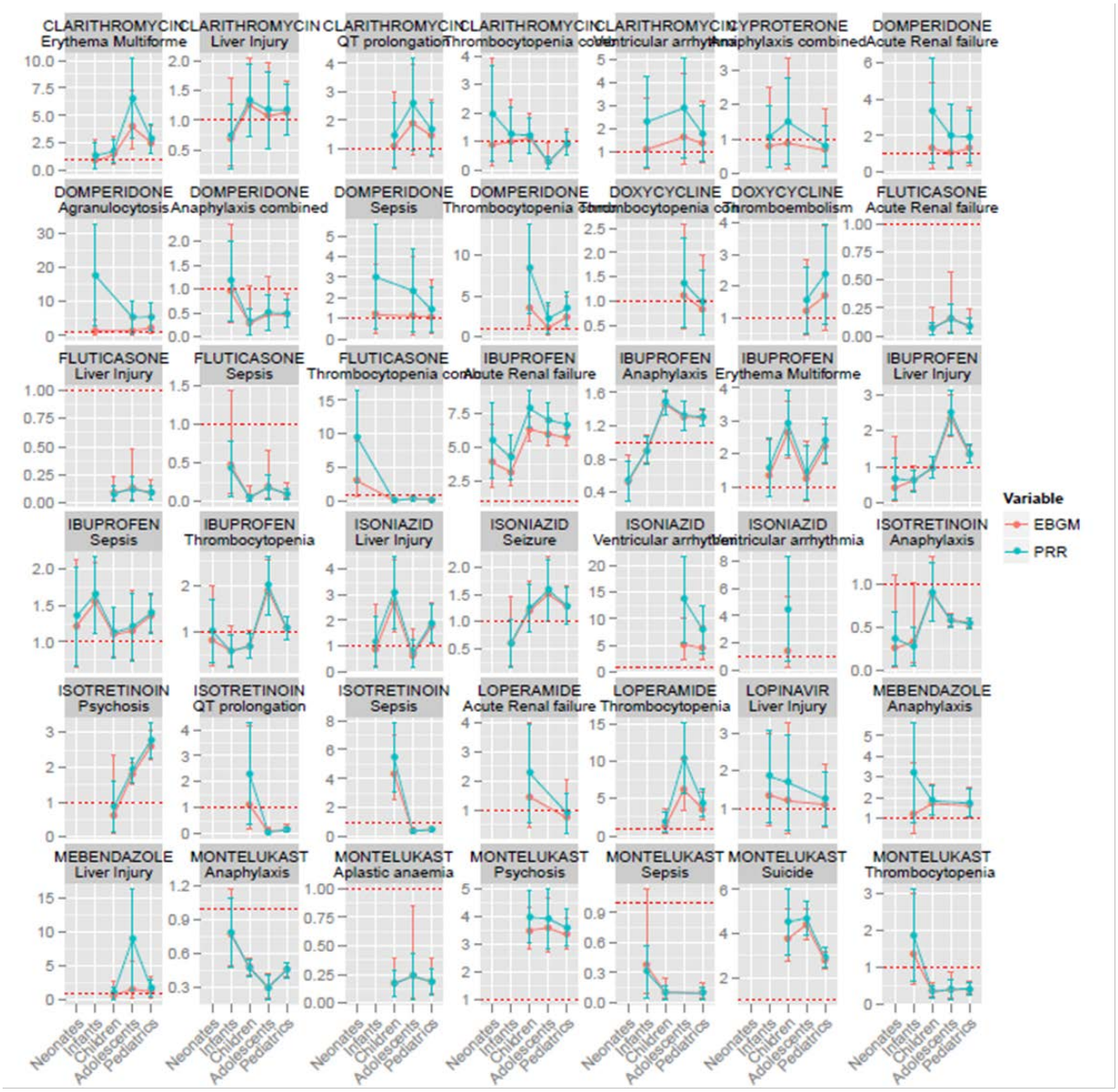
A = Reports related to the drug of interest and the event of interest

B = Reports of the exposure of interest associated with a different event

C = Reports of the event of interest associated with a different exposure

D = Reports related to exposures and events other than those of interest

Electronic Supplementary material figures 1A and 1B.



Chapter 4 Pharmacoepidemiological safety studies

Chapter 4.1 Pharmacoepidemiological safety studies in children: a systematic review

Abstract

Purpose: In order to identify challenges in pediatric pharmacoepidemiological safety studies, we assessed the characteristics of such studies that included children.

Methods: Relevant articles from inception to 2013 were retrieved from Embase and Medline. We sequentially screened titles, abstracts and full texts with independent validation. We systematically collected data regarding general information, study methods, and results.

Results: Out of 4825 unique articles, 268 full texts (5.6%) were retained; 147 (54.9%) pertained to drugs rather than vaccines. Considering the 268 studies, 202 (75.4%) concerned children and adolescents (2 to 11 years) and 14 (5.3%) included preterm newborns. Most studies originated from North America (154 [57.5%]) or Europe (92 [34.3%]). Only 47 studies (17.5%) were privately funded. The majority (174 [64.9%]) were cohort studies. Out of 268 studies, 196 (73.1%) collected data retrospectively; paper medical charts were the most common data source for the exposures (85 [31.7%]) and outcomes (122 [45.5%]). Only 3 (2.0%) drug-only studies investigated rarely used drugs. Considering all 268 studies, only 27 (10.1%) reported sample size or power calculation. Most (75 [51.0%]) drug-only studies corrected confounding by multivariate modelling unlike stratification in 66 (55.9%) vaccine-only studies. Considering 75 child-only studies without any statistically significant result, 41 (54.7%) did not discuss lack of power.

Conclusions: Although the field of pediatric pharmacoepidemiology is steadily developing evaluation seldom includes neonates, is mainly focused on few drug classes and safety outcomes and concerns mainly drug use in developed countries. Small study size is a specific challenge in paediatrics. Reporting should be improved.

Introduction

Legislation has been introduced to stimulate the conduct of clinical trials in children [26,43,44], leading to more evidence on efficacy of new drugs or new formulations of existing drugs in children [162]. This laudable action has greatly improved the evidence for new drugs but does not impact much on the available safety data since information on rare and potentially more serious safety issues cannot be obtained from randomized clinical trials (RCTs) [163,164].

Safety data can be generated more efficiently from postmarketing observational studies [165,166], particularly relevant in children among whom the use of drugs is high and frequently off-label but recorded in routine care records [167]. The availability of large scale healthcare and claims databases provides an outstanding opportunity to perform safety studies. However, since the studies are observational, their design requires extra attention to avoid misclassification and address potential confounding. Although the field of pharmacoepidemiology has grown substantially in the last 20 years, very few researchers focus on pediatrics.

As part of the Global Research in Paediatrics - Network of Excellence (http://www.grip-network.org/), we conducted a systematic review of the medical literature in order to assess the characteristics of pharmacoepidemiological studies evaluating the safety of drugs in children.

Methods

Search strategy

We conducted this review according to PRISMA guidelines [168]. We identified relevant articles by systematically searching EMBASE.COM and MEDLINE (via OvidSP) from inception to 29th November 2013. We used the following abbreviated search strategy: “children” AND “pharmacoepidemiology” AND “comparative studies”. Details of the full search strategy are included in Appendix 1. The computer-based searches were conducted by a biomedical information specialist (WB), and were limited to human research without language limitations.

One reviewer (OO) manually searched the bibliographies of relevant articles for additional relevant studies.

Study selection

All observational studies with the main objective to quantify the association between a drug exposure(s) and the occurrence of adverse drug reaction(s) in children and adolescents (≤18 years of age) were eligible for inclusion in the review. Studies that included both children and adults were also retained. Drug exposures concerned all medicinal products including vaccines, applied either systemically or locally, and adverse drug reactions (ADRs) concerned all clinical events described as adverse outcomes to an individual (or combination of) drug(s) and/or vaccine(s).

We excluded RCTs and observational studies that evaluated drug safety signal detection in spontaneous reporting systems, compliance rates to medicinal treatments, incidence or prevalence of ADRs or other diseases within a defined population, teratogenic effects of drug exposure in pregnancy or through breast milk, medication errors, accidental and intentional poisoning, drug abuse, management of ADRs or other diseases, pharmacogenomics, pharmacoeconomics, health services utilization, environmental exposures or herbal treatments. We excluded case series, case reports, abstracts, letters, duplicate studies, preliminary publications or reviews. Only studies published in English were retained for the analysis.

All titles and abstracts were initially screened by one reviewer (OO) and full texts of potentially relevant articles were retrieved. A second reviewer (FK), blinded to the initial assessment, independently screened a sample of abstracts that comprised all abstracts retained plus a random selection of abstracts rejected by the first reviewer. Any disagreements between the two reviewers were examined by a third reviewer (Gt'J). Full texts retained through this process were independently screened by two reviewers (OO and JD), disagreements were examined by a third reviewer (CF).

Data collection

We developed a standardized form that was tested on 10 randomly selected papers, and was modified accordingly.

Data collected from each study pertained to journal impact factor (measured in 2013), study design, study period, type of data, study population, exposure, outcome, statistical analysis and results. We used country of corresponding author as a proxy for study setting. In the absence of information regarding study design, designs were classified based on data reviewers' judgement. Case control studies included those studies that applied the nested case control design. Type of data implied primary versus secondary data (i.e. 'large' datasets like 'primary care (prescription) data', 'outpatient (pharmacy) dispensing data' and 'claims data'). The age of the study population was categorized according to guidelines defined by the International Conference on Harmonization (ICH)[150]: newborns (0-27 days), infants and toddlers (28 days - 23 months), children (2-11 years) and adolescents (12-18 years). We used the term drug to refer to small molecules as opposed to vaccines. Exposures and outcomes were classified as rare based on authors' definitions. For the sources of exposure data, inpatient dispensing data included electronic prescription data for hospitalized patients, medical charts at the clinic implied paper charts, outpatient dispensing data implied pharmacy dispensing records, and registry included those that recorded information on vaccination and drug use. To assess whether follow-up was long enough to observe the outcomes of interest in cohort studies, we applied the following minimum time intervals from drug exposure: fever – 1 day, other acute events – 2 weeks, cancer and other chronic (i.e. neurological and psychiatric) events – 5 years. The full data extraction form is given in Appendix 2.

Both drugs and vaccines were mapped to the World Health Organization-Anatomical Therapeutic Chemical (WHO-ATC) classification (second or fifth level codes). The outcomes were mapped to the main divisions of the International Classification of Diseases (ICD), ninth edition.

Two reviewers (OO and JD) independently collected data from all full text articles. Discrepancies were discussed with three senior reviewers (FK, DW and CF).

In order to check for the impact of the Best Pharmaceuticals for Children Act (BPCA) which was introduced in the US in 2002[26], we compared the number of pediatric studies published before and after its introduction. We compared pediatric studies to all the published studies (i.e. pertaining to the general population).

Data analysis

All continuous variables were described using medians (first [Q1] - third [Q3] quartiles) and categorical variables were summarized using counts and percentages. We performed hypothesis testing using the Mann-Whitney U test for continuous variables and Pearson chi-square, Fischer's exact test or Z test for categorical variables. Analysis was performed by utilizing Statistical Package for the Social Sciences (SPSS) version 21.

Results

The search strategy yielded 4825 unique records after de-duplication (Figure 1). After screening titles and abstracts, we retained 301 articles (inter-reviewer concordance 90%) and after full text review, we retained 268 for analysis (inter-reviewer concordance 92%).

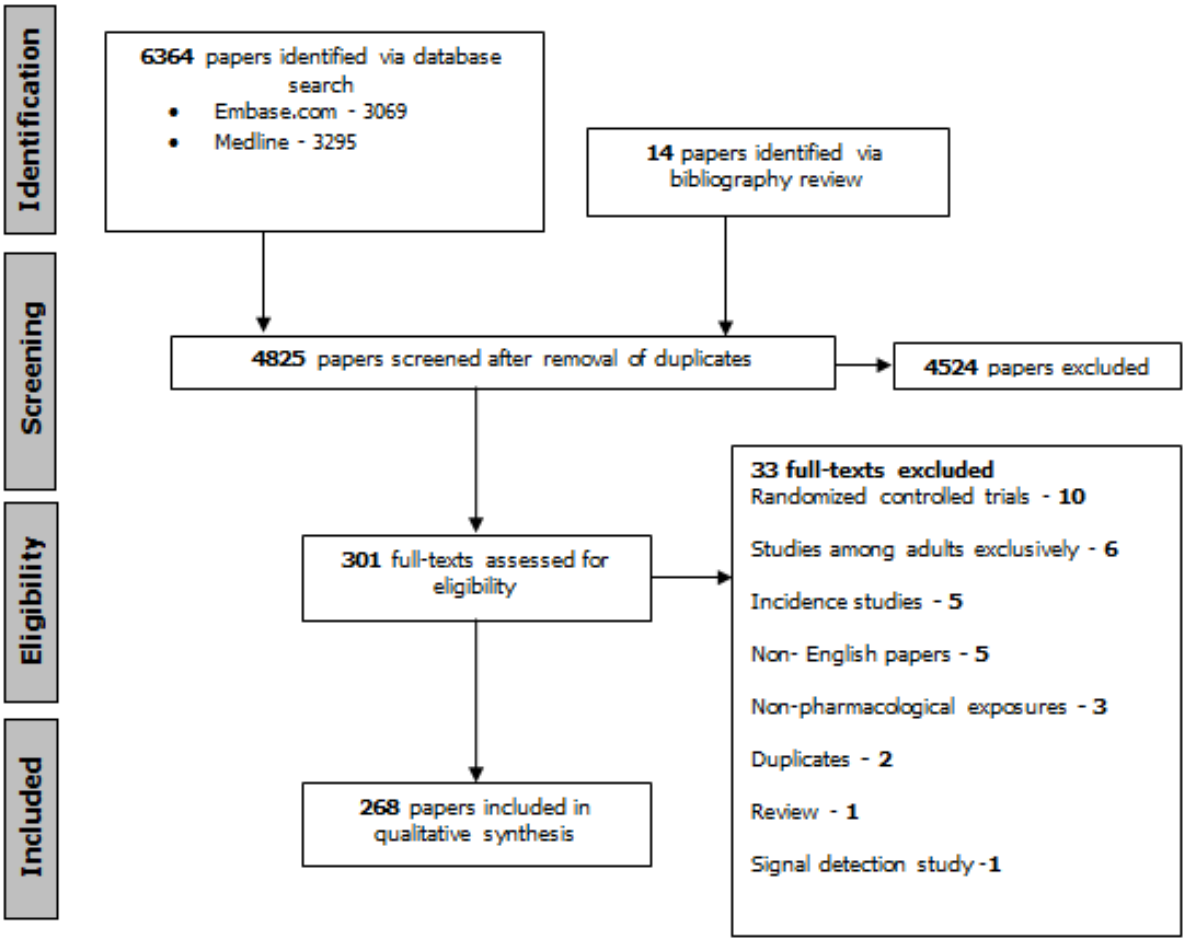


Figure 1: Flow chart depicting the selection of relevant papers

General characteristics of the studies

The 268 retained studies were published from 1979 to 2013. In figure 2, we compare the 268 studies to the total number (30,098) of studies (pertaining to the general population) published during the same period. After 2002, the number of pediatric studies steadily increased, more studies (196 [73.1%]) were published during the 10-year period from 2003 to 2013, compared to studies (72 [26.9%]) published during the preceding 24-year period.

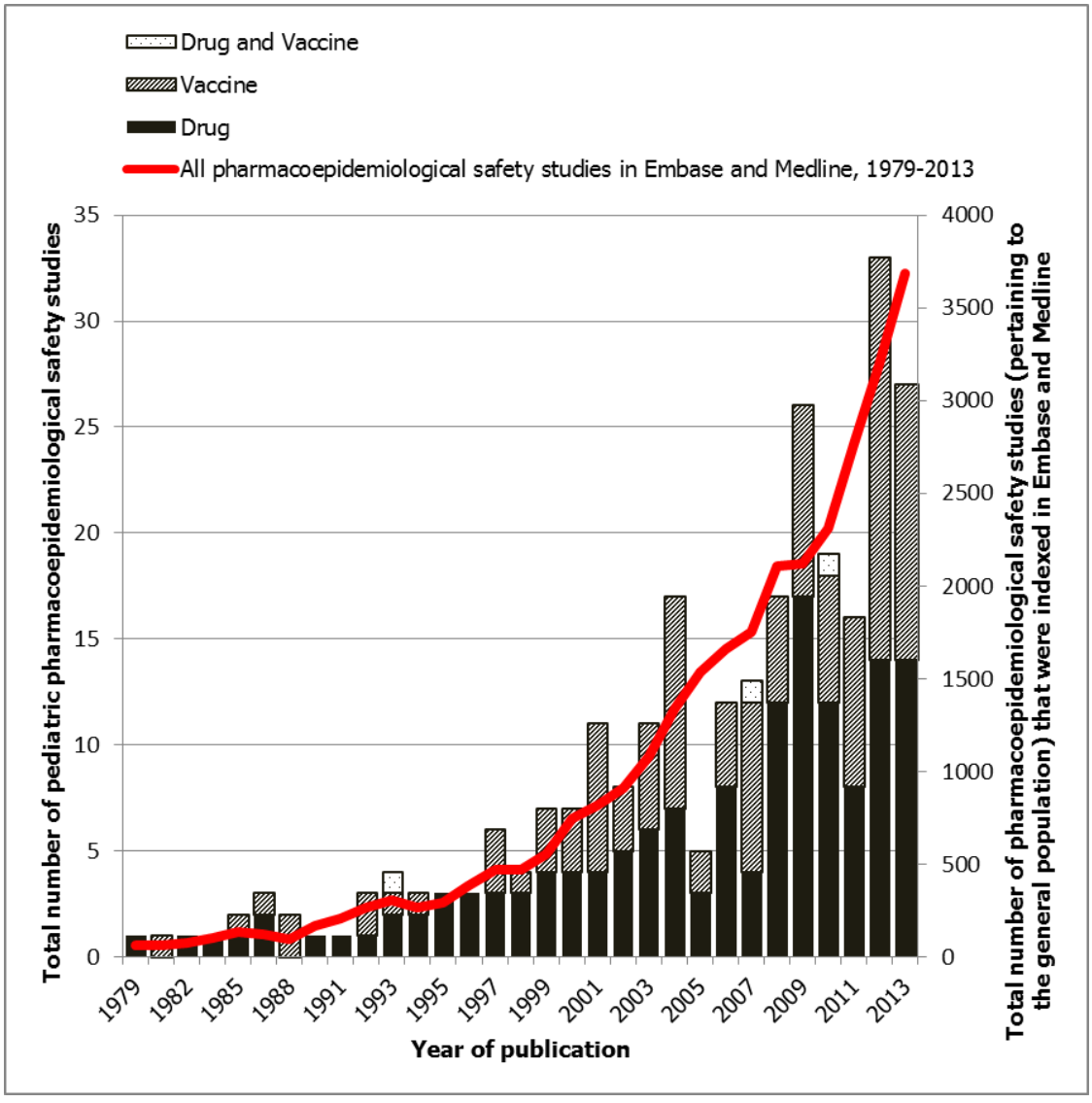


Figure 2: Number of pharmacoepidemiological safety studies in children

Note: In order to retrieve all published pharmacoepidemiological safety studies that investigated the general population, we applied the same search algorithm that was utilized for studies in children except that for the former, we did not limit to the pediatric population; papers that were published in 2013 are those papers that were indexed in Embase and Medline as at 29th November

Most studies originated from North America (154 [57.5%]) or Europe (92 [34.3%]) and most studies (147 [54.9%]) assessed only drugs. Only 3 studies (1.1%) evaluated both drugs and vaccines, the studies investigated only children for the effect of the following drug classes (WHO-ATC second level): 'corticosteroids for systemic use', 'ántibacterials for systemic use', 'cough and cold preparations', and 'anti-inflammatory and anti-rheumatic products'. The investigated vaccines were 'diphtheria-tetanus-pertussis', 'measles-mumps-rubella', 'hepatitis B virus', 'oral polio virus' and 'inactivated polio virus'.

Considering 268 studies, 183 (68.3%) included only children, the remainder studied both children and adults. Studies on drug safety evaluation included most frequently children aged 2-11 years while vaccine safety studies were most frequently conducted in infants and toddlers (Table 1). Only 14 studies (5.0%) included preterm newborns.

Table 1: General characteristics for 268 pharmacoepidemiological studies that evaluated the safety of drugs and vaccines in children (≤ 18 years)

		Type of exposure investigated		
	Total (268) number(%) or median(Q1-Q3)	Only drugs (147) number(%) or median(Q1-Q3)	Only vaccines (118) number(%) or median(Q1-Q3)	p-value
Continent of the corresponding author				0.90
North America	154 (57.5)	83 (56.5)	70 (59.3)	
Europe	92 (34.3)	52 (35.4)	39 (33.1)	
Asia	12 (4.5)	7 (4.8)	4 (3.4)	
Others	10 (3.7)	5 (3.4)	5 (4.2)	
Type of journal				0.07
Pediatric specialty	88 (32.8)	45 (30.6)	42 (35.6)	
	30 (11.2)	21 (14.3)	7 (5.9)	
Pharmacology/pharmacoepidemiology				
General medical[a]	39 (14.6)	17 (11.6)	22 (18.6)	
Others[b]	111 (41.4)	64 (43.5)	47 (39.8)	
2013 two-year journal impact factor	3.8 (3.1-5.3)	3.7 (2.6-5.5)	4.6 (3.6-5.6)	**0.01**
Missing data	18 (6.7)	14 (9.5)	4 (3.4)	
Funding sources				**<0.01**
Public	96 (35.8)	38 (25.9)	55 (46.6)	
Private	47 (17.5)	25 (17.0)	22 (18.6)	
Public and private	26 (9.7)	14 (9.5)	12 (10.2)	
No funding	7 (2.6)	5 (3.4)	2 (1.7)	
Funding not reported	92 (34.3)	65 (44.2)	27 (22.9)	
Study period, years	3.7 (1.7-8.9)	4.6 (1.7-9.0)	3.2 (1.7-7.0)	0.31
Missing data	14 (5.2)	11 (4.1)	3 (1.1)	
Study population[c]				
Age at inclusion				
Minimum age, years	0.1 (0-2.0)	0.1 (0-3.0)	0.2 (0-1.0)	0.51
Maximum age, years	16.5 (2.0-21.0)	18.0 (13.5-63.5)	5.0 (1.5-17.0)	**<0.01**
Preterm newborns				**<0.01**
Exclusively	9 (3.3)	9 (6.1)	0	
Partially	5 (1.9)	4 (2.7)	1 (0.8)	
No	254 (94.8)	134 (91.2)	117 (99.2)	
Term newborns (0-27 days)	106 (39.5)	61 (41.5)	44 (37.3)	0.49
Infants/toddlers (28 days-23months)	168 (62.9)	80 (54.4)	86 (72.9)	**<0.01**
Children (2-11 years)	202 (75.4)	117 (80.0)	82 (69.5)	0.05
Adolescents (12-18 years)	157 (58.9)	110 (74.8)	45 (38.1)	**<0.01**
Mixed (adults and children)	85 (31.7)	67 (45.6)	18 (15.3)	**<0.01**
WHO-ATC level of investigated exposure (reported name)[d]				**<0.01**
Fifth level (specific compound)	203 (75.7)	87 (59.2)	116 (98.3)	
Second,third or fourth level (class)	51 (19.0)	51 (34.7)	0	
Both	14 (5.2)	9 (6.1)	2 (1.7)	
Number of specific compounds (WHO-ATC fifth level) that were investigated[e]				0.14
1	137 (63.1)	54 (56.3)	81 (68.6)	
2	35 (16.1)	20 (20.8)	15 (12.7)	
≥3	45 (20.7)	22 (22.9)	22 (18.6)	
Number of drug/vaccine classes (WHO-ATC second, third or fourth				0.27

level) that were investigated[f]			
1	48 (73.8)	45 (75.0)	1 (50.0)
2	8 (12.3)	7 (11.7)	1 (50.0)
≥3	9 (13.8)	8 (13.3)	0

Note: Missing data is presented for only instances where it constitutes greater than 5%

NA=Not applicable

Studies assessing drugs (147) or vaccines (118) exclusively, do not add up to the total number of studies (268) because 3 studies that investigated both drugs and vaccines are not presented in the table.

[a] Refers to journals that publish wide variety of medical topics (irrespective of specialty);

[b] Journals that do not fit into any of the specified categories i.e. PLOS ONE;

[c] For the age distributions, the proportions do not add up to 100% because some studies included multiple age categories;

[d] World Health Organization-Anatomic Therapeutic Chemical;

[e] The proportions are based on only those studies that investigated specific compounds either exclusively or in combination with drug/vaccine class;

[f] The proportions are based on only those studies that investigated drug/vaccine class either exclusively or in combination with specific compounds

The median impact factor of the journals in which the studies were published was 3.8 (3.1-5.3). As seen in table 1, vaccine-only studies (4.6 [3.6-5.6]) were published in higher impact journals than drug-only studies (3.7 [2.6-5.5]) (Mann Whitney U p-value 0.01). Few studies were published in pediatric (88 [32.8%]) or pharmacoepidemiological specialty (30 [11.2%]) journals. Only 14 studies (17.5%) were privately funded, vaccine studies were more frequently publicly funded but for a large proportion the type of funding was unknown. Regardless of the type of exposure that was investigated, privately funded studies (journal impact factor=3.5; 3.1-5.3) were of lower impact than studies receiving public funding (journal impact factor=5; 3.5-7.8) (Mann Whitney U p-value<0.01).

Methodology of the studies

From the 268 studies, 202 (75.4%) reported the study design(s) and for the remaining study design was classified according to the reviewers' judgment. Cohort studies were the most common (174 [64.9%]), and 23 studies (8.6%) applied more than one design. Case-only designs were seldom used: the self-controlled case series (SCCS) design was utilized in only 30

studies (11.2%), to evaluate vaccine-related outcomes exclusively. Similarly, case-crossover studies were few (4 [1.5%]).

In most studies (196 [73.1%]), data collection was retrospective. Prospective studies (88 [32.8%]) were usually cohort studies that used mainly primary data (56 [63.6%]) and were smaller than studies with retrospective data. Secondary data was utilized for both drugs and vaccines and concerned 183 studies (68.3%). Studies using secondary data had larger sample sizes than studies using primary data collection. Exposure and outcome data were collected from mainly medical charts ((85 [31.7%]) and (122 [45.5%]) respectively) followed by claims data and primary care medical or dispensing data (Table 2).

Table 2: Methodology of 268 pharmacoepidemiological studies that evaluated the safety of drugs and vaccines in children (≤ 18 years)

		Type of exposure investigated		
	Total (268) Number(%) or median(Q1-Q3)	Only drugs (147) Number(%) or median(Q1-Q3)	Only vaccines (118) Number(%) or median(Q1-Q3)	p-value
Design[a]				
Cohort	174 (64.9)	114 (77.6)	60 (50.8)	**<0.01**
Case control	73 (27.2)	31 (21.1)	39 (33.1)	**0.03**
Self-controlled case series	30 (11.2)	0	30 (25.4)	NA
Case crossover	4 (1.5)	3 (2.0)	1 (0.8)	0.42
Others[b]	14 (5.2)	6 (4.1)	8 (6.8)	0.33
Mode of data collection[c]				
Retrospective	177 (66.0)	96 (65.3)	80 (67.8)	0.66
Prospective	69 (25.7)	41 (27.9)	26 (22.0))	0.27
Both	19 (7.1)	10 (6.8)	9 (7.6)	0.80
Unclear[d]	3 (1.1)	0	3 (2.5)	NA
Type of data				0.11
Primary	58 (21.6)	38 (25.9)	18 (15.3)	
Secondary	183 (68.3)	95 (64.6)	87 (73.7)	
Mixed	27 (10.1)	14 (9.5)	13 (11.0)	
Source of (collection method for) exposure data[e]				
Primary care (prescription) data	27 (10.1)	14 (9.5)	12 (10.2)	0.85
Outpatient (pharmacy) dispensing data	19 (7.1)	7 (4.8)	12 (10.2)	0.09
Inpatient dispensing data	21 (7.8)	18 (12.2)	2 (1.7)	**<0.01**
Paper medical chart	85 (31.7)	54 (36.7)	29 (24.6)	**0.03**
Claims data	55 (20.5)	25 (17.0)	30 (25.4)	0.09
Registry	35 (13.1)	16 (10.9)	19 (16.1)	0.21
Self-report questionnaire	12 (4.5)	7 (4.8)	5 (4.2)	0.82
Telephone call	13 (4.9)	5 (3.4)	8 (6.8)	0.20
Face to face interview	17 (6.3)	6 (4.1)	10 (8.5)	0.14
Others[f]	40 (14.9)	15 (10.2)	25 (21.2)	**0.01**
Unclear[g]	13 (4.9)	7 (4.8)	6 (5.1)	0.91
Source of (collection method for) outcome data[h]				
Primary care data	29 (10.8)	14 (9.5)	15 (12.7)	0.41
Paper medical charts	122 (45.5)	66 (44.9)	53 (44.9)	1.00
Institution, administrative or electronic heath records	60 (22.4)	23 (15.6)	37 (31.4)	**<0.01**
Claims data	71 (26.5)	32 (21.8)	38 (32.2)	0.06
Registry	38 (14.2)	21 (14.3)	17 (14.4)	0.98
Self-report questionnaire	25 (9.3)	13 (8.8)	12 (10.2)	0.70
Telephone call	13 (4.9)	8 (5.4)	5 (4.2)	0.65
Face to face interview	12 (4.5)	6 (4.1)	6 (5.1)	0.70
Others[i]	32 (11.9)	18 (12.2)	14 (11.9)	0.94
Unclear[j]	4 (1.5%)	3 (2.0)	1 (0.8)	0.42

Size of the study population per design				
Fixed cohort				
Exposed, number of participants	2050 (103-34544)	283 (51-12432)	44001 (4009-278624)	**<0.01**
Unexposed, number of participants	1073 (74-27417)	372 (58-8533)	24175 (1215-227288)	0.67
Missing data	18 (32.2)	6 (6.2)	12 (30.8)	
Dynamic cohort [person-years(PY)]				
Exposed PY	92835 (11931-731043)	62383 (3600-416018)	123287 (14708-1220006)	0.56
Unexposed PY	362142 (9235-1315038)	162622 (5485-1728969)	535375 (17496-1298601)	0.90
Case-control				
Cases	189 (68-467)	79 (30-532)	252 (133-452)	**0.03**
Number of controls per case	2.2 (1.1-4.2)	2.1 (1.0-4.4)	2.8 (2.0-4.1)	0.24
SCCS and Case Crossover, number of participants	402 (168-1380)	NA	369 (173-1334)	NA
Missing data	5 (14.7)	0	5 (16.1)	
Control of confounding [k]				
Matching	98 (36.6)	43 (29.3)	53 (44.9)	**<0.01**
Stratification	103 (38.4)	36 (24.5)	66 (55.9)	**<0.01**
Multivariate modelling adjustment	138 (51.5)	75 (51.0)	60 (50.8)	0.97

Note: Missing data is presented for only instances where it constitutes greater than 5%

NA = Not applicable

Studies assessing drugs (147) or vaccines (118) exclusively, do not add up to the total number of studies (268) because 3 studies that investigated both drugs and vaccines are not presented in the table.

[a] The proportions do not add up to 100% because some studies applied multiple designs;

[b] Includes study designs that are not listed i.e. case-time-control

[c]The proportions do not add up to 100% because some studies applied multiple data collection modes;

[d] Implies that there was inadequate information to determine if data collection was done prospectively or retrospectively;

[e] The proportions do not add up to 100% because some studies applied multiple sources (or collection modes for) exposure data;

[f] Includes data sources (or collection methods) that are not specified e.g. maternal and child health handbook;

[g] Implies that there was inadequate information to determine the source of (or collection mode for) the exposure data;

[h] The proportions do not add up to 100% because some studies applied multiple sources (or collection modes for) outcome data;

[i]Includes data sources (or collection methods) that are not specified e.g. maternal and child health handbook;

[j] Implies that there was inadequate information to determine the source of (or collection mode for) the outcome data;

[k] The proportions do not add up to 100% because some studies applied methods to control confounding;

Out of 147 studies that evaluated drugs exclusively, 87 (59.2%) assessed only exposures to specific compounds (i.e. amoxicillin), 51 (34.7%) evaluated exposures to a specific drug class (i.e. 'antibacterials for systemic use'), only 9 (6.1%) assessed both specific compound and drug class. Regarding the 96 studies that assessed specific compounds, 54 (56.3%) investigated only one compound, 20 (20.8%) assessed two compounds and 22 (22.9%) assessed three or more. Given the 60 studies that assessed drug class, 45 (75.0%) investigated only one class, 7 (11.7%) assessed two classes and 8 (13.3%) investigated three or more. Fourteen studies (23.3%) evaluated 'antibacterials for systemic use', 10 (16.7%) assessed psychoanaleptics and 7 (11.7%) assessed psycholeptics. Considering 14 drug safety studies that included preterm newborns, 'antibacterials for systemic use' were evaluated in 3 (21.4%) and 'corticosteroids for systemic use' in 2 (14.3%). For details of studied drug by age, see electronic supplementary material.

Across the 150 studies that assessed drugs whether exclusively or with vaccines, a total of 291 unique exposures representing 39 unique classes (WHO-ATC second level) were investigated. Psychoanaleptics (53 [18.2%]) were the commonest, followed by 'antibacterials for systemic use' (40 [13.7%]) and psycholeptics (38 [13.1%]). For further details, see table 3.

Table 3: Twenty most frequently investigated drug classes across the 150 studies that investigated drugs (whether exclusively or with vaccines)

Drug class (WHO-ATC second level)[a]	Code	N (%)[b]
Psychoanaleptics	N06	53 (18.2)
Antibacterials for systemic use	J01	40 (13.7)
Psycholeptics	N05	38 (13.1)
Antineoplastic agents	L01	30 (10.3)
Anti-inflammatory and Anti-rheumatic products	M01	18 (6.2)
Anti-epileptics	N03	12 (4.1)
Corticosteroids for systemic use	H02	11 (3.8)
Analgesics	N02	10 (3.4)
Contrast media	V08	8 (2.7)
Immunosuppresants	L04	7 (2.4)
Anesthetics	N01	6 (2.1)
Antihistamines for systemic use	R06	6 (2.1)
Antihemorrhagics	B02	5 (1.7)
Pituitary and hypothalamic hormones and analogues	H01	5 (1.7)
Antivirals for systemic use	J05	5 (1.7)
Drugs for obstructive airway diseases	R03	4 (1.4)
Cardiac therapy	C01	3 (1.0)
Cough and cold preparations	R05	3 (1.0)
Drugs for functional gastrointestinal disorders	A03	2 (0.7)
Agents acting on the renin-angiotensin system	C09	2 (0.7)

[a] World Health Organization-Anatomic Therapeutic Chemical classification;

[b] Proportion is based on the total number (291) of unique drug exposures that were investigated

Considering drug evaluations exclusively, only 3 studies (2.0%) assessed the effect of rarely used drugs (i.e. ciprofloxacin) and only 30 (20.0%) assessed dose-effects.

Altogether, 588 outcomes were evaluated with a median of 1 (1-2) outcome per study, 36 studies (13.4%) did not state the outcome definition. Most events (68 [39.5%]) were acute, and defined as symptoms, signs or ill-defined conditions (i.e. diarrhea) (Figure 3). Rare outcomes (i.e. Stevens-Johnson syndrome) were evaluated in only 17 studies (6.3%). Expert validation of the outcomes was frequent (172 [64.2%]) but only in 46 of those (26.7%) the experts were blinded to exposure.

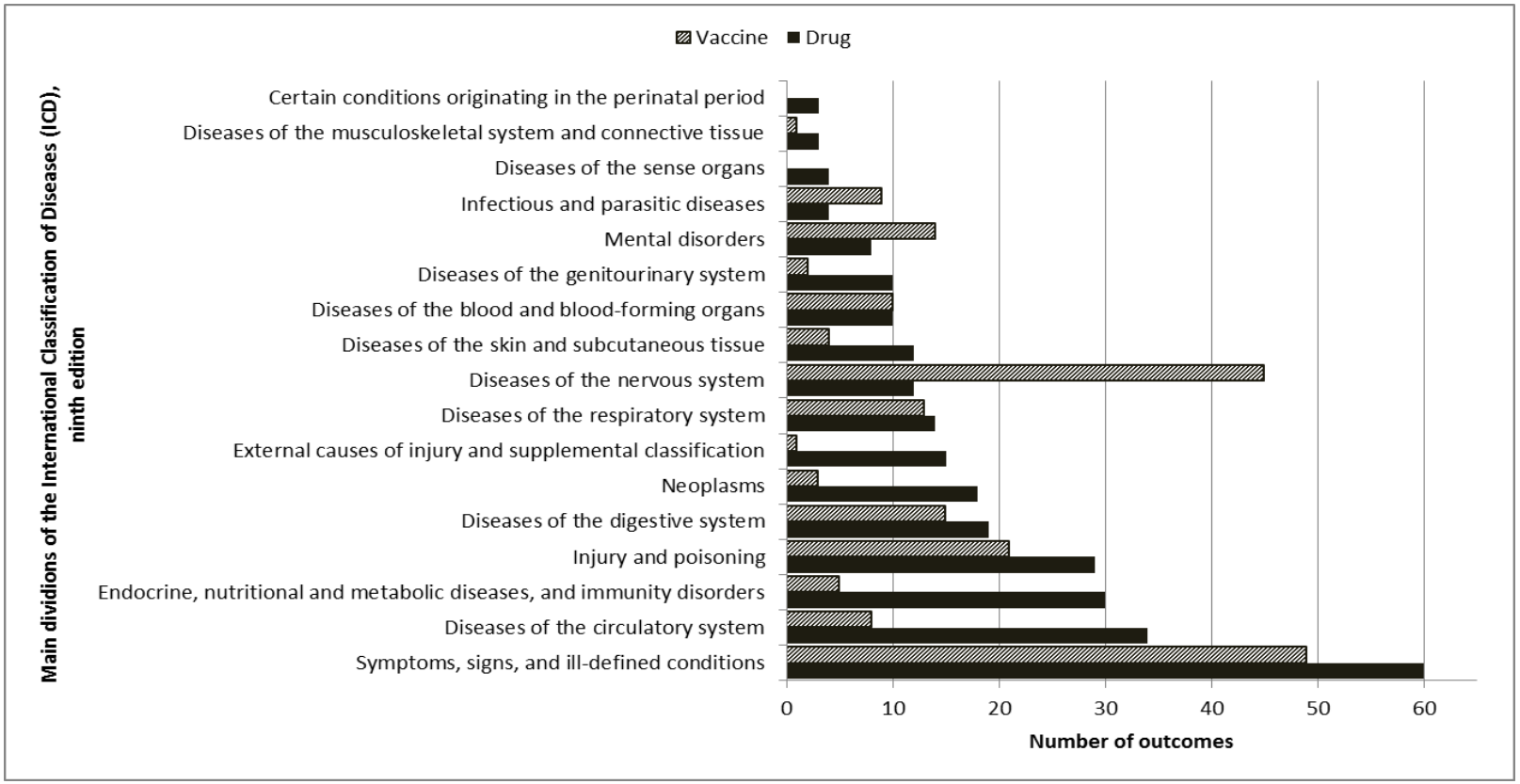


Figure 3: Distribution of papers according to the main divisions of the International Classification of diseases (ninth edition), and type of exposure

Note: 'Certain conditions originating in the perinatal period' includes 'Other conditions originating in the perinatal period'(764-779) which does not include maternal causes i.e. Necrotizing enterocolitis (777.5); 'Injury and poisoning' includes 'unspecified adverse effect of drug medicinal and biological substance not elsewhere classified' (995.2)

Out of 174 cohort studies, the follow-up time was inadequate to observe the investigated outcomes in 76 (43.7%).

Only 27 studies (10.1%) reported sample size or power calculations. Cohort studies were the largest unlike SCCS and case crossover studies which included few participants. Most studies (229 [85.4%]) adjusted for confounding either by stratification (mainly vaccine safety studies), matching or by multivariate modelling (mainly drug safety studies).

Only 133 studies (49.6%) specified a primary objective and 129 studies (48.1%) reported at least one statistically significant result. This proportion increased to 59.0% when only 183 child-specific studies were considered. Most studies with significant statistical results (97 [75.2%]) were published after 2002. Among the 75 child-specific studies that did not present any statistically significant result, 41 (54.7%) did not discuss lack of power.

Discussion

We have conducted a systematic review to assess the characteristics of pediatric pharmacoepidemiological safety studies that were published over 34 years, while aiming to identify areas for improvement of these much needed studies. The review also highlights differences in drug versus vaccine pediatric studies. Some previous reviews have summarized evidence regarding specific drug or vaccine safety issues that affect children [169-172] while others have focused on specific methodological aspects of pediatric pharmacoepidemiology [173,174] but to the best of our knowledge no review has attempted to provide a general overview of these studies.

Our main findings are: the absolute number of pediatric pharmacoepidemiological safety studies is low; in 2012 only 33 studies concerned pediatrics compared to a total of 3197 published studies (data not presented but utilized in constructing figure 2). Such studies are almost exclusively conducted in developed countries and receive very little private funding. Evaluated exposures concern few pharmaceuticals while investigating mainly intermediate clinical outcomes (signs/symptoms). As areas of improvement we recommend better global spread, interaction between pharmacoepidemiologists evaluating drugs and vaccines to apply designs

more broadly, more focus and funding of such studies, and collaboration between investigators so that larger size studies can be conducted that may have enough power to study the rarer and potentially more serious safety issues.

Although paper medical charts may be regarded as the gold standard source of patient information electronic health records and claims data comprise vast amounts of routine care information that can be readily utilized for pharmacoepidemiological safety studies, as demonstrated by several authors[175-178]. More extensive use of such data may be needed to overcome the problem of inadequate follow-up for many cohort studies as demonstrated in this review, especially if this is related to the high costs that is associated with long follow up time in some prospective studies utilizing primary data collection. Generally, the potential of secondary data has been recognized by FDA in Sentinel [179], by Health Canada in their CNODES project [180], and in Europe by the GRIP consortium and other projects [181]. We should now focus the potential of these powerful resources on pediatric studies specifically in order to quickly fill the existing gap in knowledge of drug use.

The number of pediatric safety studies started increasing steadily after 2002, following the introduction of the 'Best Pharmaceuticals for children's Act' (BPCA) [26]. Under the BPCA, the US National Institutes of Health sponsored several pharmacoepidemiological studies in children [182]. The pediatric regulation was introduced in the European Union in 2007, perhaps explaining the even steeper increase in the number of pediatric studies that is observed after 2007 (figure 2). The predominance of US and EU studies may be explained partially by these legislations but also by the number of epidemiologists and data resources. Whatever the explanation may be, this review points to a large public health need for more human capacity building and studies in many children that live in other parts of the world, particularly lower and middle income countries. From a publication and academic perspective it should be noted that the studies were published mostly in more general journals and the impact factors were well above the median in the pharmacology field.

Where should funding for such studies come from? Generally, studies relying on secondary data are affordable. In this review we observed that few studies were privately funded. We recommend that the politicians who passed the BPCA and other legislations to stimulate generation of efficacy data in children see the potential of pharmacoepidemiology rather than clinical trials to generate safety data and oblige long-term postmarketing studies in children for newly marketed drugs specifically. Studies on off-patent drugs that are frequently used in children should be investigated through public funding in both developing and developed countries.

Almost half of the evaluated drugs belong to only 3 classes (table 3): anti-infectives, psychoanaleptics and psycholeptics. Although anti-infectives are often prescribed in pediatrics across all age groups, psychoanaleptics and psycholeptics represent a minority of drug exposure in children [85]. However, these drugs have been surrounded by specific safety issues [183,184]. Specifically, psychoanaleptics (i.e. atomoxetine and methylphenidate) were commonly mentioned in pediatric case reports submitted to FAERS between 2004 and 2011[185], probably reflecting its increased use and high risk of toxicity, notably cardiovascular toxicity, as demonstrated by several authors in our review [183,184,186-188].

Very few studies evaluated rare drug exposures possibly because such studies would not have been adequately powered to detect an association. Specifically, in preterm newborns, the investigated drugs (i.e. sildenafil and morphine) are possibly associated with serious safety issues [189-191] however these studies could not confirm safety associations possibly because of their limited sample size. Inadequate sample size may account for the lack of at least one statistically significant result in 41% of the child-specific studies, even if majority of these studies did not discuss lack of power. Size issues may be addressed by implementing case-only (i.e. SCCS) designs [192]. In our review, few studies applied case-only analysis essentially to evaluate vaccine safety. However, case-only designs present strengths that are suited for the drug utilization patterns and characteristics of outcomes in children [193,194]. Further, multi-site data pooling may be necessary to acquire adequate power to study rare events in children[77,195].

International collaboration on a global scale may be required; this is the main aim of the Global Research in Pediatrics (GRIP) project.

The strength of this review is the systematic assessment of pharmacoepidemiological safety studies in children, with broad inclusion criteria. Regarding limitations, we applied minimum follow-up periods (to cohort studies) according to the type of investigated outcome; this may not have been accurate for some specific outcomes. Yet, standardization was necessary because the outcomes were numerous and highly heterogeneous. Also, the findings we have presented are based on published data reported by authors of the studies therefore if such reporting was incomplete and/or inaccurate; this may have impacted our findings. For example, several irrelevant drug exposures were assessed in neonates (electronic supplementary material), like anti-obesity preparations or antineoplastic drugs merely because authors stated that included pediatric population started at 0 years of age. Such imprecisions inevitably lead to erroneous conclusions. Also, we used country of corresponding author as a proxy for the study setting; by doing this, study setting for multi-country database studies may not have been accurately captured. Further, we used the journal impact factor as a proxy for the quality of the studies that we reviewed; the limitations of this measure have been described in the literature.

Based on the reviewed literature, we conclude that there is a need to build global collaborative capacity and funding opportunities for pediatric pharmacoepidemiology since this is one of the most powerful ways to provide evidence of drug safety in children.

Appendix 1: Full search strategy

Search criteria for Embase.com

1. 'pediatrics'/exp OR 'child'/exp OR 'childhood'/exp OR 'newborn'/exp OR ('adolescent'/exp OR 'adolescence'/exp NOT ('adult'/exp OR adult*:ab,ti))

2. child*:ab,ti OR pediatric*:ab,ti OR paediatric*:ab,ti OR infant*:ab,ti OR infancy:ab,ti OR baby:ab,ti OR babies:ab,ti OR toddler*:ab,ti OR neonate*:ab,ti OR newborn*:ab,ti OR premature*:ab,ti OR adolescen*:ab,ti OR teenage*:ab,ti OR preschool:ab,ti OR school*:ab,ti OR neonat*:ab,ti

3. 1 or 2

4. 'risk'/de OR 'attributable risk'/de OR 'risk factor'/de OR 'risk benefit analysis'/de OR 'risk assessment'/de OR 'risk management'/de OR 'risk reduction'/de OR 'incidence'/de OR 'hazard ratio'/exp OR 'logistic regression analysis'/exp

5. odds:ab,ti OR 'logistic regression':ab,ti OR 'relative risk':ab,ti OR incidence:ab,ti OR prevalence:ab,ti OR (hazard* NEAR/3 ratio*):ab,ti OR 'safety assessment':ab,ti OR (risk NEAR/3 (ratio OR attribut* OR differen* OR assess* OR adjust* OR analy* OR relativ* OR factor* OR manag* OR reduc*)):ab,ti

6. 4 or 5

7. 'drug toxicity and intoxication'/exp OR 'adverse drug reaction'/exp OR 'drug'/exp/dd_ae OR ('side effect'/exp OR 'adverse outcome'/exp AND ('drug'/exp OR 'drug therapy'/exp OR 'vaccine'/exp OR 'adjuvant'/exp OR 'immunization'/exp)) OR 'drug safety'/de

8. ((pharmacol* OR pharmaceut* OR medication* OR medicine* OR drug* OR pharmacotherap* OR medicament* OR 'medicinal product' OR vaccin* OR immunizat* OR immunisat* OR adjuvant* OR treatment* OR therap*) NEAR/6 (safet* OR toler* OR intoler* OR toxic* OR intoxic* OR react* OR aftereffect* OR fatal* OR 'side effect' OR 'side effects' OR adverse)):ab,ti OR pharmacotox*:ab,ti OR (adverse NEAR/3 (event* OR reaction* OR effect* OR outcome)):ab,ti

9. 7 or 8

10. 'epidemiology'/de OR 'pharmacoepidemiology'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'longitudinal study'/de

11. epidemiol*:ab,ti OR pharmacoepidemiol*:ab,ti OR cohort*:ab,ti OR (follow NEXT/1 up*):ab,ti OR observation*:ab,ti OR retrospectiv*:ab,ti OR prospectiv*:ab,ti

12. 10 or 11

13. 'comparative study'/de OR 'comparative toxicology'/de OR 'drug comparison'/exp OR 'controlled study'/de OR 'case control study'/exp

14. control*:ab,ti OR compar*:ab,ti OR referen*:ab,ti OR match*:ab,ti OR nested:ab,ti OR ('self controlled' NEXT/1 serie*):ab,ti OR 'case cross over':ab,ti OR 'case centered':ab,ti OR 'case coverage':ab,ti OR 'case cohort':ab,ti

15. 13 or 14

16. 12 and 15

17. 3 and 6 and 9 and 16

18. [article]/lim NOT ('pregnancy'/exp OR pregnan*:ab,ti OR fetus:ab,ti OR fetal:ab,ti OR foetus:ab,ti OR foetal:ab,ti) NOT ('clinical trial'/exp OR 'systematic review'/exp OR 'randomized controlled trial'/de OR 'randomization'/de) NOT ([animals]/lim NOT [humans]/lim)

19. 17 and 18

Search criteria for Medline (via OvidSP)

1. exp pediatrics/ or exp child/ or exp infant/ or (adolescent/ not (exp adult/ or adult*.ab,ti.))

2. (child* or pediatric* or paediatric* or infant* or infancy or baby or babies or toddler* or neonate* or newborn* or premature* or adolescen* or teenage* or preschool or school* or neonat*).ab,ti.
3. 1 or 2

4. exp risk/ or "Odds Ratio"/ or incidence/

5. (Odds or "logistic regression" or "relative risk" or incidence or prevalence or (hazard* adj3 ratio*) or "safety assessment" or (risk adj3 (ratio or attribut* or differen* or assess* or adjust* or analy* or relativ* or factor* or manag* or reduc*))).ab,ti.

6. 4 or 5

7. exp "drug toxicity"/ or exp Pharmaceutical Preparations/ae or exp drug therapy/ae or exp vaccines/ae or exp immunization/ae

8. (((pharmacol* or pharmaceut* or medication* or medicine* or drug* or pharmacotherap* or medicament* or "medicinal product" or vaccin* or immunizat* or immunisat* or adjuvant* or treatment* or therap*) adj6 (safet* or toler* or intoler* or toxic* or intoxic* or react* or aftereffect* or fatal* or "side effect" or "side effects" or adverse)) or pharmacotox* or (adverse adj3 (event* or reaction* or effect* or outcome))).ab,ti.

9. 7 or 8

10. "epidemiology"/ or epidemiology.xs. or pharmacoepidemiology/ or exp "Epidemiologic Studies"/ or observation/

11. (epidemiol* or pharmacoepidemiol* or Cohort* or (FOLLOW adj up*) or observation* or retrospectiv* or prospectiv*).ab,ti.

12. 10 or 11

13. "comparative study".pt. or "drug comparison"/ or "controlled study"/ or "case control study"/

14. (control* or compar* or referen* or match* or nested or ("self controlled" adj serie*) or "case cross over" or "case centered" or "case coverage" or "case cohort").ab,ti.

15. 13 or 14

16. 12 and 15

17. 3 and 6 and 9 and 16

18. Limit 17 to Journal Article

19. Limit 18 to humans

20. 19 not (pregnancy/ or (pregnan* or fetus or fetal or foetus or foetal).ab,ti.)

21. 20 not (clinical trial/ or systematic review/ or randomized controlled trial/ or randomization/)

Appendix 2: Data collection form

1. **General data**
   a. Unique ID |__|__|__|
   b. First author (surname) ……
   c. Year of publication |__|__|__|___|
   d. Country (corresponding author) ……..
   e. Journal (abbreviation)……
   f. Funding sources: |__| Public |__| Private |__| Public and private |__| No funding |__|unclear
2. **Study design**
   a. Was study design clearly reported? |__| Yes |__| No
      Some studies do not report on study design. If the answer to this question is 'no', provide answer to only question 'b'.
   b. Number of designs studying the same association and using the same data…….
   c. Cohort |__| Yes |__| No
   d. Case-control |__| Yes |__| No (including nested case-control studies)
   e. Case-based
      i. self-controlled case series (SCCS) |__| Yes |__| No
      ii. case cross-over |__| Yes |__| No
      iii. others |__| Yes |__| No
   f. Data collection mode
      i. prospective |__| Yes |__| No
      ii. retrospective |__| Yes |__| No
      iii. unclear |__| Yes |__| No
3. **Study period**
   a. Date of Start of study period | _|__|__|___|DDMMYYYY
   b. Date of End of study period |__|__|__|___| DDMMYYYY
4. **Type of data**
   a. Only primary |__| (data collected specifically for the study)
   b. Only secondary |__| (data collected for other purposes)
   c. Mixed (combining primary and secondary)|__|
5. **Study population (age range as in inclusion criteria)**
   a. Preterm newborns |__| Yes |__| No
   b. Minimum age |__| and unit of age: days |__| months |__| years |__|
   c. Maximum age|__| and unit of age: days |__| months |__| years |__|
   d. unclear |__|
      If 'c' then what is the minimum and maximum age given in the results (regardless of the study group)?
      a. Minimum age |__| and unit of age: days |__| months |__| years |__|

b. Maximum age|__| and unit of age: days |__| months |__| years |__|

6. Exposure

a. |__| Drug |__| Vaccine |__| Drug and Vaccine

b. Was drug class studied|__| Yes |__| No

c. Number of drug classes studied ……..

d. Drug classes studied ……..

e. Was specific drug/vaccine studied|__| Yes |__| No

f. Number of drugs/vaccines studied……..

g. Substance/vaccine name (WHO) ……..

h. ATC code reported |__| Yes |__| No ……*if yes* reported ATC code:……..

i. Characteristics of exposure in the paediatric indication (s):

   i. Rare |__| Yes |__| No |__| Unclear

   ii. Intermittent |__| Yes |__| No |__| Unclear

   iii. Chronic |__| Yes |__| No |__| Unclear

   iv. Exposure is changing medication (e.g. new dose, new formulation…) |__| Yes |__| No |__| Unclear

j. Is the effect of dose studied? |__| Yes |__| No

k. Data sources (or collection methods) of exposure data

   i. In patient dispensing data |__| Yes |__| No (electronic prescription data)

   ii. Medical charts at the clinic |__| Yes |__| No (paper prescription charts)

   iii. Primary healthcare data |__| Yes |__| No

   iv. Outpatient dispensing data (pharmacy) |__| Yes |__| No

   v. Claims data |__| Yes |__| No

   vi. Registry |__| Yes |__| No (including vaccination registry)

   vii. Self-report questionnaire or query |__| Yes |__| No

   viii. Telephone call |__| Yes |__| No

   ix. Web site |__| Yes |__| No

   x. Interview |__| Yes |__| No

   xi. Others |__| Yes |__| No

7. Outcome

a. Number of events studied……..

b. Event term(s)……..

c. Was the event(s) definition(s) clearly described or sourced by a stated reference? |__| Yes |__| No

d. Was the event(s) validated by experts? |__| Yes |__| No

e. Was the event(s) validation (s) done blinded to exposure? |__| Yes |__| No

f. Characteristics of the event (s): (more than 1 option is possible)
    a. Acute |__| Yes |__| No |__| Unclear
    b. Rare |__| Yes |__| No |__| Unclear
    c. Irreversible (e.g. mortality, handicap …) |__| Yes |__| No |__| Unclear
    d. Recurrent |__| Yes |__| No |__| Unclear

g. Data sources (or collection methods) for data about the events
    i. Institution or administrative /electronic Hospital records |__| Yes |__| No
    ii. Paper medical charts/visits at the clinic |__| Yes |__| No
    iii. Primary healthcare data |__| Yes |__| No
    iv. Claims/reimbursement data |__| Yes |__| No
    v. Registry |__| Yes |__| No
    vi. Self-report questionnaire or query |__| Yes |__| No
    vii. Telephone call |__| Yes |__| No
    viii. Web site |__| Yes |__| No
    ix. Interview |__| Yes |__| No
    x. Others |__| Yes |__| No

8. Statistical analysis and results

a. Calculation of a sample size is reported |__| Yes |__| No

If yes, required sample size calculated ……..

b. Total size of the study population
    i. Number of cases……. / Number of controls…….
    ii. Size of exposed cohort ……. / Size of unexposed cohort ……. (absolute number for fixed cohorts and person-years (PY) for dynamic cohorts)
    iii. Number of cases…….

c. Length of follow-up was summarized using: |__| mean |__|median |__|unclear (*If the answer is 'unclear', ignore questions 'i' and 'ii' that follow).*
    i. Exposed cohort ……. / unexposed cohort ……. (Cohort)
    ii. Cases……. (*SCCS*)

d. Adjustment for confounding variables has been made |__| Yes |__| No

if yes what has been performed?

Restriction |__|

Matching |__|

Stratification|__|

Multivariate modelling analysis |__|

Adjusted by study design (case-only) |__|

e. Primary statistical analysis (these questions should be completed for primary analysis, if primary objective is not described or unclear then just complete the first question and not the remaining.
    - Was the primary objective clearly defined? |__| Yes |__| No |__| unclear
    - Were results on primary analysis presented for the paediatric population? Not presented|__|adjusted|__| unadjusted|__| unclear|__|

f. There is at least one statistically significant result for the paediatric population |__| Yes |__| No

If no, the authors discussed the problem of having a lack of power |__| Yes |__| No

Chapter 4.2 Quality of published pediatric pharmacoepidemiological safety studies: Implications for evidence-based drug prescribing in pediatrics

Abstract

Background: Pharmacoepidemiological studies can yield important safety evidence for better drug use in children but such studies are prone to important challenges that may limit the credibility of evidence. Identifying important pediatric-specific study characteristics may improve the methodological evaluation of published studies.

Objective: To assess the quality of published pharmacoepidemiological safety studies in children, and its association with characteristics related to the design and conduct of the studies.

Methods: Relevant articles from inception to 2013 were retrieved from Embase.com and Medline. We sequentially screened titles, abstracts and full texts, with independent validation. We systematically evaluated the quality of retained studies with a modified Newcastle-Ottawa-scale (maximum score=9.0) and derived a summary quality score (median [25^{th}; 75^{th} percentiles]) for each study. By applying Kruskal Wallis H (KWH) and Mann Whitney U (MWU) tests, we assessed the association between quality and several characteristics including year of publication, geographical setting, funding, design, type of data and exposure.

Results: Out of 4,825 unique articles, 259 full texts were evaluated; 54.4% pertained to drugs, the remainder to vaccines. Generally, quality was high (median score=7.0; p25=6.0; p75=8.0). The characteristics that were significantly associated with quality include: year of publication (KWH p-value=0.01), geographical setting (KWH p-value=0.04), funding (KWH p-value<0.01), type of data (KWH p-value<0.01), design (KWH p-value<0.01) and exposure (MWU p-value<0.01). Studies with the highest quality were self-controlled case series (median score=7.0; p25=7.0; p75=8.0) that assessed vaccines.

Conclusion: Published pediatric pharmacoepidemiological safety studies show good quality, which has improved over time and is associated with geographical setting, design, and conduct of the studies. SCCS studies of vaccines scored the best. By applying our findings, study evaluators may find it easier to assess published studies thereby enhancing their impact on pediatric drug prescribing.

Introduction

Evidence-based medicine (EBM) may be defined as the integration of best research evidence with clinical expertise and patient values[196]. Although widely applauded, evidence-based drug prescribing is limited by the time and ability to interpret evidence appropriately.

Pharmacoepidemiological studies have become crucial for benefit-risk assessment of drugs but well-known methodological challenges still limit the validity of results and credibility of evidence[197]. Pediatric studies are prone to additional challenges. For example, inadequate sample size[77,195] often limits age-specific safety studies, which is recommended in children because of organ maturation, hormonal imbalances and varying susceptibility to adverse drug reactions (ADRs)[198]. Although detailed information about a child's age (especially for newborns and infants) and administered drug(s) is often needed when conducting pharmacoepidemiological safety studies in children, such data is often missing from many routinely utilized databases[199], but can be obtained if data is collected for research purposes specifically. Vaccines are frequently administered to children[200,201], most vaccine exposures are transient and evaluating such exposures requires the application of specific (appropriate) study designs [202]. The impact of various challenges on the methodological quality of pharmacoepidemiological safety studies in children specifically is not completely understood.

Following the introduction of drug legislations[26,43,203], more pediatric pharmacoepidemiological studies have been conducted[204]. However, the quality of these studies is not certain, has not been systematically evaluated yet is important for results' uptake and implementation in clinical practice. The US Institute of Medicine emphasizes the importance of evaluating the quality of evidence generated from postmarketing drug safety studies [205]. Although the quality of pharmacoepidemiological safety studies in the general population has been evaluated [206-210], little effort has been focused on children specifically.

As part of the Global Research in Paediatrics (GRiP) (http://www.grip-network.org/), we systematically evaluated the quality of pharmacoepidemiological safety studies that included children. We tested the association between various characteristics pertaining to the design and

conduct of the studies, and the quality. The aim was to identify features that may indicate which studies are of high quality thereby improving the critical appraisal of published studies.

Methods

Literature retrieval

Briefly, we systematically searched EMBASE.COM and MEDLINE (via OvidSP) from inception to 29th November 2013 for observational comparative drug or vaccine safety studies that included children (0-18 years). We described the characteristics of 268 retained studies published from 1979 to 2013, see appendix 1 for the full search strategy. The results have been published[204].

In the current report, we systematically evaluated the quality of 259 cohort, case control, self-controlled case series (SCCS) and/or case cross over studies, we excluded 9 studies that applied other study designs. The study design(s) was (were) classified according to the reports of the authors, otherwise it (they) were assigned based on the judgement of the reviewers. Out of 259 studies, 20 studies applied 2 designs (each) and 1 study applied 3 designs.

See appendix 2 for the article selection process.

Quality assessment tool

Currently, there is no 'gold standard' to assess the methodological quality of observational studies although several guidelines exist[211-215]. Some existing tools were not designed for pharmacoepidemiological safety studies specifically [216-219] or are meant for meta-analysis of a specific drug-event association [220,221]. We aimed at evaluating all studies irrespective of drug or event; therefore no existing tool could be readily utilized.

The Newcastle-Ottawa scale (NOS) was developed for assessing the quality of non-randomized studies that are included in systematic reviews [222,223]. It is endorsed by the Cochrane collaboration and has been widely applied since 2004 [224]. Results from many validation studies have been published [225-227]. It includes the cohort and case control versions. Each version comprises a set of questions, a manual, and an explanatory slide presentation, all freely

accessible via the website of the Ottawa Hospital Research Institute [223]. Both versions consist of eight multiple-choice questions that address three domains: subject selection, groups' comparability and the assessment of the exposure (case control) or the outcome (cohort). Each question has two to five possible answers. High-quality answers earn one 'star' and the maximum quality score for a study is 'nine stars' (the comparability question earns up to two 'stars'). All star-earning answers are categorised as 'low risk of bias' and all other responses as 'high risk of bias'.

Study quality assessment

As presented in appendix 3, both (case-control and cohort) versions of the NOS were tailored to assess the quality of studies that we reviewed. Regarding cohort studies, a star was assigned for the item 'representativeness of the exposed cohort' if the exposed cohort was identified from electronic medical records or claims data whether exclusion criteria were applied or not; 'was follow-up long enough for outcomes to occur' assesses the appropriateness of the predefined risk windows, for the current study we defined the following risk periods i.e. fever - 1 day, other acute events - 2 weeks, cancer and other chronic (including neurological and psychiatric) events - 5 years; 'adequacy of follow-up of cohorts' evaluates whether groups are comparable with respect to attrition or missing data, for this item studies were also assigned a star if the investigated population was dynamic.

For the case control version, studies were assigned a star if the exposure was ascertained from prescription or dispensing database.

For both versions, 'Select the most important factor' and 'study controls for any additional factor' require the researcher to select the appropriate factors for that systematic review. We selected age as the most important factor because it is a known confounder of many pharmacoepidemiological safety studies especially in children [228]. We selected sex [229], medical indication [230] and calendar time [231] (only for case control studies) as additional factors to be assessed.

Since the self-controlled case series (SCCS) and case-crossover designs are modifications of the cohort [192] and case control designs [232] respectively, we applied the cohort version of the NOS to SCCS studies and the case-control version to case-crossover studies.

The NOS was independently applied by two researchers (OO and JD). Disagreements were resolved by consensus.

Results obtained by applying the NOS have been presented (in other systematic reviews) with varying levels of detail: from the answer to each question for each study (maximum detail) to a summary score equal to the number of stars earned by each study (minimum detail). We derived a score summarizing the number of stars earned by each study that we evaluated.

We checked for association between the quality of studies and the year of publication, categorised into four periods (1979-1997, 2000-2002, 2005-2007, and 2010-2013) according to the introduction of the US FDA Modernization Act (1997), US Best Pharmaceuticals for children's Act (2002) and EU Pediatric Regulation (2007) respectively. We assessed the influence of other characteristics that may impact study quality, [197,233,234], including geographical setting, type of journal i.e. pediatric specialty, pharmacology/pharmacoepidemiology, general medical or others, two-year journal impact factor (measured in 2013), funding status, mode of data collection (prospective, retrospective or both), type of data (primary, secondary or mixed), design, age of the studied population i.e. only children or 'children and adults', and type of exposure i.e. drug or vaccine.

For studies applying multiple designs (one of which was the primary design), all the designs were considered in testing the association between design and quality. However for the association between quality and the other characteristics that we investigated, only the primary design was considered. Otherwise data regarding those characteristics may be unintentionally duplicated, leading to invalid results[235].

We stratified quality scores by design and type of exposure, and investigated the risk of bias that may result from each NOS domain.

Data analysis

We described the quality scores using the range and median (with corresponding 25th percentile [p25] and 75th percentile [p75]) and counts (%).

In order to test the association between study quality and two-year journal impact factor measured in 2013 (continuous variable), we applied Spearman's rank correlation coefficient; for the association with other study characteristics (categorical variables), we applied Mann-Whitney U test (variables with 2 categories) or Kruskal-Wallis H test (variables with ≥ 3 categories; with the Dunn's test for pairwise comparisons).

Data was analyzed using SPSS version 21. Statistical significance was set at alpha level 0.05.

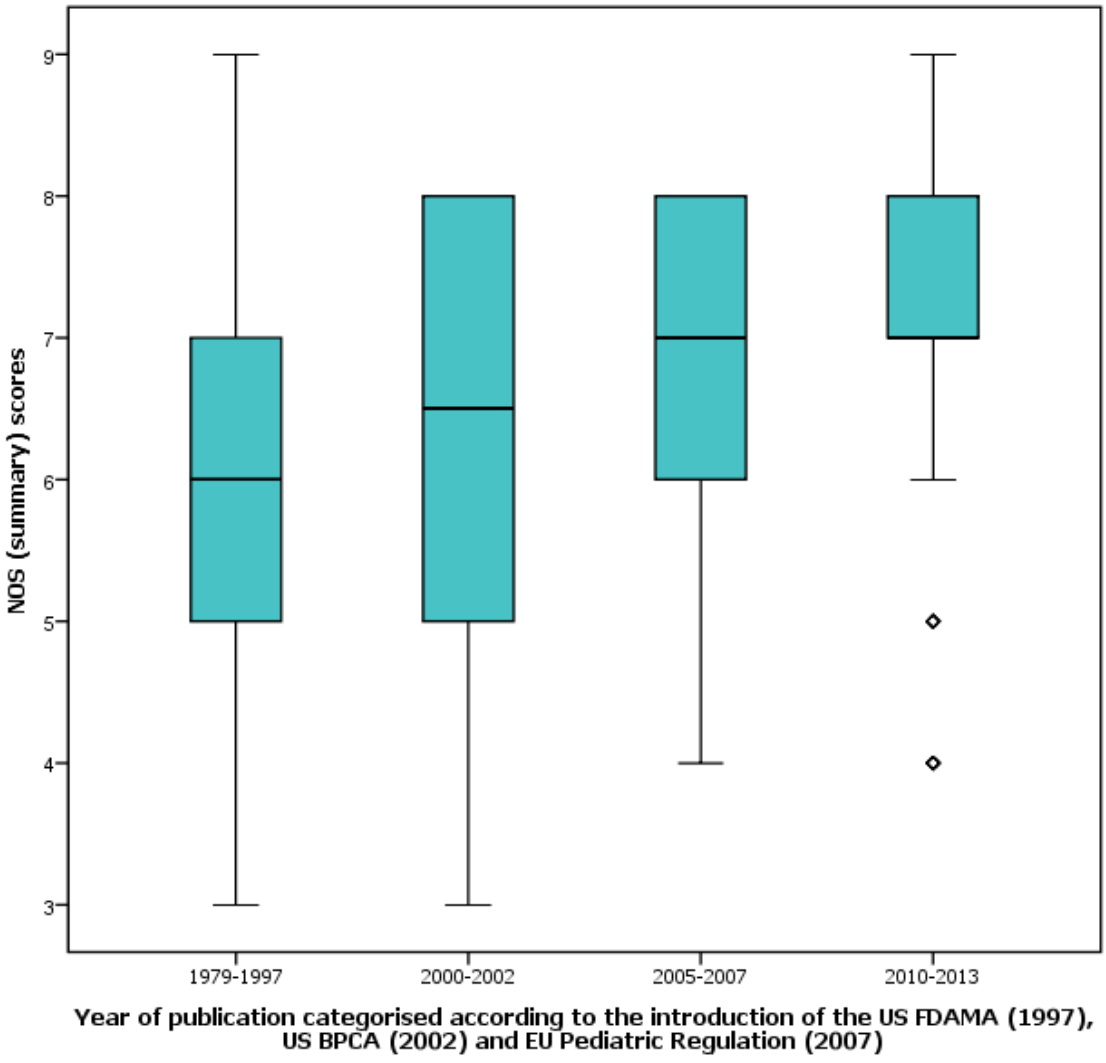
Results

Inter-rater concordance was 90.0%.

Considering 259 studies (only the primary design for studies applying multiple designs), the quality scores ranged from 1.0 to 9.0 (the range of possible scores goes from 0 through 9.0) with a median of 7.0 (p25=6.0; p75=8.0).

Out of 259 studies, only 6 (2.3%) attained the highest possible quality (score=9.0), 5 (83.3%) of which investigated vaccines exclusively. Considering the 5 studies, 2 (40.0%) were self-controlled case series (SCCS), were publicly funded, utilized retrospectively collected secondary data and originated from North America. One each was published in 2008 and 2011, both in pediatric specialty journals with 2013 two-year impact factor 5.3 and 4.2 respectively. In contrast, the 2 (0.8%) lowest-quality studies (score=1.0) assessed drugs exclusively. The source of funding for both studies was unclear; one each was a cohort or case control study with 2013 two-year journal impact factor 0 and 0.9 respectively. However, the later study (like the highest scoring studies) utilized retrospectively collected secondary data and was published recently (2009) in North America, in a pediatric specialty journal.

As seen in figure 1, the quality of studies apparently improved over time; of note, studies published from 2010 (median score=6.8; p25=7.0; p75=8.0) seemed better than those published from 1979 to 1997, confirmed by a statistically significant test (Dunn's p-value<0.01). Compared to previous years, summary quality scores for studies published between 2010 and 2013 appeared to fall within a narrower range.



Note: NOS=Newcastle-Ottawa scale; FDAMA=US FDA Modernization Act; BPCA=Best Pharmaceuticals for children's act; EU=European Union

Figure 1: Evolution of summary quality scores

North American and European studies (median score=7.0; p25=6.0; p75=8.0) were better than those from other continents although the difference in quality was statistically significant for only the former (Dunn's p-value=0.03). Studies that received only public or private funding showed similar quality but each type of study was better than those benefitting from both funding sources simultaneously. See table 1 for further details.

Table 1: Relationship between general characteristics and quality of 259 pediatric pharmacoepidemiological safety studies

Characteristic	Number of studies (%)	Summary NOS[a] score			p-value[b]
		25th percentile	Median	75th percentile	
Calendar year of publication[c]					**0.01**
1979-1997	35 (13.5)	5.0	6.0	7.0	
2000-2002	26 (10.0)	5.0	6.5	8.0	
2005-2007	90 (34.7)	6.0	7.0	8.0	
2010-2013	35 (13.5)	6.8	7.0	8.0	
Continent of the corresponding author					**0.04**
North America	149 (57.5)	6.0	7.0	8.0	
Europe	90 (34.3)	6.0	7.0	8.0	
Asia	11 (4.2)	4.0	6.0	8.0	
Others	9 (3.5)	5.0	6.0	7.0	
Type of journal					0.30
Pediatric specialty	84 (32.4)	6.0	7.0	8.0	
Pharmacology/pharmacoepidemiology	30 (11.6)	6.0	7.0	8.0	
General medical[d]	39 (15.1)	6.0	7.0	8.0	
Others[e]	106 (40.9)	6.0	7.0	8.0	
Funding sources					**<0.01**
Public	91 (35.1)	6.0	7.0	8.0	
Private	47 (18.1)	6.0	7.0	8.0	
Public and private	26 (10.0)	5.8	6.5	7.0	
No funding	7 (2.7)	6.0	7.0	7.0	
Funding not reported	88 (34.0)	5.0	6.0	7.0	

[a] Newcastle Ottawa scale;

[b] Derived from either Kruskal Wallis H or Mann Whitney U test;

[c] The proportions do not add up to 100% because we excluded studies that were published during the years 1998, 1999, 2003, 2004, 2008 and 2009 in order to allow for possible impact of the drug legislations;

[d] Refers to journals that publish wide variety of medical topics (irrespective of specialty);

[e] Journals that do not fit into any of the specified categories i.e. PLOS ONE

The mode of data collection significantly impacted study quality (Kruskal Wallis p-value<0.01), studies utilizing retrospectively collected data were the best. Interestingly, the 176 (68.0%)

studies utilizing only secondary data (median score=7.0; p25=6.0; p75=8.0), most (159 [90.3%]) of which were published from 2000, were significantly better (Dunn's p-value<0.01) than those based on primary data exclusively. Neither the 2013 two-year impact factor (Spearman rank correlation p-value=0.19) nor the type of journals in which studies were published (Kruskal Wallis H p-value=0.30) was significantly associated with quality.

All the 4 case crossover studies attained 'quality score=8', 3 (75.0%) of the studies utilized retrospectively collected secondary data and were published from 2000. Considering all the designs (for studies with multiple designs), overall, SCCS studies (median score=7.0; p25=7.0; p75=8.0) were better than both cohort (Dunn's p-value<0.01) and case control (Dunn's p-value=0.01) studies. Child-specific studies did not differ (Mann Whitney U p-value=0.21) from those that also included adults. Vaccine-specific studies (median score=7.0; p25=6.0; p75=8.0) were better (Mann-Whitney U p-value<0.01) than drug-specific studies. See table 2 for further details.

Table 2: Relationship between the methodology and quality of 259 pediatric pharmacoepidemiological safety studies

Characteristic	Number of studies (%)	Summary NOS[a] score			p-value[b]
		25th percentile	Median	75th percentile	
Mode of data collection[c]					**<0.01**
Prospective	67 (25.9)	5.0	6.0	7.0	
Retrospective	171 (66.0)	6.0	7.0	8.0	
Both	18 (6.9)	5.0	6.0	8.0	
Type of data					**<0.01**
Primary data exclusively	57 (22.0)	4.5	6.0	7.0	
Secondary data exclusively	176 (68.0)	6.0	7.0	8.0	
Mixed data	26 (10.0)	5.0	7.0	8.0	
Study design(s) that was (were) utilized[d]					**<0.01**
Cohort	174 (67.2)	5.0	7.0	8.0	
Case control	73 (28.2)	6.0	7.0	8.0	
Self-controlled case series (SCCS)	30 (11.6)	7.0	7.0	8.0	
Study population					0.21
Children exclusively	175 (67.6)	6.0	7.0	8.0	
Children and adults	84 (32.4)	6.0	7.0	8.0	
Type of exposure[e]					**<0.01**
Drug	141 (54.4)	5.0	7.0	7.0	
Vaccine	115 (44.4)	6.0	7.0	8.0	

[a] Newcastle Ottawa scale;

[b] Derived from either Kruskal Wallis H or Mann Whitney U test;

[c] Does not include 3 studies (1.2%) for which the mode of data collection was unclear;

[d] The proportions do not add up to 100% because 4 studies that applied the case crossover design are not presented, some studies utilized multiple designs which were all considered;

[e] Three studies (1.2%) that evaluated both drugs and vaccines are excluded

As seen in figure 2, all the 174 cohort studies included exposed subjects that were representative of the source population but only 9 (7.9%) out of 114 drug studies and 9 (15.0%) out of 60 vaccine studies followed subjects for enough time to observe the outcomes of interest. Also, only 52 (45.6%) drug studies and 22 (36.7%) vaccine assessments demonstrated absence of the investigated outcomes prior to start of the study. As many as 57 (50.0%) drug and 19 (31.7%) vaccine studies indicated inadequate follow-up of subjects. For 2 (66.7%) out of the 3 described NOS items that suggested high risk of bias, drug (rather than vaccine) studies were more commonly implicated.

All the SCCS studies showed low risk of bias for all the NOS items except adequacy of follow-up for which only 7 (23.3%) studies demonstrated low risk of bias. Also, only 12 (40.0%) studies demonstrated absence of the investigated outcome prior to start of the study.

Fig 2: Risk of bias by question in 174 cohort (above) and 30 SCCS (below) studies, assessed using a modified cohort version of the Newcastle-Ottawa Scale (numbers within the green bar represent the number of studies with low risk of bias and the corresponding percentage)

Figure 3 shows that all the case control studies assessing vaccines showed low risk of bias relating to age differences between the cases and controls. However regarding the rate of non-response (exposure ascertainment) between cases and controls, only 11 (35.5%) drug and 18 (46.2%) vaccine assessments showed low risk of bias. Also, only 14 (35.9%) vaccine studies

defined controls as not experiencing the outcome of interest. Of note, none of the items comprising the NOS was favorably addressed by all the case control studies.

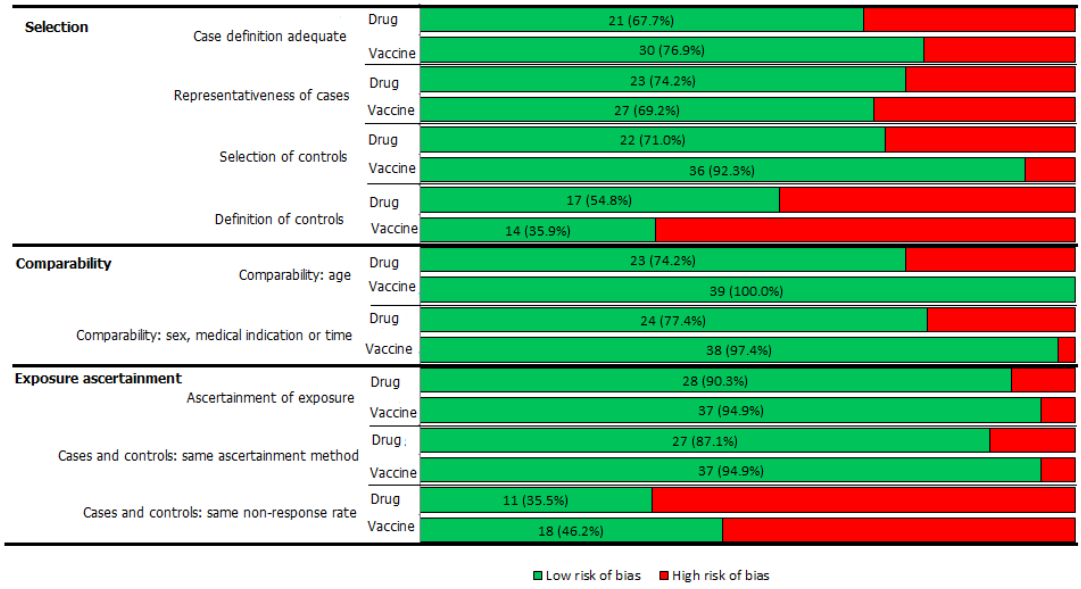


Fig 3: Risk of bias by question in 70 case control studies, assessed using a modified case-control version of the Newcastle-Ottawa Scale (numbers within the green bar represent the number of studies with low risk of bias and the corresponding percentage)

Note: Three case control studies that investigated both drugs and vaccines are not presented in the figure

Further details (per NOS question) of the quality scores (per design) derived for all the studies that we evaluated are presented in the *electronic supplementary material tables 1 to 4.*

Discussion

We present the quality of pediatric pharmacoepidemiological safety studies spanning 34 years. Generally the studies showed good quality. The 'best' studies were published from 2010 onwards, originated from North America and Europe, reported funding source to be public or private but not both and utilized retrospectively collected secondary data. The studies assessed vaccines, using the SCCS design. Cohort studies were most likely to be biased because prevalent cases of the investigated outcomes were not identified before the study started and because the subjects were not followed for enough time to observe occurrence of the outcome(s). Case control studies were most likely to be biased because controls were not

defined as not experiencing the outcome and because of differences in non-response rate (regarding ascertainment of the exposure) between the cases and controls.

The quality of studies may have been generally high, especially from 2010, because of the pediatric drug legislations that were introduced including the US Best Pharmaceuticals for Children Act (BPCA) (2002), and EU pediatric regulation (2007). Although the legislations were primarily aimed at stimulating clinical trials, pediatric pharmacoepidemiological studies were conducted as part of the BPCA. The increased focus on such studies may have resulted in the utilization of better methods particularly in Europe and North America. Specifically, SCCS studies were the best. The SCCS studies investigated only vaccines, perhaps accounting for the better quality of vaccine-specific studies compared to those that assessed only drugs. We recommend that where feasible, the SCCS design should be applied to more studies, also of drug assessments. That neither the journal impact factor nor type of journal in which the studies were published significantly impacted the quality is not surprising. Impact factor may not accurately indicate the quality of a journal or studies that are published by that journal [236]. Also, we utilized two-year impact factor measured in 2013, even though some studies were published as far back as 1979, possibly influencing our findings. Whether a study was conducted in only children or included both children and adults did not impact its quality, possibly because the same methods were applied to adult and pediatric studies. The need for researchers that are trained in pediatric pharmacoepidemiology specifically has been emphasized[199], providing such training is an aim of the Global Research in Pediatrics (GRIP).

The majority of retrospective studies utilizing only secondary data showed good quality possibly because most of them were published from the year 2000, a period during which extensive research effort has been focused on improving the quality and utilization of such data [237-240]. Detailed patient information is now recorded in many healthcare databases especially electronic health records (EHR), thereby improving the utility of secondary data when compared to primary data collection. When utilizing EHR data for cohort studies, it should be possible to exclude prevalent cases of the outcome before commencing the studies. However this was not our finding. This may have occurred because in some studies that we evaluated, the

researchers aimed to investigate new episodes of the outcomes of interest in subjects that previously experienced that outcome. For such assessments, stratified analysis may be performed, comparing measures of association between subjects with a history of the outcome and those without a history. It is possible that prevalent cases were indeed excluded but this was not reported by the authors. Regarding the case control studies, incomplete reporting may also account for the lack of definition of controls. The impact of reporting on quality (assessment) of research has been emphasized[197,241,242]. Recently the RECORD statement was introduced, aimed at encouraging better reporting of studies based on EHR specifically [233].

Documents have been published, designed to improve the design, conduct and reporting of pharmacoepidemiological studies[243,244], by shedding light on important aspects of such studies required for proper evaluation of their quality. Still, pediatric-specific aspects were not emphasized. For adequate assessment of pediatric studies specifically, detailed information about various characteristics is required including specific date of birth (rather than just birth year), gestational age at birth, birthweight/length, small for gestational age status, school performance, and mental health status[199]. Also, detailed information about drug doses, concomitant medication, indication for treatment and reasons for changes to dose or therapy is required. We recommend complete reporting of the aforementioned information in pediatric studies specifically.

Our findings show that the following factors were significantly associated with the quality of the studies that we evaluated: recently published studies, studies conducted in Europe and North America, utilization of retrospectively collected secondary data, and the application of the SCCS design. We propose that when appraising pediatric pharmacoepidemiological safety studies, clinicians (or other evaluators) with limited knowledge of pediatric pharmacoepidemiology may check if any of the aforementioned characteristics and/or design choices were applied. This may indicate that a study is of good quality. When there are many studies to be appraised, focusing on studies with these characteristics and/or design choices may make the evaluation more efficient. Also, appraising a study may be more efficient if the most likely sources of bias are known. Our findings show that for cohort studies, selection bias arising from non-ascertainment

of the outcome prior to study start occurs commonly. For case-control studies, unclear definition of controls and differential non-response rate (regarding ascertainment of exposure) between cases and controls are probable sources of bias.

The use of an appropriate tool is crucial for an adequate assessment of study quality. Yet, many available quality assessment tools do not include critical assessment elements (i.e. confounding by indication) that are relevant to pharmacoepidemiological safety studies specifically. Moreover, no existing tool was developed for pediatric studies specifically. Margulis et al. compared the NOS and RTI item bank, concluding that the latter allows a more complete quality assessment than the former but is more burdensome. Similarly, the 'Risk of Bias In Non-randomized Studies - of Interventions' (ROBINS-I) tool allows a more detailed and transparent assessment of study quality[245] but the NOS is easier to use. Also, the ROBINS-I tool is most relevant for cohort studies; although it can be modified for case-control studies, this may not be easy. Meanwhile the NOS has a separate version for case control studies specifically, its face and content validity is based on critical review of its items by many experts in the field, and it has been refined based on experience of its use in several projects. We recommend further research to develop a tool that can easily be utilized to evaluate pediatric studies specifically.

To our knowledge, this is the first study that evaluated the quality of pharmacoepidemiological safety studies in children specifically. We sought to evaluate vaccine studies separately, which is particularly important in children since they are frequently exposed to vaccines. Although the advantages of the SCCS design are known, to our knowledge no study previously quantified its impact on the quality of published studies.

Although the NOS is useful, it is not completely suited for assessing the quality of pharmacoepidemiological safety studies specifically. We modified the NOS to make it more applicable for the current assessment. Given the heterogeneity of outcomes that were investigated in the cohort studies that we evaluated, we defined minimum time intervals in order to assess whether follow-up was long enough to observe the outcomes in such (cohort) studies. However, such time intervals may not have been accurate for specific safety outcomes.

Conclusion

Published pediatric pharmacoepidemiological safety studies show good quality which has improved over time and is associated with geographical setting, design and conduct of the studies. Specifically, SCCS studies of vaccines are the best. By applying our findings, study evaluators may find it easier to assess published studies thereby enhancing their implementation in pediatric drug prescribing.

Appendix 1: Full search strategy

Search criteria for Embase.com

20. 'pediatrics'/exp OR 'child'/exp OR 'childhood'/exp OR 'newborn'/exp OR ('adolescent'/exp OR 'adolescence'/exp NOT ('adult'/exp OR adult*:ab,ti))

21. child*:ab,ti OR pediatric*:ab,ti OR paediatric*:ab,ti OR infant*:ab,ti OR infancy:ab,ti OR baby:ab,ti OR babies:ab,ti OR toddler*:ab,ti OR neonate*:ab,ti OR newborn*:ab,ti OR premature*:ab,ti OR adolescen*:ab,ti OR teenage*:ab,ti OR preschool:ab,ti OR school*:ab,ti OR neonat*:ab,ti

22. 1 or 2

23. 'risk'/de OR 'attributable risk'/de OR 'risk factor'/de OR 'risk benefit analysis'/de OR 'risk assessment'/de OR 'risk management'/de OR 'risk reduction'/de OR 'incidence'/de OR 'hazard ratio'/exp OR 'logistic regression analysis'/exp

24. odds:ab,ti OR 'logistic regression':ab,ti OR 'relative risk':ab,ti OR incidence:ab,ti OR prevalence:ab,ti OR (hazard* NEAR/3 ratio*):ab,ti OR 'safety assessment':ab,ti OR (risk NEAR/3 (ratio OR attribut* OR differen* OR assess* OR adjust* OR analy* OR relativ* OR factor* OR manag* OR reduc*)):ab,ti

25. 4 or 5

26. 'drug toxicity and intoxication'/exp OR 'adverse drug reaction'/exp OR 'drug'/exp/dd_ae OR ('side effect'/exp OR 'adverse outcome'/exp AND ('drug'/exp OR 'drug therapy'/exp OR 'vaccine'/exp OR 'adjuvant'/exp OR 'immunization'/exp)) OR 'drug safety'/de

27. ((pharmacol* OR pharmaceut* OR medication* OR medicine* OR drug* OR pharmacotherap* OR medicament* OR 'medicinal product' OR vaccin* OR immunizat* OR immunisat* OR adjuvant* OR treatment* OR therap*) NEAR/6 (safet* OR toler* OR intoler* OR toxic* OR intoxic* OR react* OR aftereffect* OR fatal* OR 'side effect' OR 'side effects' OR adverse)):ab,ti OR pharmacotox*:ab,ti OR (adverse NEAR/3 (event* OR reaction* OR effect* OR outcome)):ab,ti

28. 7 or 8

29. 'epidemiology'/de OR 'pharmacoepidemiology'/de OR 'cohort analysis'/de OR 'observational study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'longitudinal study'/de

30. epidemiol*:ab,ti OR pharmacoepidemiol*:ab,ti OR cohort*:ab,ti OR (follow NEXT/1 up*):ab,ti OR observation*:ab,ti OR retrospectiv*:ab,ti OR prospectiv*:ab,ti

31. 10 or 11

32. 'comparative study'/de OR 'comparative toxicology'/de OR 'drug comparison'/exp OR 'controlled study'/de OR 'case control study'/exp

33. control*:ab,ti OR compar*:ab,ti OR referen*:ab,ti OR match*:ab,ti OR nested:ab,ti OR ('self controlled' NEXT/1 serie*):ab,ti OR 'case cross over':ab,ti OR 'case centered':ab,ti OR 'case coverage':ab,ti OR 'case cohort':ab,ti

34. 13 or 14

35. 12 and 15

36. 3 and 6 and 9 and 16

37. [article]/lim NOT ('pregnancy'/exp OR pregnan*:ab,ti OR fetus:ab,ti OR fetal:ab,ti OR foetus:ab,ti OR foetal:ab,ti) NOT ('clinical trial'/exp OR 'systematic review'/exp OR 'randomized controlled trial'/de OR 'randomization'/de) NOT ([animals]/lim NOT [humans]/lim)

38. 17 and 18

Search criteria for Medline (via OvidSP)

22. exp pediatrics/ or exp child/ or exp infant/ or (adolescent/ not (exp adult/ or adult*.ab,ti.))

23. (child* or pediatric* or paediatric* or infant* or infancy or baby or babies or toddler* or neonate* or newborn* or premature* or adolescen* or teenage* or preschool or school* or neonat*).ab,ti.
24. 1 or 2

25. exp risk/ or "Odds Ratio"/ or incidence/

26. (Odds or "logistic regression" or "relative risk" or incidence or prevalence or (hazard* adj3 ratio*) or "safety assessment" or (risk adj3 (ratio or attribut* or differen* or assess* or adjust* or analy* or relativ* or factor* or manag* or reduc*))).ab,ti.

27. 4 or 5

28. exp "drug toxicity"/ or exp Pharmaceutical Preparations/ae or exp drug therapy/ae or exp vaccines/ae or exp immunization/ae

29. (((pharmacol* or pharmaceut* or medication* or medicine* or drug* or pharmacotherap* or medicament* or "medicinal product" or vaccin* or immunizat* or immunisat* or adjuvant* or treatment* or therap*) adj6 (safet* or toler* or intoler* or toxic* or intoxic* or react* or aftereffect* or fatal* or "side effect" or "side effects" or adverse)) or pharmacotox* or (adverse adj3 (event* or reaction* or effect* or outcome))).ab,ti.

30. 7 or 8

31. "epidemiology"/ or epidemiology.xs. or pharmacoepidemiology/ or exp "Epidemiologic Studies"/ or observation/

32. (epidemiol* or pharmacoepidemiol* or Cohort* or (FOLLOW adj up*) or observation* or retrospectiv* or prospectiv*).ab,ti.

33. 10 or 11

34. "comparative study".pt. or "drug comparison"/ or "controlled study"/ or "case control study"/

35. (control* or compar* or referen* or match* or nested or ("self controlled" adj serie*) or "case cross over" or "case centered" or "case coverage" or "case cohort").ab,ti.

36. 13 or 14

37. 12 and 15

38. 3 and 6 and 9 and 16

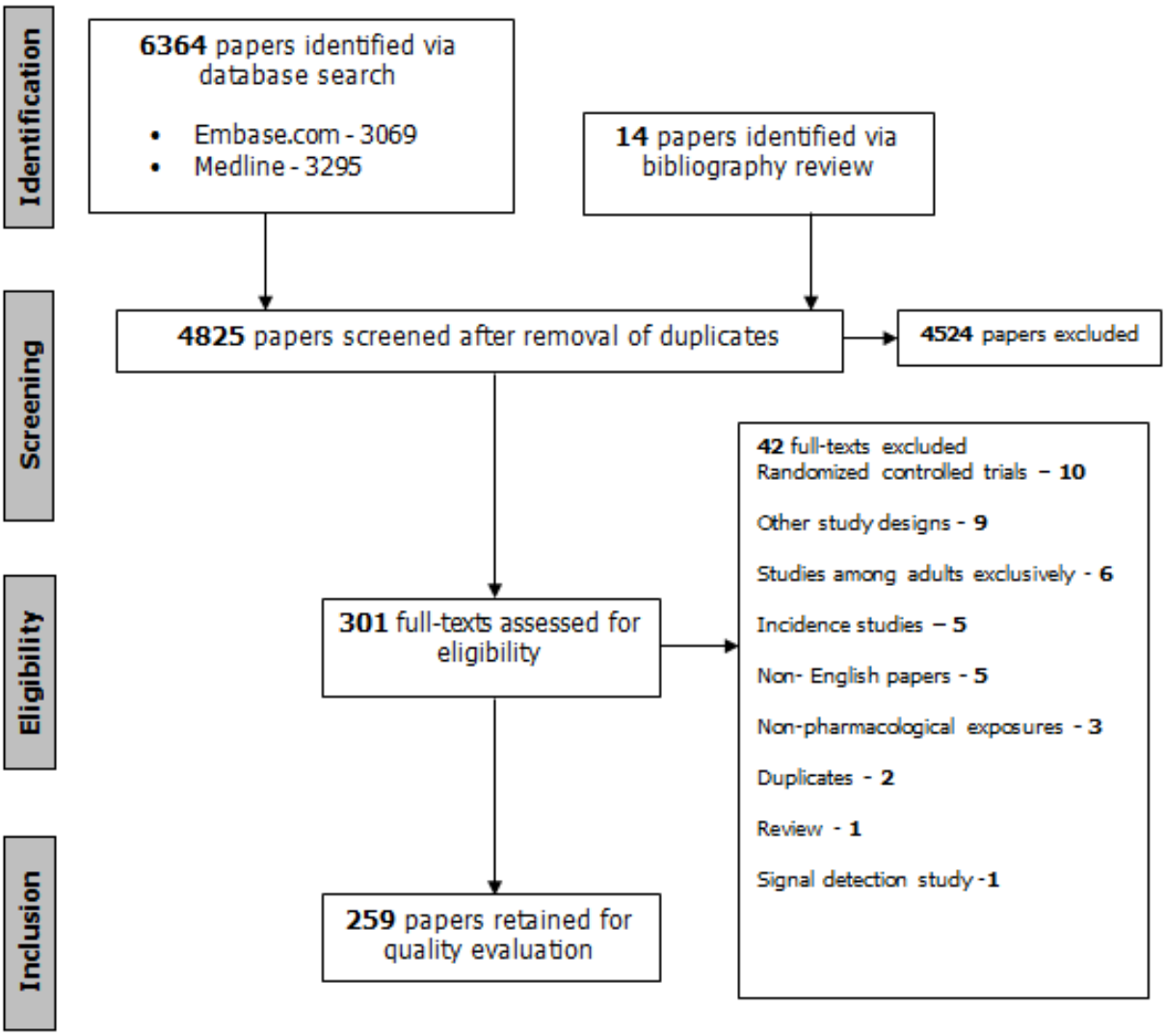
39. Limit 17 to Journal Article

40. Limit 18 to humans

41. 19 not (pregnancy/ or (pregnan* or fetus or fetal or foetus or foetal).ab,ti.)

42. 20 not (clinical trial/ or systematic review/ or randomized controlled trial/ or randomization/)

Appendix 2: Flow chart depicting the selection of relevant papers



Appendix 3: Modified Newcastle-Ottawa Scale

A. COHORT STUDIES (Scale)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be awarded for comparability

Selection

1. Representativeness of the exposed cohort

a. truly representative of the average _____ (describe) in the community* (if in general population with claims/medical records and no exclusion criteria)
b. somewhat representative of the average _____ in the community* (if in general population with claims/medical records and exclusion criteria)
c. selected group of users e.g. nurses, volunteers (e.g. from setting, if only in hospital whereas drug is also used outpatient)
d. no description of the derivation of the cohort

2. Selection of the non-exposed cohort

a. drawn from the same community as the exposed cohort*
b. drawn from a different source
c. no description of the derivation of the non-exposed cohort

3. Ascertainment of exposure

a. secure record (e.g. surgical records) *
b. structured interview *
c. written self-report
d. no description

4. Demonstration that outcome of interest was not present at start of study

a. yes *
b. no

Comparability

5. Comparability of cohorts on the basis of the design or analysis

a. study controls for age (select the most important factor) *****

b. study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.) (sex and medical indication)

Exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Outcome

6. Assessment of outcome

a. independent blind assessment *****
b. record linkage *****
c. self-report
d. no description

7. Was follow-up long enough for outcomes to occur

a. yes (select an adequate follow up period for outcome of interest) *****
b. no

8. Adequacy of follow up of cohorts (please assess whether fixed (reporting cumulative incidence with persons as denominator) or dynamic cohort (person-time as denominator))

a. complete follow up in fixed cohort- all subjects accounted for *****
b. subjects lost to follow up in fixed cohort unlikely to introduce bias - small number lost - > __80%__ % (select an adequate %) follow up, or description provided of those lost) *****
c. dynamic cohort study *
d. follow up rate < ____% (select an adequate %) and no description of those lost in fixed cohort
e. no statement in fixed cohort

B. CASE-CONTROL

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1. **Is the case definition adequate?**
    a. yes, with independent validation *
    b. yes, e.g. record linkage or based on self-reports
    c. no description

2. **Representativeness of the cases**
    a. consecutive or obviously representative series of cases *
    b. potential for selection biases or not stated

3. **Selection of Controls**
    a. community controls *
    b. hospital controls
    c. no description

4. **Definition of Controls**
    a. no history of disease (endpoint) *
    b. no description of source

Comparability

5. **Comparability of cases and controls on the basis of the design or analysis**
    a. study controls for age (Select the most important factor.) *
    b. study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.) time, sex, indication

Cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Exposure

6. Ascertainment of exposure

a. secure record (e.g. surgical records, medical charts) *
b. structured interview where blind to case/control status * or dispensing databases or prescription data or medical records *
c. interview not blinded to case/control status
d. written self-report
e. no description

7. Same method of ascertainment for cases and controls

a. yes *
b. no

8. Non-Response rate

a. Similar response rate for both cases and controls *
b. non respondents described
c. rate different and no designation
d. non-response rate not reported

Electronic Supplementary Material

Table 1: Quality scores derived for 174 cohort studies, assessed using a modified cohort version of the Newcastle Ottawa scale (NOS)

S/N	First author	Year	Title	Investigated exposure	NOS Questions									Total NOS score
					Q1	Q2	Q3	Q4	Q5a	Q5b	Q6	Q7	Q 8	
1	Zangwill K.M.	2008	A Population-Based, Postlicensure Evaluation of the Safety of a Combination Diphtheria, Tetanus, Acellular Pertussis, Hepatitis B, and Inactivated Poliovirus Vaccine in a Large Managed Care Organization	vaccine	yes	no	yes	no	yes	yes	yes	no	no	**5**
2	Young H. A.	2008	Thimerosal exposure in infants and neurodevelopmental disorders: An assessment of computerized medical records in the Vaccine Safety Datalink	vaccine	yes	yes	yes	no	yes	no	yes	no	yes	**6**
3	Winterstein A. G.	2012	Cardiovascular safety of central nervous system stimulants in children and adolescents: population based cohort study	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
4	Winterstein A. G.	2009	Cardiac Safety of Methylphenidate Versus Amphetamine Salts in the Treatment of ADHD	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
5	Winterstein A. G.	2007	Cardiac Safety of Central Nervous System Stimulants in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
6	The Victorian Infant Collaborative study group	2000	Postnatal corticosteroids and sensorineural outcome at 5 years of age	drug	yes	no	yes	no	no	no	yes	no	no	**3**
7	Verstraeten T.	2003	Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases	vaccine	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
8	Velentgas P.	2012	Risk of Guillain–Barré syndrome after meningococcal conjugate vaccination	vaccine	yes	yes	yes	no	no	no	yes	no	yes	**5**
9	Van Staa T. P.	2004	Are inhaled corticosteroids associated with an increased risk of fracture in children?	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**

10	Van Dijken T. D.	2011	Development of inflammatory bowel disease in patients with juvenile idiopathic arthritis treated with etanercept	drug	yes	no	yes	yes	no	no	yes	no	yes	**5**
11	Van Der Linden P. D.	1998	Skin Reactions to Antibacterial Agents in General Practice	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
12	Vainionpaa L.	1995	Vincristine Therapy for Children With Acute Lymphoblastic Leukemia Impairs Conduction in the Entire Peripheral Nerve	drug	yes	no	no	no	yes	yes	no	no	no	**3**
13	Tyczynski J. E.	2012	Safety assessment of an anti-obesity drug (sibutramine): a retrospective cohort study.	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
14	Tutar H. E.	1999	Effects of cisapride on ventricular repolarization in children	drug	yes	no	no	no	no	no	no	no	no	**1**
15	Tucker M. A.	1987	Leukemia After Therapy With Alkylating Agents for Childhood Cancer	drug	yes	no	no	no	no	no	yes	no	yes	**3**
16	Tseng H. F.	2013	Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children	vaccine	yes	yes	yes	no	no	no	yes	no	yes	**5**
17	Tse A.	2012	Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
18	Toback S. L.	2013	A postlicensure evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 24–59 months of age	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
19	Thorp A. W.	2009	Ketamine-Associated Vomiting. Is it Dose-Related?	drug	yes	yes	yes	no	yes	no	yes	no	no	**5**
20	Terrin G.	2012	Ranitidine is Associated With Infections, Necrotizing Enterocolitis, and Fatal Outcome in Newborns	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
21	Ter Wolbeek M.	2013	Early life intervention with glucocorticoids has negative effects on motor development and neuropsychological function in 14—17 year-old adolescents	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
22	Tahara T.	2013	Safety of oseltamivir in infants less than one year old: Prospective surveillance during the 2004–2005	drug	yes	yes	yes	no	no	no	yes	no	no	**4**

			influenza season in Japan										
23	Szer I. S.	1991	Paucity of renal complications associated with nonsteroidal antiinflammatory drugs in children with chronic arthritis	drug	yes	yes	yes	yes	no	no	yes	no	no	**5**
24	Szekely A.	2008	Aprotinin and renal dysfunction after pediatric cardiac surgery	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
25	Sun Y.	2012	Risk of Febrile Seizures and Epilepsy After Vaccination With Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus, and Haemophilus Influenzae Type b	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
26	Sugawara T.	2009	Diarrhea as a Minor Adverse Effect Due to Oral Polio Vaccine	vaccine	yes	yes	no	no	yes	yes	no	no	no	**4**
27	Stohr W.	2006	Comparison of epirubicin and doxorubicin cardiotoxicity in children and adolescents treated within the German Cooperative Soft Tissue Sarcoma Study (CWS)	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
28	Staffa J. A.	1995	Risk of Selected Serious Cardiac Events Among New Users of Antihistamines	drug	yes	yes	yes	yes	no	no	yes	no	no	**5**
29	Spycher B. D.	2009	Routine Vaccination Against Pertussis and the Risk of Childhood Asthma: A Population-Based Cohort Study	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
30	Spitzer T. R.	1994	Etoposide in combination with cyclophosphamide and total body irradiation or busulfan as conditioning for marrow transplantation in adults and children	drug	yes	yes	yes	no	no	no	yes	no	yes	**5**
31	Shui I. M.	2012	Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants	vaccine	yes	yes	yes	yes	yes	no	yes	no	yes	**7**
32	Seagroatt V.	2003	Crohn's disease, ulcerative colitis, and measles vaccine in an English population, 1979–1998	vaccine	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
33	Schneeweiss S.	2009	Topical Treatments with Pimecrolimus, Tacrolimus and Medium- to High-Potency Corticosteroids, and Risk of Lymphoma	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
34	Schneeweiss S.	2010	Comparative Safety of Antidepressant Agents for Children and Adolescents	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**

			Regarding Suicidal Acts										
35	Schechter T.	2012	Safety of anticoagulants in children with arterial ischemic stroke	drug	yes	yes	yes	no	no	no	yes	no	no	**4**
36	Roze J. C.	2008	Prolonged Sedation and/or Analgesia and 5-Year Neurodevelopment Outcome in Very Preterm Infants	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
37	Roke Y.	2012	Risk of Hyperprolactinemia and Sexual Side Effects in Males 10–20 Years Old Diagnosed with Autism Spectrum Disorders or Disruptive Behavior Disorder and Treated with Risperidone	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
38	Roelofzen J. H. J.	2010	No Increased Risk of Cancer after Coal Tar Treatment in Patients with Psoriasis or Eczema	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
39	Ritwik P.	2013	Post-sedation Events in Children Sedated for Dental Care	drug	yes	yes	yes	no	no	no	no	no	yes	**4**
40	Risnes K. R.	2011	Antibiotic Exposure by 6 Months and Asthma and Allergy at 6 Years: Findings in a Cohort of 1,401 US Children	drug	yes	yes	no	yes	no	no	no	no	no	**3**
41	Quinn C. T.	1997	Elevation of Homocysteine and Excitatory Amino Acid Neurotransmitters in the CSF of Children Who Receive Methotrexate for the Treatment of Cancer	drug	yes	yes	no	no	no	no	yes	no	yes	**4**
42	Pratt C. M.	1994	Risk of Developing Life-Threatening Ventricular Arrhythmia Associated with Terfenadhe in Comparison with Over-the-Counter Antihistamines, Mwprofen and CIemastine	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
43	Petousis-Harris H.	2012	Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: The importance of routine active safety surveillance	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
44	Pallavicini F. B.	2010	Tumour necrosis factor antagonist therapy and cancer development: Analysis of the LORHEN registry	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
45	Olfson M.	2012	Tumour recurrence and enlargement in patients with craniopharyngioma with and without GH replacement therapy during more than 10 years of	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**

			follow-up										
46	Nohynek H.	2012	AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland	vaccine	yes	yes	yes	no	no	no	yes	no	yes	**5**
47	Niu M. T.	1998	Comparative Safety of Two Recombinant Hepatitis B Vaccines in Children: Data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD)	vaccine	yes	yes	yes	no	yes	no	yes	no	yes	**6**
48	Neudorfer M.	2012	Ocular Adverse Effects of Systemic Treatment With Isotretinoin	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
49	Nelson J. C.	2013	Adapting Group Sequential Methods to Observational Postlicensure Vaccine Safety Surveillance: Results of a Pentavalent Combination DTaP-IPV-Hib Vaccine Safety Study	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
50	Needelman H.	2008	Effects of Postnatal Dexamethasone Exposure on the Developmental Outcome of Premature Infants	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
51	Myleus A.	2012	Early Vaccinations Are Not Risk Factors for Celiac Disease	vaccine	yes	yes	yes	yes	no	no	yes	no	yes	**6**
52	Mustieles C.	1995	Male Gonadal Function After Chemotherapy in Survivors of Child hood Malignancy	drug	yes	no	yes	yes	no	no	yes	no	yes	**5**
53	Mulheran M.	2001	Occurrence and Risk of Cochleotoxicity in Cystic Fibrosis Patients Receiving Repeated High-Dose Aminoglycoside Therapy	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
54	Mrozek-Budzyn D.	2013	Measles, mumps and rubella (MMR) vaccination has no effect on cognitive development in children – The results of the Polish prospective cohort study	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
55	Morris D. L.	2000	Measles Vaccination and Inflammatory Bowel Disease: A National British Cohort Study	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
56	Mikaeloff Y.	2007	Hepatitis B vaccine and risk of relapse after a first childhood episode of CNS inflammatory demyelination	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
57	McKee M. R.	2008	Oral Analgesia Before Pediatric Ketamine Sedation is not Associated with an Increased Risk of Emesis and	drug	yes	yes	yes	no	no	yes	yes	no	yes	**6**

			Other Adverse Events											
58	McIntyre R. S.	2008	Metabolic and Cardiovascular Adverse Events Associated With Antipsychotic Treatment in Children and Adolescents	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
59	McCarthy N. L.	2013	Evaluating the safety of influenza vaccine using a claims-basedhealth system	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
60	McAlvin B.	2007	Routine Immunizations and Adverse Events in Infants With Single-Ventricle Physiology	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
61	Martin A.	2000	Risperidone-Associated Weight Gain in Children and Adolescents: A Retrospective Chart Review	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
62	Maraqa N. F.	2002	Higher Occurrence of Hepatotoxicity and Rash in Patients Treated with Oxacillin, Compared with Those Treated with Nafcillin and Other Commonly Used Antimicrobials	drug	yes	yes	yes	no	no	no	yes	no	no	**4**
63	Main M. L.	2008	Acute Mortality in Hospitalized Patients Undergoing Echocardiography With and Without an Ultrasound Contrast Agent (Multicenter Registry Results in 4,300,966 Consecutive Patients)	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
64	Madsen K. M.	2002	A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
65	Loughlin J.	2012	Postmarketing Evaluation of the Short-term Safety of the Pentavalent Rotavirus Vaccine	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
66	Loughlin J.	2010	Tegaserod and the Risk of Cardiovascular Ischemic Events: An Observational Cohort Study	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
67	Lindqvist H.	2013	Folinic Acid Supplementation in Higher Doses is Associated with Graft Rejection in Pediatric Hematopoietic Stem Cell Transplantation	drug	yes	yes	yes	no	no	yes	yes	no	no	**5**
68	Leyvi G.	2011	A Comparison of the Effect of Aprotinin and -Aminocaproic Acid on Renal Function in Children Undergoing Cardiac Surgery	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
69	Leonard C. E.	2011	Antidepressants and the risk of sudden cardiac death and ventricular	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**

			arrhythmia										
70	Lee J.	2006	Frequency of apnea, bradycardia, and desaturations following first diphtheria-tetanus-pertussis-inactivated polio-Haemophilus influenzae type B immunization in hospitalized preterm infants	vaccine	yes	yes	yes	no	yes	yes	yes	no	no	**6**
71	Lee J. S.	2008	Comparison of Methohexital and Propofol Use in Ambulatory Procedures in Oral and Maxillofacial Surgery	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
72	Lawrence R.	1988	The Risk of Zoster after Varicella Vaccination in Children with Leukemia	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
73	Lackmann G. M.	2004	Comparative investigation of the safety of hexavalent vaccines for primary scheduled infant immunizations in Germany over a time period of 2 years	vaccine	yes	yes	yes	no	no	no	no	no	no	**3**
74	Kuppala V. S.	2011	Prolonged Initial Empirical Antibiotic Treatment is Associated with Adverse Outcomes in Premature Infants	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
75	Krawczynska H.	1979	Goitre and hypothyroidism in children and adolescents during long-term anticonvulsive therapy	drug	yes	no	yes	no	no	no	yes	no	no	**3**
76	Kramarz P.	2000	Does Influenza Vaccination Exacerbate Asthma? Analysis of a Large Cohort of Children With Asthma	vaccine	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
77	Klein N. P.	2010	Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
78	Klein N. P.	2010	Post-Marketing Safety Evaluation of a Tetanus Toxoid, Reduced Diphtheria Toxoid and 3-Component Acellular Pertussis Vaccine Administered to a Cohort of Adolescents in a United States Health Maintenance Organization	vaccine	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
79	Klein N. P.	2012	Safety of Quadrivalent Human Papillomavirus Vaccine Administered Routinely to Females	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
80	Kim J. Y.	2009	Effects of highly active antiretroviral therapy (HAART) on cholesterol in HIV-1 infected children: a	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**

			retrospective cohort study											
81	Khan R. A.	2009	Effects of Olanzapine and Risperidone on Metabolic Factors in Children and Adolescents: A Retrospective Evaluation	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
82	Kemp T.	1997	Is infant immunization a risk factor for childhood asthma or allergy?	vaccine	yes	yes	yes	no	yes	yes	yes	no	no	**6**
83	Katayama H.	1990	Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media.	drug	yes	yes	yes	no	no	no	yes	no	yes	**5**
84	Karvonen M.	1999	Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study	vaccine	yes	yes	no	no	no	no	yes	no	yes	**4**
85	Karsies T. J.	2010	Thrombotic Risk of Recombinant Factor Seven in Pediatric Cardiac Surgery: A Single Institution Experience	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
86	Karikas G. A.	2006	Lipids, Lipoproteins, Apolipoproteins, Selected Trace Elements and Minerals in the Serum of Children on Valproic Acid Monotherapy	drug	yes	no	yes	no	yes	no	yes	no	no	**4**
87	Karavitaki N.	2006	GH replacement does not increase the risk of recurrence in patients with craniopharyngioma	drug	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
88	Judkins J.H.	1996	Intraoperative Ketorolac and Posttonsillectomy Bleeding	drug	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
89	Johnson C. C.	2005	Antibiotic exposure in early infancy and risk for childhood atopy	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
90	Jerrell J. M.	2010	Neurological and Cardiovascular Adverse Events Associated with Antimanic Treatment in Children and Adolescents	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
91	Jerrell J. M.	2010	Adverse events associated with psychotropic treatment in African American children and adolescents.	drug	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
92	Jerrell J. M.	2010	Neuroendocrine-Related Adverse Events Associated with Antidepressant Treatment in Children and Adolescents	drug	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
93	Jerrell J. M.	2010	Metabolic, Digestive, and Reproductive Adverse Events Associated With Antimanic Treatment in Children and Adolescents: A Retrospective Cohort	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**

			Study											
94	Jerrell J. M.	2009	Cardiovascular and neurological adverse events associated with antidepressant treatment in children and adolescents	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
95	Jerrell J. M.	2008	Neurological Adverse Events Associated with Antipsychotic Treatment in Children and Adolescents	drug	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
96	Jerrell J. M.	2009	Hyperprolactinemia-related adverse events associated with antipsychotic treatment in children and adolescents	drug	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
97	Jerrell J. M.	2008	Adverse events in children and adolescents treated with antipsychotic medications.	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
98	Jacobsen S. J.	2009	Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting	vaccine	yes	no	yes	yes	yes	yes	yes	yes	yes	**8**
99	Jackson L. A.	2013	Vaccination Site and Risk of Local Reactions in Children 1 Through 6 Years of Age	vaccine	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
100	Iftikhar U.	2013	Risk of hearing loss in children exposed to gentamicin for the treatment of sepsis in young infancy: A community based cohort study in Pakistan	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
101	Hviid A.	2003	Association Between Thimerosal-Containing Vaccine and Autism	vaccine	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
102	Hviid A.	2009	Antibiotic use and intussusception in early childhood	drug	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
103	Huerta C.	2002	Risk of clinical blood dyscrasia in a cohort of antibiotic users	drug	yes	yes	yes	yes	no	no	yes	yes	yes	**7**
104	Huang W. T.	2010	Lack of Association Between Acellular Pertussis Vaccine and Seizures in Early Childhood	vaccine	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
105	Hornik C. P.	2013	Adverse Events Associated With Meropenem Versus Imipenem/Cilastatin Therapy in a Large Retrospective Cohort of Hospitalized Infants	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
106	Horen B.	2002	Adverse drug reactions and off-label drug use in paediatric outpatients	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
107	Henderson J.	1999	Pertussis vaccination and wheezing illnesses in young children:	vaccine	yes	yes	yes	no	yes	yes	no	no	no	**5**

			prospective cohort study											
108	Harrison C. N.	1999	High-dose BEAM chemotherapy with autologous haemopoietic stem cell transplantation for HodgkinÕs disease is unlikely to be associated with a major increased risk of secondary MDS/AML	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
109	Hamed S. A.	2009	The risk of asymptomatic hyperammonemia in children with idiopathic epilepsy treated with valproate: Relationship to blood carnitine status	drug	yes	no	yes	yes	yes	yes	yes	no	no	**6**
110	Hall G. C.	2004	Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice.	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
111	Hall A. S.	2003	The effects of corticosteroids on behavior in children with nephrotic syndrome	drug	yes	yes	yes	yes	no	no	no	no	yes	**5**
112	Guthrie S. O.	2004	Initial Dosing of Inhaled Nitric Oxide in Infants with Hypoxic Respiratory Failure	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
113	Greene S. K.	2013	Risk of adverse events following oseltamivir treatment in influenza outpatients, Vaccine Safety Datalink Project, 2007–2010	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
114	Greene S. K.	2010	Near Real-Time Surveillance for Influenza Vaccine Safety: Proof-of-Concept in the Vaccine Safety Datalink Project	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
115	Geier D. A.	2010	Thimerosal exposure & increasing trends of premature puberty in the vaccine safety datalink	vaccine	yes	yes	yes	no	yes	yes	yes	no	no	**6**
116	Geier D. A.	2005	A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis	vaccine	yes	yes	yes	no	yes	yes	yes	no	no	**6**
117	Gee J.	2011	Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
118	Gasse C.	2009	Preadmission use of SSRIs alone or in combination with NSAIDs and 30-day mortality after peptic ulcer bleeding	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**

119	Garcia Rodriguez L. A.	1996	Risk of Acute Liver Injury Associated With the Combination of Amoxicillin and Clavulanic Acid	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
120	France E. K.	2008	Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	yes	**9**
121	Fosbol E. L.	2010	Cause-Specific Cardiovascular Risk Associated With Nonsteroidal Antiinflammatory Drugs Among Healthy Individuals	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
122	Fosbol E. L.	2009	Risk of Myocardial Infarction and Death Associated With the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Among Healthy Individuals: A Nationwide Cohort Study	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
123	Fleischhaker C.	2007	Weight gain associated with clozapine, olanzapine and risperidone in children and adolescents	drug	yes	yes	yes	yes	no	no	yes	yes	yes	**7**
124	Finer N. N.	1984	Vitamin E and Necrotizing Enterocolitis	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
125	Fine R.N.	2003	Adverse events with rhGH treatment of patients with chronic renal insufficiency and end-stage renal disease	drug	yes	yes	yes	no	no	no	yes	no	yes	**5**
126	Filippi L.	2010	Oral Topiramate in Neonates with Hypoxic Ischemic Encephalopathy Treated with Hypothermia: A Safety Study	drug	yes	yes	yes	yes	no	no	yes	no	no	**5**
127	Fang A. Y. W.	2013	The effect of sildenafil on retinopathy of prematurity in very preterm infants	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
128	Eriksen E. M.	2004	Lack of Association Between Hepatitis B Birth Immunization and Neonatal Death. A Population-Based Study From the Vaccine Safety Datalink Project	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
129	Enders J.	2006	Morphine-related apnoea in CPAP-treated preterm neonates	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
130	Drossou-Agakidou V.	2004	Use of ciprofloxacin in neonatal sepsis: lack of adverse effects up to one year	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
131	Donahue J. G.	2009	Varicella Vaccination and Ischemic Stroke in Children: Is There an Association?	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**

132	Dieleman J.	2011	Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe	vaccine	yes	yes	yes	no	yes	yes	yes	no	no	**6**
133	Delbe-Bertin L.	2013	Does rituximab induce hypogammaglobulinemia in patients with pediatric idiopathic nephrotic syndrome?	drug	yes	yes	yes	yes	yes	yes	yes	no	no	**7**
134	De Wals P.	2012	Risk of Guillain-Barre´ Syndrome Following H1N1 Influenza Vaccination in Quebec	vaccine	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
135	De Wals P.	2008	Risk of Guillain-Barre´ Syndrome following Serogroup C Meningococcal Conjugate Vaccine in Quebec, Canada	vaccine	yes	yes	yes	no	yes	no	yes	yes	yes	**7**
136	De Oliveira L. H.	2000	Vaccine-associated paralytic poliomyelitis: a retrospective cohort study of acute flaccid paralyses in Brazil.	vaccine	yes	yes	no	no	yes	yes	yes	no	no	**5**
137	De Bruin M. L.	2008	Treatment-related risk factors for premature menopause following Hodgkin lymphoma	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
138	Dayton J. D.	2011	Role of immunosuppression regimen in post-transplant lymphoproliferative disorder in pediatric heart transplant patients	drug	yes	yes	yes	no	no	no	yes	no	no	**4**
139	Davis R. L.	2004	Post-marketing evaluation of the short term safety of COMVAX	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
140	Davenport M. S.	2013	Effect of Abrupt Substitution of Gadobenate Dimeglumine for Gadopentetate Dimeglumine on Rate of Allergic-like Reactions	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
141	Dahllof G.	1997	Impact of conditioning regimens on salivary function, caries-associated microorganisms and dental caries in children after bone marrow transplantation. A 4-year longitudinal study	drug	yes	no	yes	yes	yes	yes	yes	no	no	**6**
142	Czaja A. S.	2013	Comparative safety of selective serotonin reuptake inhibitors among pediatric users with respect to adverse cardiac events	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
143	Cullinan P.	2004	Early prescriptions of antibiotics and the risk of allergic disease in adults: a	drug	yes	yes	yes	no	yes	no	yes	no	no	**5**

			cohort study										
144	Correll C. U.	2009	Cardiometabolic Risk of Second-Generation Antipsychotics During First-Time Use in Children and Adolescents	drug	yes	yes	yes	yes	no	no	yes	no	no	**5**
145	Cooper W. O.	2011	ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
146	Connor D. F.	2001	Neuroleptic-related dyskinesias in children and adolescents.	drug	yes	yes	yes	no	no	no	yes	no	no	**4**
147	Clark R. H.	2006	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	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
148	Center K. J.	2009	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.	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
149	Celedon J. C.	2002	Lack of Association between Antibiotic Use in the First Year of Life and Asthma, Allergic Rhinitis, or Eczema at Age 5 Years	drug	yes	yes	yes	no	yes	no	no	no	no	**4**
150	Casscells S. W.	2009	The association between oseltamivir use and adverse neuropsychiatric outcomes among TRICARE beneficiaries, ages 1 through 21 years diagnosed with influenza	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
151	Brehler R.	2000	Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections	drug	yes	yes	no	no	no	no	no	no	yes	**3**
152	Borgna-Pignatti C.	2006	Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**

153	Blumentals W. A.	2007	The Safety of Oseltamivir in Patients with Influenza: Analysis of Healthcare Claims Data from Six Influenza Seasons	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
154	Bloomgren G.	2012	Assessment of malignancy risk in patients with multiple sclerosis treated with intramuscular interferon beta-1a: retrospective evaluation using a health insurance claims database and postmarketing surveillance data	drug	yes	yes	yes	no	yes	yes	yes	no	no	**6**
155	Black S.	1999	Postmarketing evaluation of the safety and effectiveness of varicella vaccine	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
156	Bertolini P.	2004	Platinum Compound-Related Ototoxicity in Children. Long-Term Follow-Up Reveals Continuous Worsening of Hearing Loss	drug	yes	yes	yes	yes	no	no	yes	no	no	**5**
157	Belongia E. A.	2010	Real-Time Surveillance to Assess Risk of Intussusception and Other Adverse Events After Pentavalent, Bovine-Derived Rotavirus Vaccine	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
158	Bell J.	2010	Long-Term Safety of Recombinant Human Growth Hormone in Children	drug	yes	no	yes	no	no	no	yes	no	yes	**4**
159	Baxter R.	2012	A postmarketing evaluation of the safety of Ann Arbor strain live attenuated influenza vaccine in children 5 through 17 years of age	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
160	Barlow W. E.	2001	The Risk of Seizures after Receipt of Whole-Cell Pertussis or Measles, Mumps, and Rubella Vaccine	vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
161	Baird E. A.	1992	Effect of maintenance chemotherapy in childhood on numbers of melanocytic naevi	drug	yes	no	no	no	yes	no	yes	no	yes	**4**
162	Backer C. L.	2007	Aprotinin is safe in pediatric patients undergoing cardiac surgery	drug	yes	no	yes	no	yes	yes	no	no	yes	**5**
163	Ayuk F.	2008	Comparison of Two Doses of Antithymocyte Globulin in Patients Undergoing Matched Unrelated Donor Allogeneic Stem Cell Transplantation	drug	yes	yes	no	no	yes	yes	no	no	no	**4**
164	August K. J.	2013	Comparison of Hypersensitivity Reactions to PEG-Asparaginase in Children After Intravenous and Intramuscular Administration	drug	yes	yes	yes	no	no	no	yes	no	no	**4**
165	Ashraf E.	1999	Safety profile of ibuprofen suspension	drug	yes	yes	no	no	no	no	no	no	no	**2**

			in young children											
166	Arnheim-Dahlstrom L.	2013	Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
167	Armstrong P. K.	2011	Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine	vaccine	yes	yes	yes	no	yes	no	yes	no	no	**5**
168	Archambault P.	2012	Adrenal inhibition following a single dose of etomidate in intubated traumatic brain injury victims	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
169	Apter A. J.	2006	Is There Cross-Reactivity Between Penicillins and Cephalosporins?	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
170	Andrews N.	2004	Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association	vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
171	Anderson H. D.	2012	Rates of 5 Common Antidepressant Side Effects Among New Adult and Adolescent Cases of Depression: A Retrospective US Claims Study	drug	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
172	Aljadhey H.	2012	The safety of H1N1 vaccine in children in Saudi Arabia: a cohort study using modern technology in a developing country.	vaccine	yes	yes	yes	no	yes	yes	no	no	no	**5**
173	Schelleman H.	2011	Cardiovascular Events and Death in Children Exposed and Unexposed to ADHD Agents	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
174	Heron J.	2004	Thimerosal Exposure in Infants and Developmental Disorders: A Prospective Cohort Study in the United Kingdom Does Not Support a Causal Association	vaccine	yes	yes	yes	no	no	no	no	no	no	**3**

Note: Q1 to Q8 correspond to the eight questions of the Newcastle Ottawa scale (cohort version); Q5a and Q5b correspond to the two questions that assess whether a study controlled for selected confounding factors; for the current study, Q5a assessed control of confounding by age and Q5b assessed control of confounding by sex or medical indication;

For each study, the total NOS score is derived by adding up all the 'yes' responses; yes=implies that the study earned a star for that NOS question; no= implies that the study did not earn a star for that NOS question

Table 2: Quality scores derived for 30 studies that applied the self-controlled case series (SCCS) design, assessed using a modified cohort version of the Newcastle Ottawa scale (NOS)

S/N	First author	Year	Title	NOS Questions									Total NOS score
				Q1	Q2	Q3	Q4	Q5a	Q5b	Q6	Q7	Q 8	
1	Yih W. K.	2012	Surveillance for Adverse Events Following Receipt of Pandemic 2009 H1N1 Vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009–2010	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
2	Wilson K.	2011	Adverse Events following 12 and 18 Month Vaccinations: a Population-Based, Self Controlled Case Series Analysis	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
3	Ward K. N.	2007	Risk of Serious Neurologic Disease After Immunization of Young Children in Britain and Ireland	yes	yes	yes	no	yes	no	yes	no	yes	**6**
4	Velazquez F. R.	2012	Postmarketing Surveillance of Intussusception Following Mass Introduction of the Attenuated Human Rotavirus Vaccine in Mexico	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
5	Tse A.	2012	Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
6	Taylor B.	2007	No increased risk of relapse after meningococcal C conjugate vaccine in nephrotic syndrome	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
7	Sun Y.	2012	Risk of Febrile Seizures and Epilepsy After Vaccination With Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus, and Haemophilus Influenzae Type b	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**
8	Stehr-Green P.	2007	The risk of bronchiolitis hospitalisation following administration of a group B meningococcal vaccine in New Zealand	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
9	Stehr-Green P.	2008	The risk of simple febrile seizures after immunisation with a new group B meningococcal vaccine, New Zealand	yes	yes	yes	yes	yes	yes	yes	no	yes	**8**

10	Patel M. M.	2011	Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil	yes	yes	yes	no	yes	yes	yes	no	yes		**7**
11	O'Leary S. T.	2012	The Risk of Immune Thrombocytopenic Purpura After Vaccination in Children and Adolescents	yes	yes	yes	yes	yes	yes	yes	no	yes		**8**
12	Naleway A. L.	2009	Risk of immune hemolytic anemia in children following immunization	yes	yes	yes	yes	yes	yes	yes	no	yes		**8**
13	Murphy T. V.	2001	Intussusception among Infants Given an Oral Rotavirus Vaccine	yes	yes	yes	yes	yes	yes	yes	no	yes		**8**
14	Mullooly J.P.	2002	Wheezing lower respiratory disease and vaccination of full-term infants	yes	yes	yes	yes	yes	yes	yes	no	yes		**8**
15	Morgan T. M.	2011	Vaccines Are Not Associated With Metabolic Events in Children With Urea Cycle Disorders	yes	yes	yes	yes	yes	yes	yes	no	yes		**8**
16	Miller E.	2013	Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis	yes	yes	yes	yes	yes	yes	yes	no	yes		**8**
17	Miller E.	2001	Idiopathic thrombocytopenic purpura and MMR vaccine	yes	yes	yes	no	yes	yes	yes	no	yes		**7**
18	Kramarz P.	2000	Does Influenza Vaccination Exacerbate Asthma? Analysis of a Large Cohort of Children With Asthma	yes	yes	yes	no	yes	yes	yes	yes	yes		**8**
19	Huang W. T.	2010	Lack of Association Between Acellular Pertussis Vaccine and Seizures in Early Childhood	yes	yes	yes	no	yes	yes	yes	yes	yes		**8**
20	Hanf M.	2013	Validation of the French national health insurance information systemas a tool in vaccine safety assessment: Application to febrileconvulsions after pediatric measles/mumps/rubella immunization	yes	yes	yes	no	yes	yes	yes	no	yes		**7**
21	Hambidge S. J.	2012	Trivalent Inactivated Influenza Vaccine Is Not Associated With Sickle Cell Crises in Children	yes	yes	yes	no	yes	yes	yes	yes	yes		**8**
22	Hambidge S. J.	2006	Safety of Trivalent Inactivated Influenza Vaccine in Children 6 to 23 Months Old	yes	yes	yes	no	yes	yes	yes	yes	yes		**8**
23	Greene S. K.	2010	Near Real-Time Surveillance for Influenza Vaccine Safety: Proof-of-Concept in the Vaccine Safety Datalink Project	yes	yes	yes	no	yes	yes	yes	no	yes		**7**
24	Glanz J. M.	2011	Safety of Trivalent Inactivated Influenza Vaccine in Children Aged 24 to 59 Months	yes	yes	yes	yes	yes	yes	yes	yes	yes		**9**

			in the Vaccine Safety Datalink										
25	France E. K.	2008	Risk of Immune Thrombocytopenic Purpura After Measles-Mumps-Rubella Immunization in Children	yes	yes	yes	yes	yes	yes	yes	yes	yes	**9**
26	Donegan K.	2013	Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
27	De Wals P.	2012	Risk of Guillain-Barre´ Syndrome Following H1N1 Influenza Vaccination in Quebec	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
28	Benchimol E. I.	2013	Safety and Utilization of Influenza Immunization in Children With Inflammatory Bowel Disease	yes	no	yes	yes	yes	yes	yes	no	yes	**7**
29	Asturias E. J.	2013	Post-authorization safety surveillance of a liquid pentavalentvaccine in Guatemalan children	yes	yes	yes	no	yes	yes	yes	no	yes	**7**
30	Andrews N.	2007	Post-Licensure Safety of the Meningococcal Group C Conjugate Vaccine	yes	yes	yes	no	yes	yes	yes	no	yes	**7**

Note: Q1 to Q8 correspond to the eight questions of the Newcastle Ottawa scale (cohort version); Q5a and Q5b correspond to the two questions that assess whether a study controlled for selected confounding factors; for the current study, Q5a assessed control of confounding by age and Q5b assessed control of confounding by sex or medical indication;

For each study, the total NOS score is derived by adding up all the 'yes' responses;

yes=implies that the study earned a star for that NOS question; no= implies that the study did not earn a star for that NOS question

Table 3: Quality scores derived for 73 case-control studies, assessed using a modified case control version of the Newcastle Ottawa scale (NOS)

S/N	First author	Year	Title	Investigated exposure	NOS Questions									Total NOS score
					Q1	Q2	Q3	Q4	Q5a	Q5b	Q6	Q7	Q 8	
1	White J. R.	2003	Discontinuation of levetiracetam because of behavioral side effects. A case-control study	drug	yes	yes	yes	yes	no	no	yes	yes	no	**6**
2	Walker A. M.	1988	Neurologic Events Following Diphtheria-Tetanus-Pertussis Immunization	vaccine	no	yes	yes	yes	yes	yes	yes	yes	no	**7**
3	The Victorian Infant Collaborative study group	2000	Postnatal corticosteroids and sensorineural outcome at 5 years of age	drug	yes	yes	no	no	yes	yes	yes	no	no	**5**
4	Van Staa T. P.	2004	Are inhaled corticosteroids associated with an increased risk of fracture in children?	drug	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
5	Uno Y.	2012	The combined measles, mumps, and rubella vaccines and the total number of vaccines are not associated with development of autism spectrum disorder: The first case–control study in Asia	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
6	Tucker M. A.	1987	Leukemia After Therapy With Alkylating Agents for Childhood Cancer	drug	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
7	Tanihara S.	2002	A Case-control Study of Asthma Death and Life-threatening Attack:Their Possible Relationship with Prescribed Drug Therapy in Japan	drug	no	yes	yes	yes	yes	yes	yes	yes	no	**7**
8	Takahashi H.	2003	An epidemiological study on Japanese autism concerning routine childhood immunization history.	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**

9	Sutter R. W.	1992	Attributable risk of DTP (diphtheria and tetanus toxoids and pertussis vaccine) injection in provoking paralytic poliomyelitis during a large outbreak in Oman	vaccine	yes	yes	yes	no	yes	no	yes	yes	no	**6**
10	Stehr-Green P.	2007	The risk of bronchiolitis hospitalisation following administration of a group B meningococcal vaccine in New Zealand	vaccine	no	yes	yes	yes	yes	yes	yes	yes	yes	**8**
11	Spiro D. M.	2003	Association Between Antibiotic Use and Primary Idiopathic Intussusception	drug	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
12	Smeeth L.	2004	MMR vaccination and pervasive developmental disorders: a case-control study	vaccine	no	yes	yes	yes	yes	yes	yes	yes	yes	**8**
13	Schumock G. T.	2012	Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: A nested case-control study	drug	no	yes	yes	yes	yes	yes	yes	yes	yes	**8**
14	Schneeweiss S.	2009	Topical Treatments with Pimecrolimus, Tacrolimus and Medium- to High-Potency Corticosteroids, and Risk of Lymphoma	drug	no	yes	yes	yes	no	no	yes	yes	yes	**6**
15	Rzany B.	1999	Risk of S tevens-Johnson syndrome and toxic epider m a l necrolysis during first weeks of antiepileptic therapy: a casecontrol study	drug	yes	yes	no	yes	yes	yes	yes	yes	no	**7**
16	Ray P.	2006	Encephalopathy After Whole-Cell Pertussis or Measles Vaccination Lack of Evidence for a Causal Association in a Retrospective Case–Control Study	vaccine	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
17	Rawson N. S.	1998	Hospitalizations for Aplastic Anemia and Agranulocytosis in Saskatchewan: Incidence and Associations with Antecedent Prescription Drug Use	drug	yes	yes	yes	yes	yes	yes	yes	yes	yes	**9**
18	Plumb J.	2001	Exposures and Outcomes of Children With Urticaria Seen in a Pediatric Practice-Based Research NetworkA Case-Control Study	drug	yes	yes	yes	no	yes	yes	no	yes	no	**6**
19	M. M. Patel	2011	Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil	vaccine	yes	yes	yes	no	yes	yes	yes	yes	no	**7**

20	Olsson D. S.	2012	Tumour recurrence and enlargement in patients with craniopharyngioma with and without GH replacement therapy during more than 10 years of follow-up	drug	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
21	Myleus A.	2012	Early Vaccinations Are Not Risk Factors for Celiac Disease	vaccine	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
22	Murphy T. V.	2001	Intussusception among Infants Given an Oral Rotavirus Vaccine	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
23	Mullooly J. P.	2007	Vaccines, antibiotics, and atopy	drug and vaccine	yes	no	yes	yes	yes	yes	yes	yes	yes	**8**
24	Mullooly J. P.	2002	Wheezing lower respiratory disease and vaccination of full-term infants	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	yes	**9**
25	Miller D.	1993	Pertussis immunisation and serious acute neurological illnesses in children	vaccine	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
26	Miller D. L.	1981	Pertussis immunisation and serious acute neurological illness in children	vaccine	yes	yes	yes	no	yes	yes	yes	no	no	**6**
27	Mikaeloff Y.	2009	Hepatitis B vaccine and the risk of CNS inflammatory demyelination in childhood	vaccine	no	yes	yes	no	yes	yes	yes	yes	no	**6**
28	Mikaeloff Y.	2007	Hepatitis B Vaccination and the Risk of Childhood-Onset Multiple Sclerosis	vaccine	yes	no	yes	no	yes	yes	yes	yes	no	**6**
29	Menniti-Ippolito F.	2001	Niflumic acid and cutaneous reactions in children	drug	yes	yes	no	yes	no	no	yes	yes	no	**5**
30	Melendez E.	2009	Serious Adverse Events During Procedural Sedation With Ketamine	drug	yes	yes	no	yes	no	yes	yes	yes	yes	**7**
31	Martinez C.	2005	Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study	drug	yes	yes	yes	no	yes	yes	yes	no	yes	**7**

32	Mallol-Mesnard N.	2007	Vaccination and the risk of childhood acute leukaemia: the ESCALE study (SFCEy)	vaccine	yes	no	yes	no	yes	yes	yes	yes	no	**6**
33	Maher J. E.	2004	Infant vaccinations and childhood asthma among full-term infants	vaccine	no	no	yes	no	yes	yes	yes	yes	yes	**6**
34	Magnus P.	2009	Vaccination as teenagers against meningococcal disease and the risk of the chronic fatigue syndrome	vaccine	no	no	yes	no	yes	yes	no	yes	no	**5**
35	Li S. T. T.	2004	Intussusception and Oral Poliovirus Vaccination: Is There an Association?	vaccine	no	no	yes	no	yes	yes	yes	yes	yes	**6**
36	Kahn A.	1982	Phenothiazines and Sudden Infant Death Syndrome	drug	yes	no	yes	yes	no	no	yes	yes	no	**5**
37	Kaatsch P.	2009	Case–control study on the therapy of childhood cancer and the occurrence of second malignant neoplasms in Germany	drug	no	no	yes	no	yes	yes	yes	yes	yes	**6**
38	Jonville-Bera A. P.	2001	Sudden unexpected death in infants under 3 months of age and vaccination status ± a case-control study	vaccine	yes	yes	yes	no	yes	yes	yes	no	no	**6**
39	Joffe L. S.	1992	Diphtheria-tetanus toxoids-pertussis vaccination does not increase the risk of hospitalization with an infectious illness	vaccine	yes	no	yes	no	yes	yes	yes	yes	no	**6**
40	Jick H.	2004	Antidepressants and the Risk of Suicidal Behaviors	drug	no	no	yes	yes	yes	yes	yes	yes	yes	**7**
41	Jick H.	2001	Live attenuated polio vaccine and the risk of intussusception	vaccine	yes	no	yes	no	yes	yes	yes	yes	yes	**7**
42	Hurwitz E. S.	1985	Public Health Service Study on Reye's Syndrome and Medications. Report of the Pilot Phase	drug	yes	no	yes	yes	yes	yes	no	yes	no	**6**
43	Hurwitz E. S.	1987	Public Health Service Study of Reye's Syndrome and Medications. Report of the Main Study	drug	yes	no	yes	no	yes	yes	no	yes	no	**5**
44	Huerta C.	2002	Risk of clinical blood dyscrasia in a cohort of antibiotic users.	drug	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
45	Hoffman H. J.	1987	Diphtheria-Tetanus-Pertussis Immunization and Sudden Infant	vaccine	yes	no	yes	no	yes	yes	yes	yes	no	**6**

			Death: Results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors											
46	Hamilton R. A.	1998	Frequency of hospitalization after exposure to known drug-drug interactions in a Medicaid population.	drug	no	yes	yes	yes	no	no	yes	yes	yes	**6**
47	Hambidge S. J.	2012	Trivalent Inactivated Influenza Vaccine Is Not Associated With Sickle Cell Crises in Children	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	yes	**9**
48	Hambidge S. J.	2006	Safety of Trivalent Inactivated Influenza Vaccine in Children 6 to 23 Months Old	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	yes	**9**
49	Grimaldi-Bensouda L.	2011	Guillain-Barre´ Syndrome, Influenzalike Illnesses, and Influenza Vaccination During Seasons With and Without Circulating A/H1N1 Viruses	vaccine	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
50	Greco D.	1985	Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	no	**8**
51	Goodman M. J.	2006	The Safety of Trivalent Influenza Vaccine Among Healthy Children 6 to 24 Months of Age	vaccine	yes	yes	no	yes	yes	yes	yes	yes	yes	**8**
52	Gale J. L.	1994	Risk of Serious Acute Neurological Illness After Immunization With Diphtheria-Tetanus-Pertussis Vaccine A Population-Based Case-Control Study	vaccine	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
53	Gabb G. M.	1996	Epidemiological study of angioedema and ACE inhibitors	drug	no	yes	no	yes	yes	yes	yes	yes	no	**6**
54	Feeney M.	1997	A case-control study of measles vaccination and inflammatory bowel disease	vaccine	yes	yes	yes	no	yes	yes	yes	yes	no	**7**
55	Ernst P.	1993	Is the Association between Inhaled Beta-Agonist Use and Life-threatening Asthma because of Confounding by Severity?	drug	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
56	Dieleman J.	2011	Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe	vaccine	yes	yes	no	no	yes	yes	yes	yes	yes	**7**

57	DeStefano F.	2001	Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus	vaccine	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
58	Deivanayagam N.	1993	Intramuscular injection as a provoking factor for paralysis in acute poliomyelitis. A case control study.	drug and vaccine	yes	yes	no	no	yes	yes	yes	yes	no	**6**
59	Dawkins T. N.	2009	Safety of intravenous use of ketorolac in infants following cardiothoracic surgery	drug	no	no	no	no	no	no	yes	no	no	**1**
60	Davis R. L.	2001	Measles-mumps-rubella and other measles-containing vaccines do not increase the risk for inflammatory bowel disease: a case-control study from the Vaccine Safety Datalink project.	vaccine	yes	yes	yes	no	yes	yes	yes	yes	yes	**8**
61	Dauvilliers Y.	2013	Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France	vaccine	yes	no	yes	yes	yes	yes	no	yes	no	**6**
62	Campbell J. R.	2000	Systemic Candidiasis in Extremely Low Birth Weight Infants Receiving Topical Petrolatum Ointment for Skin Care: A Case–Control Study	drug	no	yes	no	no	yes	yes	yes	no	yes	**5**
63	Bremner S. A.	2005	Timing of routine immunisations and subsequent hay fever risk	vaccine	no	no	yes	yes	yes	yes	yes	yes	yes	**7**
64	Bremner S. A.	2003	Early-life exposure to antibacterials and the subsequent development of hayfever in childhood in the UK: case–control studies using the General Practice Research Database and the Doctors' Independent Network	drug	no	no	yes	no	yes	yes	yes	yes	yes	**6**
65	Boyce T. G.	2004	Pertussis Vaccination and the Risk of Respiratory Syncytial Virus-Associated Hospitalization	vaccine	no	no	yes	no	yes	yes	yes	yes	yes	**6**
66	Black S.	1997	Risk of hospitalization because of aseptic meningitis after measles-mumps-rubella vaccination in one- to two-year-old children: an analysis of the Vaccine	vaccine	yes	yes	yes	yes	yes	yes	yes	yes	yes	**9**
67	Black C.	2003	MMR vaccine and idiopathic thrombocytopaenic purpura	vaccine	yes	yes	no	no	yes	yes	yes	yes	yes	**7**

68	Bertuola F.	2010	Association between drug and vaccine use and acute immune thrombocytopenia in childhood: a case-control study in Italy.	drug and vaccine	yes	no	no	yes	no	no	yes	yes	no	**4**
69	Bellis J.R.	2013	Adverse drug reactions and off-label and unlicensed medicines in children: a nested case–control study of inpatients in a pediatric hospital	drug	yes	yes	no	yes	yes	yes	yes	yes	no	**7**
70	Anderson H. R.	2005	Bronchodilator treatment and deaths from asthma: case-control study	drug	yes	yes	no	no	yes	yes	yes	yes	no	**6**
71	Ahlgren C.	2009	A population-based case–control study on viral infections and vaccinations and subsequent multiple sclerosis risk	vaccine	yes	no	yes	no	yes	yes	yes	yes	yes	**7**
72	Centers of Disease Control and Prevention	1993	Ceftriaxone-Associated Biliary Complications of Treatment of Suspected Disseminated Lyme Disease\p=m-\NewJersey, 1990-1992	drug	yes	yes	yes	no	no	no	yes	yes	no	**5**
73	Gould M.S.	2009	Sudden Death and Use of Stimulant Medications in Youths	drug	yes	no	yes	yes	yes	yes	yes	yes	no	**7**

Note: Q1 to Q8 correspond to the eight questions of the Newcastle Ottawa scale (case-control version); Q5a and Q5b correspond to the two questions that assess whether a study controlled for selected confounding factors; for the current study, Q5a assessed control of confounding by age and Q5b assessed control of confounding by sex, medical indication or calendar time;

For each study, the total NOS score is derived by adding up all the 'yes' responses;

yes=implies that the study earned a star for that NOS question; no= implies that the study did not earn a star for that NOS question

Table 4: Quality scores derived for 4 case crossover studies, assessed using a modified case control version of the Newcastle Ottawa scale (NOS)

S/N	First author	Year	Title	Investigated exposure	NOS Questions									Total NOS score
					Q1	Q2	Q3	Q4	Q5a	Q5b	Q6	Q7	Q 8	
1	France E. K.	2004	Safety of the Trivalent Inactivated Influenza Vaccine Among Children	vaccine	no	yes	yes	yes	yes	yes	yes	yes	yes	**8**
2	Fosbol E. L.	2010	Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals.	drug	no	yes	yes	yes	yes	yes	yes	yes	yes	**8**
3	Fosbol E. L.	2009	Risk of Myocardial Infarction and Death Associated With the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Among Healthy Individuals: A Nationwide Cohort Study	drug	no	yes	yes	yes	yes	yes	yes	yes	yes	**8**
4	Biskupiak J. E.	2006	Gastrointestinal complications of over-the-counter nonsteroidal antiinflammatory drugs.	drug	no	yes	yes	yes	yes	yes	yes	yes	yes	**8**

Note: Q1 to Q8 correspond to the eight questions of the Newcastle Ottawa scale (case-control version); Q5a and Q5b correspond to the two questions that assess whether a study controlled for selected confounding factors; for the current study, Q5a assessed control of confounding by age and Q5b assessed control of confounding by sex, medical indication or calendar time;

For each study, the total NOS score is derived by adding up all the 'yes' responses;

yes=implies that the study earned a star for that NOS question; no= implies that the study did not earn a star for that NOS question

Chapter 5 Comparative (pharmacoepidemiological) effectiveness studies

Chapter 5.1 Comparing drug effectiveness in children: a systematic review

Abstract

Context: In order to overcome the lack of knowledge about effects of drugs in children, data on drug effectiveness that can be generated using routine health care data might be useful.

Objective: We conducted a systematic review of published pharmacoepidemiological studies that evaluated drug effectiveness in children to assess the current state of the art and potential gaps and areas of improvement.

Data Sources: Relevant articles from inception to February 2015 were retrieved from Embase and Medline.

Study Selection: We sequentially screened titles, abstracts and full texts, with independent validation.

Data Extraction: Data regarding general information and study methods including statistical analysis were extracted systematically. Study quality was assessed with a modified Newcastle-Ottawa-scale (NOS) Investigated drugs were ranked and compared with data on prevalence of pediatric drug use.

Results: Out of 4926 unique articles, 164 full texts were retained. Most studies were from North America (46.7%). Only 78 studies (47.6%) reported the design: 90.9% were cohort studies. Neonates were least investigated. The drugs that were most often studied included systemic antibacterials (11.4%), psycholeptics (7.9%) and antiepileptics (7.6%). Adjustment for confounding was made using propensity scores in 8.5% of the studies. Studies that did not report the design were of lower quality. Many effectiveness studies were done on antineoplastic agents, which are not frequently used and few studies on analgesics and drugs for obstructive airway diseases which are frequently prescribed.

Limitations:

Conclusions: There is ample opportunity to improve the comparative effectiveness research for drugs used in pediatrics; routinely prescribed drugswere seldom investigated. Modern methods for confounding adjustment, such as propensity scores, were rarely used.

Introduction

Randomized Controlled Trials (RCTs) generate important drug efficacy evidence[246,247] but such evidence may not be generalizable to routine clinical practice. Children were seldom included in RCTs prior to the pediatric regulation[247] and therefore evidence on the effects of older (and most frequently used) drugs is often lacking, which leads to high frequencies of unlicensed or "off label" drug use[22,248,249] Prescribing is then based on physician's extrapolation from adults, but organ maturation and hormonal changes may impact drug pharmacokinetics and pharmacodynamics as children are not small adults, nor are the formulations always adequate or resulting in similar pharmacokinetics[198,250]. To address the lack of knowledge on the effectiveness of drugs in children, we should produce better evidence to guide routine drug prescribing in pediatrics. Comparative effectiveness research, that is based on routine health care data may therefore be especially important for this population[251].

We conducted a systematic review of the medical literature to assess the characteristics, quality and potential gaps of observational comparative studies that evaluated the effectiveness of drugs in children.

Methods

Search strategy

This systematic review was conducted in accordance with PRISMA guidelines[252]. We identified relevant studies by searching Embase.com and Medline (via OvidSP) from inception to 24th February 2015. We applied the following abbreviated search strategy: "children" AND "pharmacoepidemiology" AND "comparative studies". Details of the search strategy are included in Appendix 1.The search was limited to human research.

Study selection

We included all observational studies which have as objective to quantify and compare the effectiveness of a drug exposure(s) within the pediatric population (age 0-18 years). Drug exposures concerned all medicinal products, applied either systemically or locally. We excluded experimental studies and observational studies pertaining to case reports/series, compliance

rates to medicinal treatments, herbal treatment, non-pharmacological treatments, pharmacoeconomics, health services utilization, adults exclusively, vaccine exposures, abstracts, letters, duplicate studies, preliminary publications or reviews, and other languages (besides English).

Validity assessment

All retrieved titles and abstracts were initially screened by one reviewer (JD) and full texts of potentially relevant articles were obtained. A second reviewer (OO) who was blinded to the initial assessment independently screened a sample of abstracts that comprised all abstracts for which the first reviewer obtained full text, plus a random selection of abstracts rejected at the initial screening. Any disagreements between the two reviewers were examined by a third reviewer (CF). Full texts retained through this process were independently screened by two reviewers (JD and KP), while disagreements were examined by a third reviewer (OO). In order to validate the final set of selected articles, a random sample of all the articles retained by agreement between JD and KP was assessed by OO. Further disagreements were resolved by discussion.

Data extraction

For data extraction from the papers, we developed a standardized form that was pre-tested in 10% (random selection) of the retained articles. The extracted data pertained to: general information (first author, year of publication, country of corresponding author and journal), funding source, study period, type of data, study population, study design, outcome, exposure, and statistical analysis (details in Appendix 2). Age categories were based on guidelines recommended by the international Conference on Harmonization (0-27days, 28days-23 months, 2-11years, and 12-18 years)[150]. Two researchers (JD and KP) independently extracted data from the final set of included articles. Differences were resolved by discussion between the authors.

All exposures were mapped to World Health Organization-Anatomical Therapeutic Chemical (WHO-ATC). When individual drugs were investigated, they were cross checked against the labels, using Micromedex Solutions for studies conducted in the USA and Health Canada Drug Product database for studies conducted in Canada.

Quality assessment

.We applied a slightly modified form of the Newcastle-Ottawa-scale (NOS) [223]. The NOS has been widely used and endorsed by The Cochrane Collaboration in its 2011 handbook [206]. There are two versions, a cohort and case control version which both consist of eight multiple-choice questions that address subject selection, comparability (of cases and controls in case-control studies and of cohorts in cohort studies) and the assessment of the exposure (case control) or the outcome (cohort). The number of possible answers per question ranges from two to five and high quality responses earn one star totalling up to 9 stars (the comparability question earns up to 2 stars). The modified version of the NOS can be found in Appendix 3. Two researchers (JD and KP) independently assessed the quality of included articles using the NOS, disagreements were resolved through discussion between the authors.

Data analysis

Categorical variables are described using counts (proportions) and continuous variables with the median value and the interquartile (IOR) range. Ranks were assigned to the frequency of drug class in the review (1-20) and from outpatient drug utilization rates (1-51) based on a recent study in the BMJ[248]. Drug classes with the same frequency of investigation were assigned the same rank. In the same way, drug classes with the same utilization rate were assigned the same rank. To investigate the association between funding source on one hand and BPCA, and reporting of study design and BPCA on the other hand, Pearson's chi-square test was applied.All analyses were performed using Microsoft Excel 2010 and Statistical Package for the Social Sciences (SPSS) version 21.

Results

The literature search yielded 4926 unique records after de-duplication. Following title and abstract screening, 275 articles were retained and evaluated for inclusion (agreement between the researches was 87.6 %). After the full text review, 164 articles were retained (agreement between the researchers was 95.0%).The list of retained articles is available in the supplementary material (table 1). Details of the study selection process are presented in Figure 1.

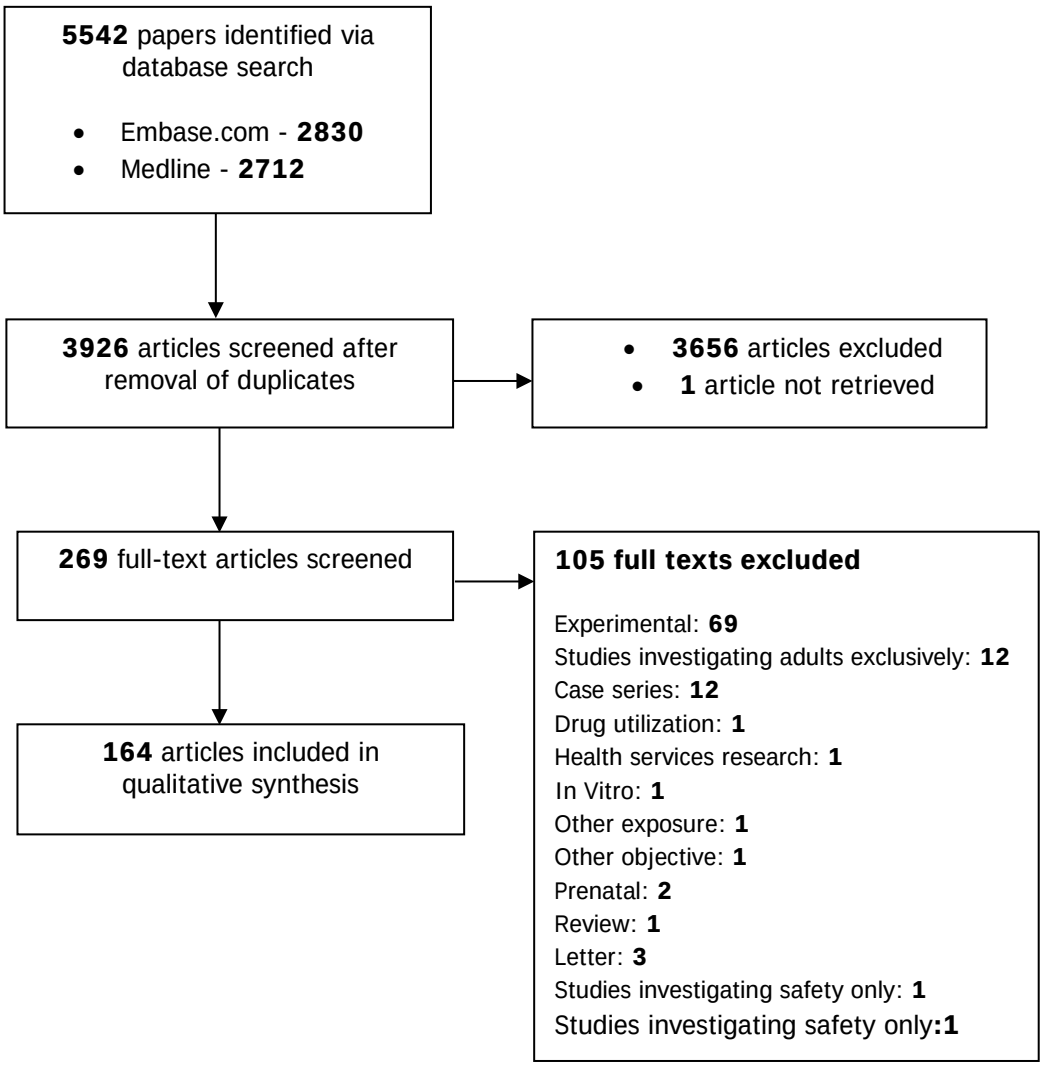


Figure 1: Flow chart depicting the selection of relevant articles

Compared to the total number of published epidemiological studies that were indexed in Embase.com, the number of published pediatric comparative effectiveness studies increased more rapidly over time (figure 2).

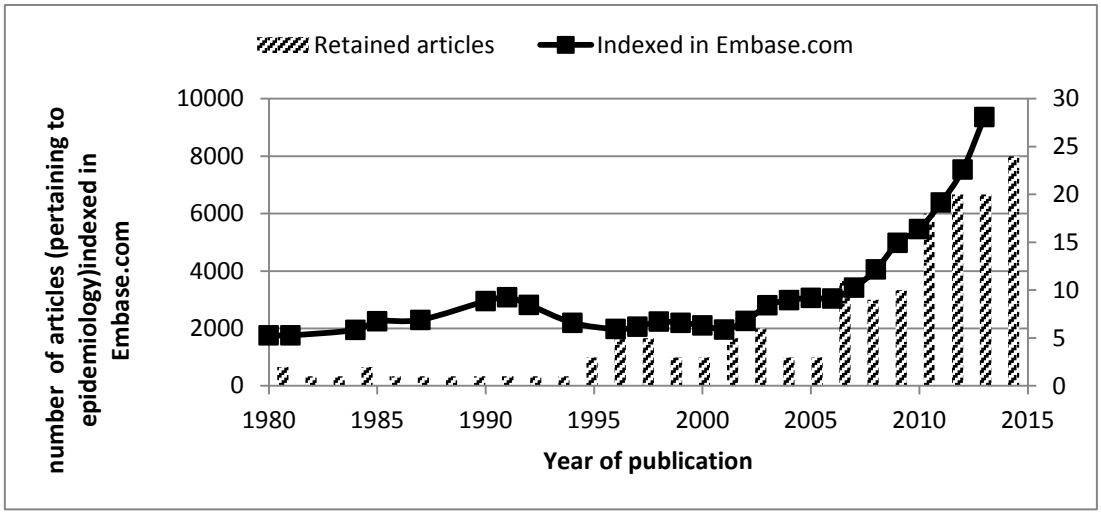


Figure 2: Distribution of retained articles by year of publication

Most of the included studies were from North America (46.7%), Europe (29.7%) and Asia (15.2%). In 53.0 % of the studies the funding source was not reported. Public and private funding was reported in 17.1% and 15.9% respectively; while 7.3 percent of the studies reported that they didn't receive any funding (private or public). The number of studies with unclear funding source decreased from 63.6 % to 51.5% after the introduction of the Best Pharmaceuticals for Children's Act (BPCA) in 2002, more studies reported public funding in the period after the introduction of the BPCA

The study design was reported in 47.6% of the studies. Before the BPCA only 18.2% of the studies reported study design, while in the time period after the adoption study design was reported in 54.5% of the studies Cohort studies were the most common designs (90.8%) while case-control, self-controlled case series and case crossover designs accounted for 4.0%, 1.0% and 1.0% of the studies respectively. More than half of the studies (65.8%) investigated the pediatric population exclusively, the remainder pertained to adults and children. The most frequently investigated pediatric age groups were children (74.4%) and adolescents (72%). Less represented age groups were infants (45.1%) and neonates (31.1%).

Antibacterials for systemic use (WHO-ATC 2nd level J01) were the most frequently investigated drug class (11.4%), followed by antiepileptics (WHO-ATC 2nd level N03) and psycholeptics (WHO-ATC 2nd level N05) (table 1).

Table 1: Twenty most frequently investigated therapeutic drug classes with median number of stars for all the studies investigating that drug class, assessed using the Newcastle Ottawa Scale

Therapeutic Drug Class	WHO-ATC	N(%)[a]	Median NOS (IQR)
Antibacterials For Systemic Use	J01	45(11.4)	6.0 (5.0-7.0)
Psycholeptics	N05	31(7.9)	5.0 (3.75-7.0)
Antiepileptics	N03	30 (7.6)	5.0 (4.0-6.0)
Antineoplastic Agents	L01	25 (6.3)	5.0 (5.0-8.0)
Immunosuppressants	L04	20 (5.1)	4.0 (4.0-5.0)
Corticosteroids For Systemic Use	H02	19 (4.8)	5.0 (4.0-6.0)
Antivirals For Systemic Use	J05	16 (4.1)	6.0 (5.0-9.0)
Analgesics	N02	15 (3.8)	4.0 (4.0-6.0)
Antimycotics For Systemic Use	J02	14 (3.7)	6.0 (5.0-7.0)
Drugs For Obstructive Airway Diseases	R03	14 (3.6)	7.0 (6.0-8.0)
Nasal Preparations	R01	12 (3.0)	7.0 (7.0-7.0)
Psychoanaleptics	N06	11 (2.8)	5.0 (5.0-5.0)
Antiinflammatory And Antirheumatic Products	M01	10 (2.6)	4.5 (4.0-6.0)
Antimycobacterials	J04	9 (2.4)	6.0 (5.5-8.0)
Anesthetics	N01	8 (2.1)	4.5 (3.0-5.0)
Immune Sera And Immunoglobulins	J06	8 (2.1)	8.0 (6.0-8.0)
Antithrombotic Agents	B01	8 (2.1)	6.0 (6.0-7.0)
Beta Blocking Agents	C07	7 (1.8)	5.0 (4.0-8.0)
Cardiac Therapy	C01	7 (1.8)	8.0 (5.0-8.0)
Antidiarrheals,Intestinal, Antiinflammatory/Antiinfective Agents	A07	5 (1.3)	5.0 (3.0- 5.5)

[a] Proportion is based on the total number (394) of drugs investigated.

When the analysis was performed per age subgroup, a difference was observed only in neonates (table 2).

Table 2: Most frequently investigated drug classes in specific age subgroups

Age group	ATC-WHO (N %)[a]									
Neonates	N03	J01	J02	J05	L01	M01	N05	C01	J06	J04
	(10.0)	(9.2)	(8.3)	(6.7)	(6.7)	(5.8)	(5.8)	(4.2)	(4.2)	(3.3)
Infants	J01	N03	N05	J05	L01	J02	H02	J06	N02	C01
	(21.2)	(11.6)	(7.9)	(6.3)	(6.3)	(5.3)	(3.7)	(3.2)	(3.2)	(2.6)
Children	J01	N03	L01	N05	H02	L04	R03	J05	J02	J04
	(13.6)	(9.5)	(7.9)	(7.6)	(4.7)	(4.4)	(4.4)	(3.8)	(3.2)	(2.8)
Adolescents	J01	L01	N03	L04	H02	N05	J02	R01	R03	NO2
	(11.7)	(8.1)	(7.8)	(5.8)	(5.2)	(5.2)	(4.5)	(3.9)	(3.9)	(3.6)

[a] Proportions are presented from left to right in a descending order

The most frequently investigated drug classes in this subgroup were antiepileptics (WHO-ATC 2nd level N03), followed by antibacterials for systemic use (WHO-ATC 2nd level J01) and antimycotics for systemic use (WHO-ATC 2nd level J02). Half of the drugs investigated in North American studies were based on off-label use. Dose response relationships were investigated in only 12.2 % of the studies, which included antihelmintics, antibacterials for systemic use and psycholeptics. Figure 3 shows the ranking of drug classes by prevalence of use as reported in the literature and the frequency of publications on effectiveness.

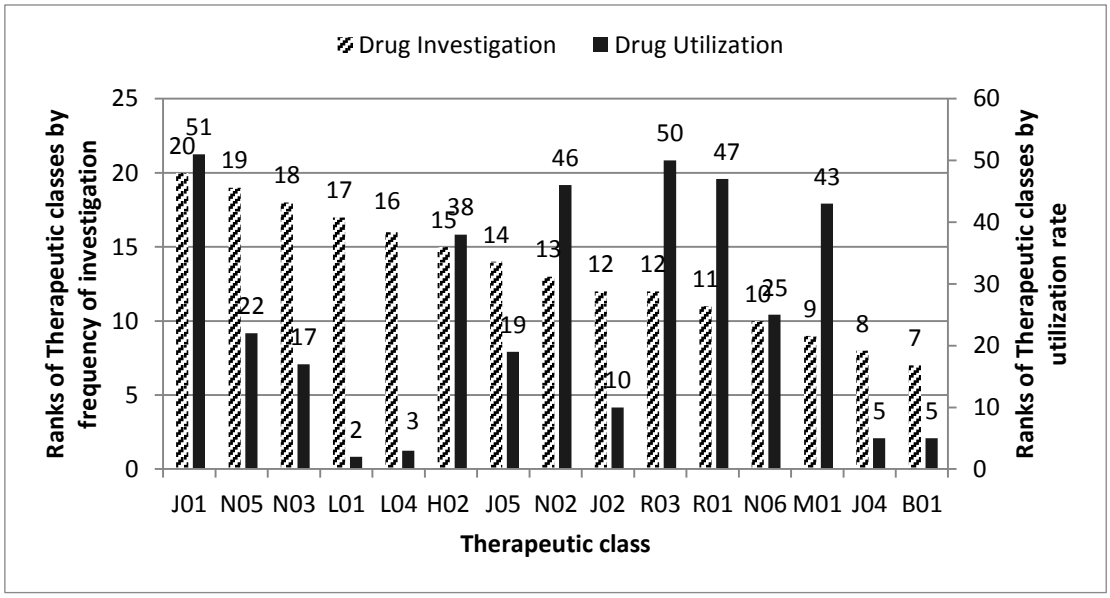


Figure 3: Ranking of drug classes in published studies on effectiveness and prevalence of drug use for the fifteen most frequently investigated therapeutic drug classes

The biggest gap can be observed for analgesics (WHO-ATC NO2) and drugs for obstructive airway diseases (WHO-ATC R03), anti-inflammatory and Antirheumatic (WHO-ATC M01) as well as the nasal preparations (WHO-ATC R01) which are all frequently utilized drug classes in the peediatric population but infrequently studied in comparative effectiveness research. On the other hand, for drug classes like Antineoplastic agents (WHO-ATC L01) and Immunosuppressants (WHO-ATC L04) for which the prevalence of use is low, comparative effectiveness studies were conducted frequently.

More than half of the studies (60.4%) investigated only intermediate outcomes. Clinical outcomes were investigated in 27.4% of the studies, while 12.2% of the studies investigated both clinical and intermediate outcomes. Multiple outcomes were studied in 56.1% of the studies. Median number of outcomes investigated was 2 (IQR: 1-3).

Most of the studies were based on retrospective re-use of data collected for other purposes (79.3%). The exact data-source for exposure and outcome was not clearly stated in 22.5% and 14.0% of the studies, respectively. For the studies reporting the data source, medical charts were the most frequently used data source for both exposure (48.8%) and outcome (57.9%). Claims data were used in 10.0% of the studies and medical records from general practitioners in only 3.7 % of articles for exposure and 3.0 % for the outcome.

Adjustment for confounding was applied in 52.4% of studies, through restriction, matching and propensity scores adjustment in 12.8%, 14.0% and 8.5% of the studies respectively. Adjustment on instrumental variables was not applied in any study.

The results of the quality assessment are reported in figure 4, 5 and 6.

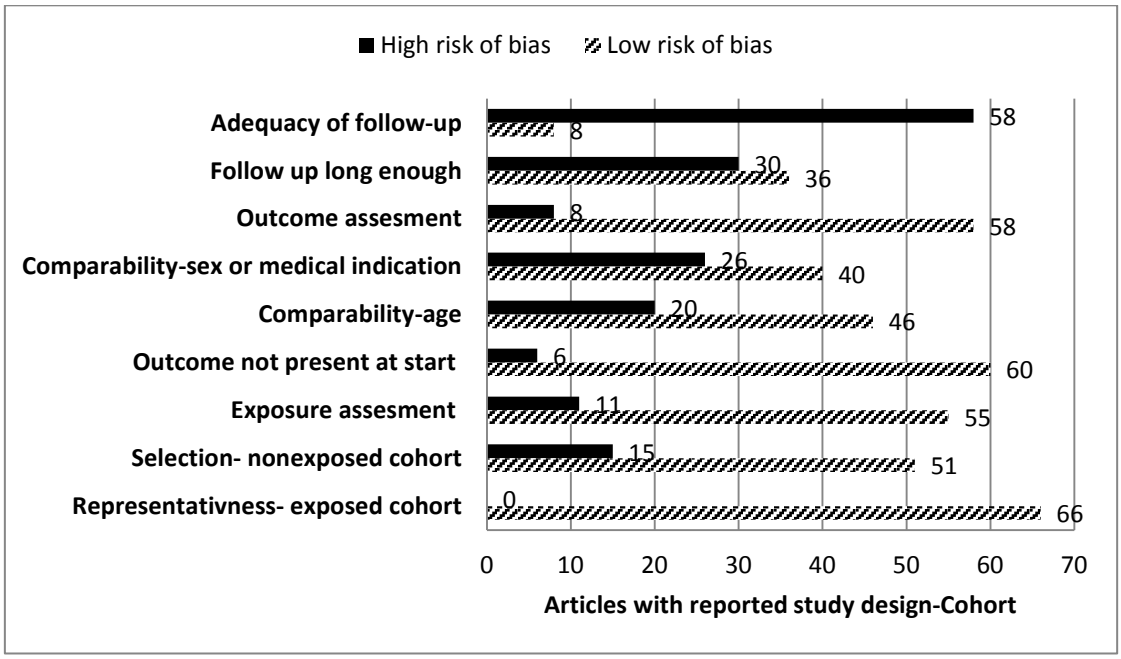


Figure 4: Risk of bias in Cohort studies where design was reported (evaluated using NOS)

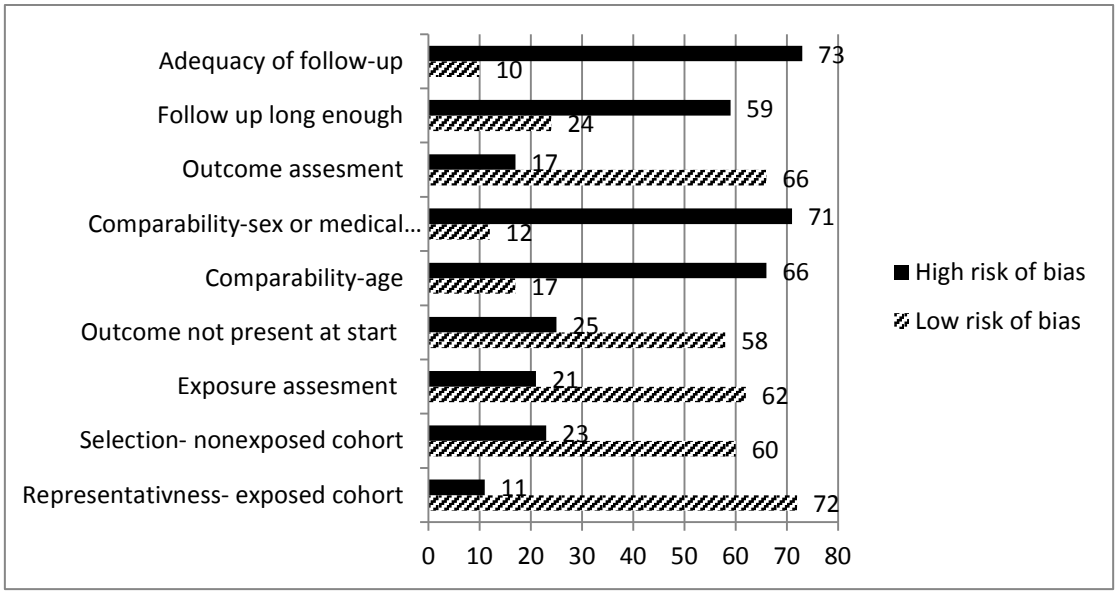


Figure 5: Risk of bias in studies not reporting study design, where design was assessed as Cohort (evaluated using NOS)

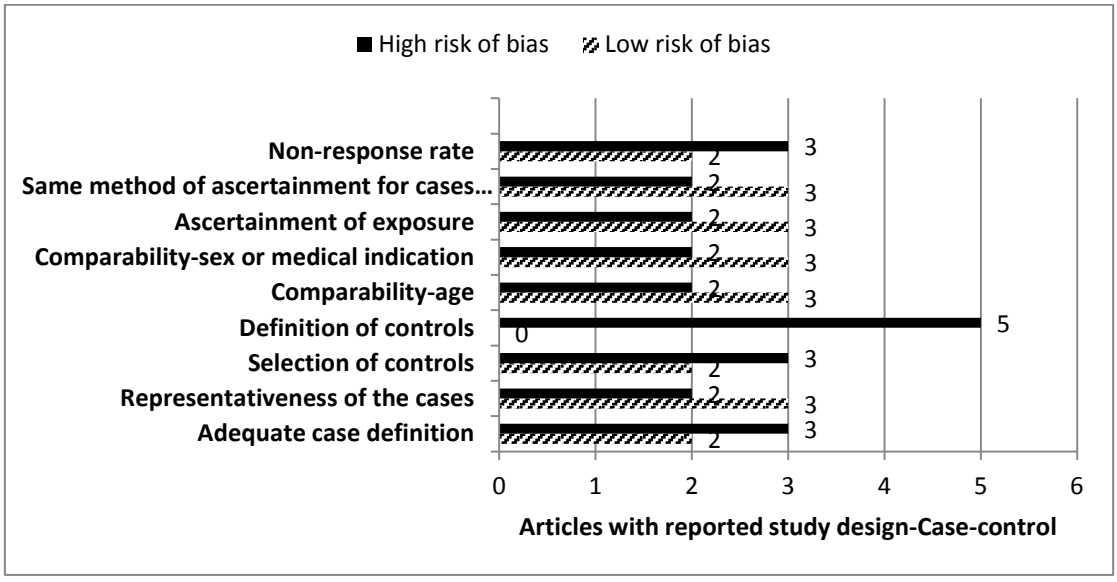


Figure 6: Risk of bias in case control studies (evaluated using NOS)

All cohort studies earned a star for the representativeness of the exposed cohort, while only 8 studies earned a star for the adequacy of follow up question (low follow up rate or follow up not reported). Median number of stars was 7.0 (IQR: 5.0 – 8.0). For the articles in which the study design was not reported, we classified the study design and evaluated the quality using Newcastle Ottawa Scale. Median number of stars was 5.0 (IQR: 4.5-5.0).

In total, five studies used a case-control design. Median number of stars was 4.0 (IQR: 2.5 – 6.5). The quality of studies that investigated dose-response is provided in figure 7.

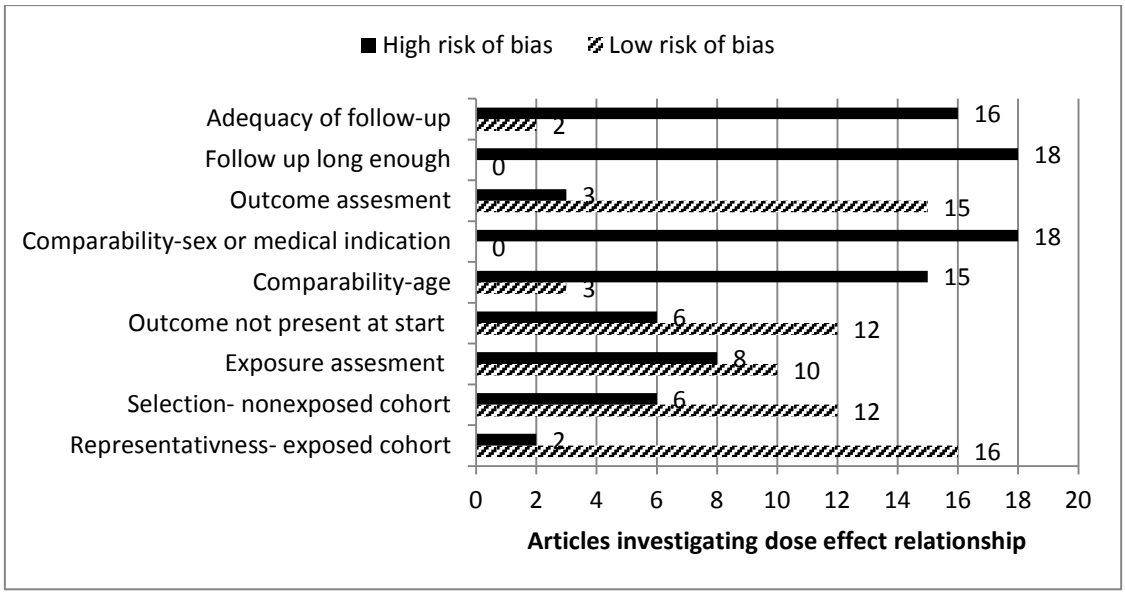


Figure 7: Risk of bias in studies investigating dose effect relationship (evaluated using NOS)

Discussion

This paper provides a systematic overview of observational comparative studies evaluating drug effectiveness in children. It showed several important points and areas of improvement and opportunities. The number of pharmacoepidemiological studies that focus on comparative effectiveness in children is very low, even if it is growing over time. Funding from private sources seems to be low, although in half of the studies, the funding source was not reported. Most of the studies are from North America and Europe, possibly resulting from the introduction of the "Best Pharmaceuticals for Children's Act" (BPCA) in 2002 (and amended in 2007) in the United States and "The Paediatric Regulation" in 2007 in Europe[26,43]. The legislations may have stimulated pediatric pharmacoepidemiological research. Cohort design was most commonly used, which is a good choice when multiple outcomes are studied, and most of the studies did look at more than one outcome. Often, these were intermediate outcomes, which is a missed opportunity since clinical trials also often use intermediate endpoints, whereas better evidence is needed on the clinical endpoints. To be able to identify the gaps in comparative drug

effectiveness research in children, we compared our findings with the prevalence of drug use in three European countries[4] (figure 3). Although commonly utilized, analgesics (WHO-ATC NO2), drugs for obstructive airway diseases (WHO-ATC R03), anti-inflammatory and Antirheumatic (WHO-ATC M01) drugs and nasal preparations (WHO-ATC R01) were seldom studied, possibly because effects can be investigated in clinical trials. Although seldom utilized, Antineoplastic agents (WHO-ATC L01) and Immunosuppressants (WHO-ATC L04) were frequently studied, The reason for this may be the well-known adverse effects, for which their benefit-risk profile needs to be continuously evaluated. In addition, studying the beneficial effects of these drugs will require long-term studies that are only feasible in observational research. The same pattern existed in the different pediatric age groups. Detailed information on dose was often absent and only few studies investigated dose-effect relationship. We recommend closer collaboration between pediatricians, clinical pharmacologists and pharmacoepidemiolgists in conducting dose-effect studies, which represents a missed opportunity to not investigate dose effects[250].

Only few studies used Electronic Healthcare Records databases, even though their great potential for pediatric research has been demonstrated[253]. It shows that the full potential of available data sources is not being exploited for comparative effectiveness research in children.

Confounding by indication is a serious problem in comparative effectiveness research and needs to be dealt with properly. The studies that we reviewed applied mostly traditional methods such as multivariate modelling analysis, matching and restriction. The more modern methods were applied in only few studies. Propensity scores were not used frequently although these are particularly suited for comparative effectiveness studies[247,254].

Based on quality assessment with the Newcastle-Ottawa scale, cohort studies had higher scores than case control studies. Unfortunately there is no established threshold to label studies as having low or high risk of bias[206]. Metwally et al used a cut-off of five[255], while Chowdhury et al used a cut-off of seven for medium risk of bias and nine for low risk of bias[256]. Studies on analgesics and immunosuppressants had the lowest median scores. The low number of stars for analgesics, a frequently utilized drug class, may be explained by the specific challenges in pain studies. Firstly, it is difficult to define pain as an outcome, which can lead to misclassification of

the outcome and secondly, it is difficult to assess the use of over-the-counter medications and medications that are used as needed in various doses[257].

Since this review didn't focus on any specific exposure or outcome, we introduced the most important restrictions (such as "Randomized Controlled Trial" as keywords) in the search algorithms in order to retrieve the most relevant articles and make the review process more feasible. This means that some relevant studies may have been missed. However, considering the size and the objectives of this review, we believe that this would not significantly influence our conclusions. Also, our review was limited to studies published in English language.

Based on the systematic review and the reported results we conclude that comparative effectiveness research in pediatric pharmacoepidemiology is heavily underdeveloped underlining the big potential that is available to improve our knowledge on the effects of drugs in children. State of the art methods should be applied to control for confounding, and many frequently drugs lack proper effectiveness studies and do not properly use the wealth of big data that is available. Collaboration between pharmacoepidemiologists, pediatricians and pediatric clinical pharmacologists should be boosted to improve the quantity and quality of the studies. With improvements in recognized areas, comparative effectiveness research might considerably contribute to better drug use in children.

Appendix 1: Full search strategy

Search criteria for Embase.com

((('drug therapy'/exp OR drug/exp OR 'drug therapy':lnk OR ((medication* OR medicine* OR drug* OR pharmac* OR medicament* OR 'medicinal product' OR 'medicinal products') NEAR/3 (therap* OR treatment* OR effect*)):ab,ti) AND ('comparative effectiveness'/de OR ((compar* NEAR/3 effect*)):ab,ti)) OR ('drug comparison'/exp OR ((medication* OR medicine* OR drug* OR pharmac* OR medicament* OR 'medicinal product' OR 'medicinal products') NEAR/3 (effectiv* OR efficien* OR compar*)):ab,ti)) AND ('epidemiology'/de OR pharmacoepidemiology/de OR 'cohort analysis'/de OR 'observational study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'longitudinal study'/de OR 'case control study'/exp OR 'Cross-sectional study'/exp OR (epidemiol* OR pharmacoepidemiol* OR (Cross NEXT/1 section*) OR (population NEXT/1 bas*) OR Cohort* OR (follow NEXT/1 up*) OR observation* OR Longitudinal OR retrospectiv* OR prospectiv* OR (case NEAR/3 (referen* OR match* OR nested OR 'cross over' OR centered OR coverage OR control*)) OR ('self controlled' NEXT/1 serie*)):ab,ti) AND (pediatrics/exp OR child/exp OR childhood/exp OR newborn/exp OR ((adolescent/exp OR adolescence/exp) NOT (adult/exp)) OR (child* OR pediatric* OR paediatric* OR infant* OR infancy OR baby OR babies OR toddler* OR neonate* OR newborn* OR premature* OR adolescen* OR teenage* OR preschool OR school* OR neonat*):ab,ti) NOT (vaccine/exp OR vaccination/exp OR 'randomized controlled trial'/exp OR 'traditional medicine'/exp OR homeopathy/exp OR 'alternative medicine'/exp OR (vaccin*):ti OR 'randomized controlled trial':ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Paper]/lim OR [Editorial]/lim) NOT ([animals]/lim NOT [humans]/lim)

Search criteria for Medline (via OvidSP)

(((exp drug therapy/ OR drug therapy.xs. OR ((medication* OR medicine* OR drug* OR pharmac* OR medicament* OR medicinal product OR medicinal products) ADJ3 (therap* OR treatment* OR effect*)).ab,ti.) AND (exp Comparative Effectiveness Research/ OR ((compar* ADJ3 effect*)).ab,ti.)) OR (((medication* OR medicine* OR drug* OR pharmac* OR medicament* OR medicinal product OR medicinal products) ADJ3 (effectiv* OR efficien* OR compar*)).ab,ti.)) AND (epidemiology/ OR epidemiology.xs. OR Epidemiologic Studies/ ORexp Cohort Studies/ OR observational study.pt. OR Case-Control Studies/ OR Cross-Sectional Studies/ OR (epidemiol* OR pharmacoepidemiol* OR (Cross ADJ section*) OR (population ADJ bas*) OR Cohort* OR (follow ADJ up*) OR observation* OR Longitudinal OR retrospectiv* OR prospectiv* OR (case ADJ3 (referen* OR match* OR nested OR cross over OR centered OR coverage OR control*)) OR (self controlled ADJ serie*)).ab,ti.) AND (exppediatrics/ OR exp child/ OR exp infant/ OR ((adolescent/) NOT (exp adult/)) OR (child* OR pediatric* OR paediatric* OR infant* OR infancy OR baby OR babies OR toddler* OR neonate* OR newborn* OR premature* OR adolescen* OR teenage* OR preschool OR school* OR neonat*).ab,ti.) NOT (exp vaccines/ OR exp vaccination/ OR exp Medicine, Traditional/ OR homeopathy/ OR exp Complementary Therapies/ OR randomized controlled trials.pt. OR (vaccin*).ti. OR randomized controlled trial.ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. NOT (exp animals/ NOT humans/)

Appendix 2: Data extraction form

General data

a. Unique ID |__|__|__|

b. First author (surname) ……

c. Year of publication |__|__|__|___|

d. Country (corresponding author) ……..

e. Journal (abbreviation)…….

f. Funding sources: |__| Public |__| Private |__| Public and private|__| No funding |__|unclear

Study design

a. Was study design clearly reported? |__| Yes |__| No

Some studies do not report on study design. If the answer to this question is 'no', provide answer to only question 'b'. In addition, answer the questions for quality assessment.

b. Number of designs studying the same association and using the same data…….

c. Cohort |__| Yes |__| No

d. Case-control |__| Yes |__| No (including nested case-control studies)

e. Case-based

i. self-controlled case series (SCCS) |__| Yes |__| No

ii. case cross-over |__| Yes |__| No

iii. case-time-control |__| Yes |__| No

iv. others |__| Yes |__| No

f. Data collection mode

i. prospective |__| Yes |__| No

ii. retrospective |__| Yes |__| No

iii. unclear |__| Yes |__| No

Study period

a. Date of Start of study period | _|__|__|___|DDMMYYYY

b. Date of End of study period |__|__|__|___| DDMMYYYY

Type of data

a. Only primary |__| (data collected specifically for the study)

b. Only secondary |__| (data collected for other purposes)

c. Mixed (combining primary and secondary)|__|

Study population (age range as in inclusion criteria)

a. Minimum age |__| and unit of age: days|__| months|__| years|__|

b. Maximum age|__| and unit of age: days|__| months|__| years|__|

c. unclear |__|

If 'c' then what is the minimum and maximum age given in the results (regardless of the study group)?

a. Minimum age |__| and unit of age: days|__| months|__| years|__|

b. Maximum age|__| and unit of age: days|__| months|__| years|__|

Outcome

a. Number of events studied……..

b. Event term(s)……..

c. Intermediate outcome |__| Yes |__| No

d. Clinical outcome |__| Yes |__| No

e. Was the event(s) definition(s) clearly described or sourced by a stated reference? |__| Yes |__| No

f. Was the event(s) validated by experts? |__| Yes |__| No

g. Was the event(s) validation (s) done blinded to exposure? |__| Yes |__| No

h. Characteristics of the event (s): (more than 1 option is possible)

a. Acute |__| Yes |__| No |__| Unclear

b. Rare |__| Yes |__| No |__| Unclear

c. Irreversible (e.g. mortality, handicap …) |__| Yes |__| No |__| Unclear

d. Recurrent |__| Yes |__| No |__| Unclear

e. Sudden onset |__| Yes |__| No |__| Unclear

i. Data sources from which data about the events were extracted

i. Institution or administrative /electronic Hospital records |__| Yes |__| No

ii. Paper medical charts/visits at the clinic |__| Yes |__| No

iii. Primary healthcare database |__| Yes |__| No

iv. Claims/reimbursement database |__| Yes |__| No

v. Registry |__| Yes |__| No

vi. Self-report questionnaire or query |__| Yes |__| No

vii. Telephone call |__| Yes |__| No

viii. Web site |__| Yes |__| No

ix. Interview |__| Yes |__| No

x. Others |__| Yes |__| No

Exposure

a. Was drug class studied|__| Yes |__| No

b. Number of drug classes studied ……..

c. Drug classes studied ……..

d. Was specific drug studied|__| Yes |__| No

e. Number of drugs studied……..

f. Substance name (WHO) ……..

g. ATC code reported |__| Yes |__| No ……if yes reported ATC code:……..

h. Characteristics of exposure in the paediatric indication (s):

i. Rare |__| Yes |__| No |__| Unclear

ii. Intermittent |__| Yes |__| No |__| Unclear

iii. Chronic |__| Yes |__| No |__| Unclear

iv. Exposure is changing medication (e.g. new dose, new formulation…) |__| Yes |__| No |__| Unclear

i. Is the effect of dose studied? |__| Yes |__| No

j. Data sources of exposure data

i. In patient dispensing data |__| Yes |__| No (electronic prescription data)

ii. Medical charts at the clinic |__| Yes |__| No (paper prescription charts)

iii. Primary healthcare database |__| Yes |__| No

iv. Outpatient dispensing data (pharmacy/claims) |__| Yes |__| No

v. Registry |__| Yes |__| No (including vaccination registry)

vi. Self-report questionnaire or query |__| Yes |__| No

vii. Telephone call |__| Yes |__| No

viii. Web site |__| Yes |__| No

ix. Interview |__| Yes |__| No

x. Others |__| Yes |__| No

Statistical analysis and Results

a. Calculation of a sample size is reported |__| Yes |__| No

If yes, required sample size calculated ……..

b. Total size of the study population

i. Number of cases……. / Number of controls…….

ii. Size of exposed cohort ……. / Size of non-exposed cohort ……. (absolute number for fixed cohorts and PY for dynamic cohorts)

iii. Number of cases…….

c. Length of follow-up was summarized using: |__| mean |__|median |__|unclear (If the answer is 'unclear', ignore questions 'i' and 'ii' that follow).

i. Exposed cohort ……. / Non-exposed cohort ……. (Cohort)

ii. Cases……. (SCCS)

d. Adjustment for confounding variables has been made |__| Yes |__| No

If yes what has been performed?

Restriction |__|

Matching |__|

Stratification|__|

Propensity score matching/adjusting/stratifying|__|

Instrumental variable |__|

Multivariate modelling analysis |__|

Adjusted by study design (case-only) |__|

e. Primary statistical analysis (these questions should be completed for primary analysis, if primary objective is not described or unclear then just complete the first question and not the remaining.

☐ Was the primary objective clearly defined? |__| Yes |__| No |__| unclear

☐ Were results on primary analysis presented for the paediatric population? Not presented|__| adjusted|__| unadjusted|__| unclear|__|

f. There is at least one statistically significant result for the paediatric population |__| Yes |__| No

If no, the authors discussed the problem of having a lack of power |__| Yes |__| No

Appendix 3: Quality assessment (Modified Newcastle-Ottawa Scale)

A. COHORT STUDIES (Scale)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be awarded for comparability

Selection

1. Representativeness of the exposed cohort

a. truly representative of the average _____ (describe) in the community* (if in general population with claims/medical records and no exclusion criteria)

b. somewhat representative of the average _____ in the community* (if in general population with claims/medical records and exclusion criteria)

c. selected group of users e.g. nurses, volunteers (e.g. from setting, if only in hospital whereas drug is also used outpatient)

d. no description of the derivation of the cohort

2. Selection of the non-exposed cohort

a. drawn from the same community as the exposed cohort*

b. drawn from a different source

c. no description of the derivation of the non-exposed cohort

3. Ascertainment of exposure

a. secure record (e.g. surgical records) *

b. structured interview *

c. written self-report

d. no description

4. Demonstration that outcome of interest was not present at start of study

a. yes *

b. no

Comparability

5. Comparability of cohorts on the basis of the design or analysis

a. study controls for age *

b. study controls for any additional factor *(sex or medical indication)

Exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Outcome

6. Assessment of outcome

a. independent blind assessment *

b. record linkage *

c. self-report

d. no description

7. Was follow-up long enough for outcomes to occur

a. yes (select an adequate follow up period for outcome of interest) *

b. no

8. Adequacy of follow up of cohorts (please assess whether fixed (reporting cumulative incidence with persons as denominator or dynamic cohort (person-time as denominator))

a. complete follow up in fixed cohort- all subjects accounted for *

b. subjects lost to follow up in fixed cohort unlikely to introduce bias - small number lost - > __80%__ % (select an adequate %) follow up, or description provided of those lost) *

c. dynamic cohort study *

d. follow up rate < ____% (select an adequate %) and no description of those lost in fixed cohort

e. no statement in fixed cohort

B. CASE-CONTROL

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

9. Is the case definition adequate?

a. yes, with independent validation *

b. yes, e.g. record linkage or based on self-reports

c. no description

10. Representativeness of the cases

a. consecutive or obviously representative series of cases *

b. potential for selection biases or not stated

11. Selection of Controls

a. community controls *

b. hospital controls

c. no description

12. Definition of Controls

a. no history of disease (endpoint) *

b. no description of source

Comparability

13. Comparability of cases and controls on the basis of the design or analysis

a. study controls for age *

b. study controls for any additional factor *(sex or indication)

Cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Exposure

14. Ascertainment of exposure

a. secure record (e.g. surgical records, medical charts) *

b. structured interview where blind to case/control status * or dispensing databases or prescription data or medical records *

c. interview not blinded to case/control status

d. written self-report

e. no description

15. Same method of ascertainment for cases and controls

a. yes *

b. no

16. Non-Response rate

a. Similar response rate for both cases and controls *

b. non respondents described

c. rate different and no designation

d. non-response rate not reported

Chapter 5.2 Comparing drug effectiveness in children using propensity scores based on different durations of patient history: a retrospective cohort study

Abstract

Purpose: In order to control for confounding by indication in comparative (drug) effectiveness studies, propensity scores (PS) methods may be utilized. Since childhood disease or outcomes are often acute we compared the impact of using different look back periods in electronic health care data, for the construct of the PSs. This was applied to a comparison of asthma exacerbations in combinations of corticosteroids/long-acting beta-2-agonists (ICS+LABA), either as fixed combination or used as loose combination (2 separate inhaler devices).

Methods: We created a cohort of children (5-17 years) diagnosed with asthma from the Dutch Integrated Primary Care information (IPCI) database. This cohort was subdivided in new users of inhaled corticosteroids/long-acting beta-2-agonists (ICS+LABA), either as fixed combination or used as loose combination (2 separate inhaler devices). The outcome of interest was moderate to severe asthma exacerbations. Propensity scores for type of treatment were fitted using co-morbidity and drug use history in different time windows namely 1 week, 1 month, 3 months, 1 year and full history prior to the start of treatment. Time to first asthma exacerbation was analysed with a Cox Proportional Hazard regression. PSs were used for matching, for inverse probability treatment weighting and as adjustment variable. We compared our results to published clinical trials on the efficacy of ICS+LABA in the prevention of asthma exacerbations.

Results: Out of 39,682 asthmatic children, 3,500 (8.8%) were new users of either ICS+LABA fixed (3,324 [95.0%]) or loose (176 [5.0%]). The crude HR for an asthma exacerbation, comparing ICS+LABA fixed to loose was 0.366 (95% confidence interval [CI]: 0.202; 0.664). PS-matched HR (1-week, 1-month and 3-month) were 0.480 (95% CI: 0.222; 1.036); 0.601 (95% CI: 0.262; 1.376) and 0.699 (95% CI: 0.311; 1.571) respectively.

Conclusions: PS models can be used to control for confounding in pediatric comparative (drug) effectiveness studies, the impact of different look back periods and the choice of the way to implement the PS is important. The results are comparable to clinical trial data on the comparison between fixed and loose ICS+LABA combinations in preventing worsening of asthma in children.

Introduction

Historically, children have been underrepresented in randomized clinical trials (RCTs) because of ethical, scientific and technical issues as well as commercial priorities[258]. Yet doctors prescribe approved drugs for children based on mainly evidence extrapolated from adults. Appropriate pediatric doses and formulations are often lacking. To evaluate the 'real-world' effectiveness of drug therapies in pediatrics, comparative effectiveness studies can be conducted. In such studies, drug exposure is dependent on prescribers' decisions taking into account the clinical (including disease severity), functional and/or behavioral characteristics of patients. In addition, the prescribers' preferences may vary over time. Selective prescribing can result in confounding by indication[259], which should be adequately controlled to obtain valid study results.

Asthma is a common and chronic condition in children. Inadequate treatment can result in poor quality of life. The Global Initiative for Asthma (GINA) recommends a step-wise approach to treating asthma, depending on the severity[21]. Step 3 and step 4 of asthma treatment consist of use of inhaled corticosteroids (ICS) in combination with long-acting beta-2-agonists (LABA)[260]. Both drugs can be combined in a single device (ICS+LABA fixed) thereby improving adherence to treatment with better outcomes, especially in children in whom treatment adherence may be worse[261]. Clinical trials already investigated the efficacy and safety of fixed combination of ICS+LABA compared to ICS in children with asthma. Clinical guidelines promote the use of ICS+LABA as fixed compared to loose combination as observational studies have shown that treatment adherence is higher for the fixed combination. In young children (<6 years), few studies, and to our knowledge none in children only, investigated the effectiveness of ICS+LABA as fixed combination vs loose combination in the prevention of asthma exacerbations. To obtain valid results, confounding by indication resulting from varying levels of asthma severity or from other patient characteristics should be adequately controlled.

Methods for confounding control depend on the type of design and treatment pattern(intermittent or chronic), but one of the most recommended strategies for controlling confounding by indication in cohort studies is the propensity score, especially when the number of events are small and the set of measurable risk factors high[262]. The PS is an estimated

probability of receiving a specific treatment rather than another, given a set of baseline characteristics[263]. It can be used to adjust for imbalances between treatment groups.

The factors that exacerbate asthma and result in treatment step-up are likely to occur shortly before such step-up but the relevant period over which confounding occurs is not clear. Since there is no clear guidance on the impact of, or use of different look-back periods to build the propensity score model we investigated this using a real life example of a comparison of the effectiveness of loose and fixed combinations of ICS + LABA on the prevention of asthma exacerbations as a prototype.

Methods

Study design and data source

We conducted a retrospective cohort study utilizing data from the Dutch Integrated Primary Care Information database (IPCI), a population-based general practice database. IPCI is a longitudinal observational dynamic database containing the complete electronic medical records of approximately 1,500,000 patients from about 450 general practitioners in the Netherlands. Regarding the Dutch healthcare system, patients register with a single General Practitioner (GP) who acts as a gatekeeper for secondary care. Patients' records comprise anonymized data pertaining to demographics, symptoms and diagnoses, referrals, laboratory tests and results, drug prescriptions, hospitalizations and discharge letters. Details of the data source have been published elsewhere [47]. Diagnoses are coded according to the International Classification for Primary Care (ICPC) [48], and drug names are coded following the World Health Organization-Anatomic Therapeutic Chemical (WHO-ATC) classification system. The study and access to the database were approved by the IPCI Governance Board (reference number 3/2012).

Study population

We created a cohort of all children (5-17 years) with asthma who were registered in the database for at least one year during the period January 1 2008 to December 31 2013. In order to enter the asthma cohort, the children had to be enrolled in IPCI for at least one year and have at least one asthma-specific disease code (ICPC='R96') together with prescription of asthma drugs within 3 months before or after an asthma code. The asthma drugs comprised

the following: inhaled corticosteroids (ICS), short-acting beta-2-agonists (SABA), long-acting beta-2-agonists (LABA), ICS+LABA fixed, leukotriene receptor antagonist (LTRA), short-acting muscarinic antagonist (SAMA), fixed combination of SABA+SAMA, xanthenes and anti-IgE treatment. Information on drug use was retrieved from prescription records by searching on the corresponding ATC codes. The codes are presented in appendix 1.

From the cohort of children with asthma, children entered the study cohort upon the 'first' prescription of ICS+LABA - either fixed (primary exposure) or loose (figure 1). For both treatment groups, use of the treatment (ICS+LABA fixed and ICS and LABA loose respectively) in the year before cohort entry was an exclusion criterium. All the children in the study cohorts were allowed to use other drugs for asthma. Start of follow-up was from cohort entry and end of follow-up was defined as the first of the following dates: leaving the GP practice, becoming 18 years old, switching from ICS+LABA fixed to the loose combination or vice versa, first occurrence of the study outcome or end of the study period.

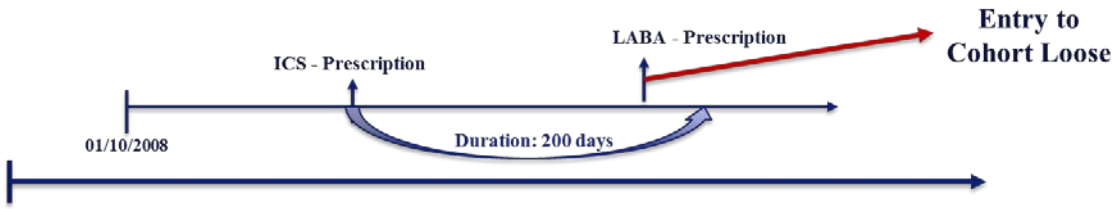


Figure 1: Entry of children with asthma into the 'ICS+LABA' (loose) group

Outcome

The study outcome was a first episode of moderate to severe asthma exacerbation. A moderate asthma exacerbation was defined as the need for systemic corticosteroids for treatment of asthma. Severe asthma exacerbation was defined as visit to the emergency department or hospitalization because of asthma exacerbation[264].

Covariates included in the propensity score models

Usually when calculating PS, all potential confounders (i.e. baseline characteristics related to either the outcome and/or exposure) are included in the PS model [265,266]. For the current study, the following characteristics were included in the PS models based on clinical knowledge and evidence from literature: [264,267-275]: Age (years), sex, calendar year of treatment start, season of treatment start (winter, spring, summer, and autumn), severity of asthma (medical history of exacerbations or use of high-dose ICS), history (or concomitant use) of SABA, SAMA and LTRA, comorbidity (obesity) and history of use (or concomitant use) of antacids, hypnotics, anxiolytics, antidepressants, anti-histamines, antibiotics, nasal preparations and aspirin. Previous history or current episodes of the following comorbidities were initially considered but since the drugs for treating the comorbidities were also included in the PS model, the comorbidities were excluded so that the model could converge: gastrointestinal reflux disease, anxiety, psychosis and lower respiratory tract infection. In order to investigate the impact of the different look back periods the aforementioned characteristics were extracted in the following periods prior to cohort entry (figure 2): 1 week, 1 month, 3 months, 1 year and the full history (within IPCI) of each study subject. It should be noted that the covariate information included for each successively longer period was incremental when compared to the previous period. Therefore the previous period was not nested within the longer period.

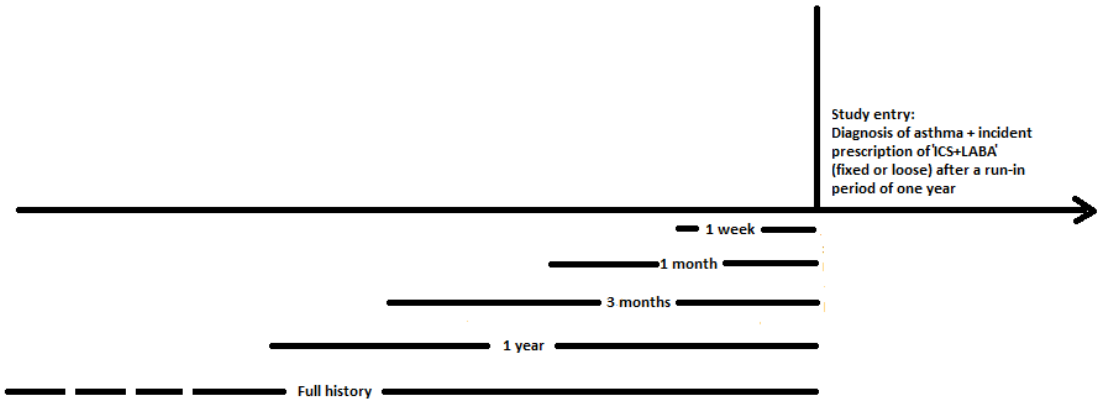


Figure 2: The different periods (before study entry) in which covariates were assessed, which were included in the calculation of propensity scores

Statistical analyses

Comparison of baseline characteristics prior to calculation of the propensity score was done using Chi-square test for categorical variables and analysis of variance for continuous variables. Cox proportional hazards regression models were applied to compare the time to first episode of exacerbation for children receiving incident prescription of ICS+LABA fixed versus loose. We calculated hazard ratios (HR) and corresponding 95% confidence intervals (CIs).

We used binary logistic regression to estimate the propensity score and compared the PS distribution between the exposure groups graphically.

We compared the crude HRs with the HRs from conventional multivariate modelling and from analyses using different PS methods: matching (PS-matching), inverse probability of treatment weighting (PS-IPTW), and adjustment (PS-adjustment) [276]. For matching, we applied caliper matching without replacement [276,277]. Compared to ICS+LABA fixed, fewer children received the loose combination and therefore, each subject receiving the loose combination was matched with a maximum of five subjects receiving ICS+LABA fixed. As recommended by Austin 2011, the matched subjects (from the group receiving ICS+LABA fixed) had to be within the caliper width of 0.2 of the standard deviation of the logit of the PS[278]. Both conventional multivariate modelling and the PS methods were repeated for each investigated period (figure 2). Analyses were conducted using SAS software, version 9.3 (SAS Institute).

Results

Study population

Out of 39,682 asthmatic children (5-17 years) that were identified during the study period, 3,500 (8.8%) received incident prescriptions of either ICS+LABA fixed (3324 [95.0%]) or loose (176 [5.0%]). Age, sex, season and year of cohort entry did not differ between the treatment groups, mean age was around 12 years (12.7 [fixed cohort] vs 11.6 [loose cohort]) and the majority was male (56%[fixed cohort] vs 54.5% [loose cohort]). Baseline characteristics of the varying co-variates during the different look back periods are provided in table 1.

Table 1: Baseline characteristics of the study population before propensity scores matching, according to the investigated periods

Look back-period Characteristics	1 week			1 month			3 months			1 year			Full history		
	Fixed[a] (3,324)	Loose[b] (176)	p-val.	Fixed (3,324)	Loose (176)	p-val.	Fixed (3,324)	Loose (176)	p-val.	Fixed (3,324)	Loose (176)	p-val.	Fixed (3,324)	Loose (176)	p-val.
History of moderate to severe asthma exacerbations (Yes; n [%])	34 (1.0)	11 (6.3)	**<0.01**	65 (2.0)	18(10.2)	**<0.01**	113(3.4)	25 (14.2)	**<0.01**	242 (7.3)	42 (23.9)	**<0.01**	1031 (31.0)	94 (53.4)	**<0.01**
History of use (or concomitant use) of specific anti-asthma drugs (Yes; n [%])															
SABA	620 (18.7)	63 (35.8)	**<0.01**	684 (20.6)	69 (39.2)	**<0.01**	836 (25.2)	77 (43.8)	**<0.01**	1,489(44.8)	105(59.7)	**<0.01**	2,559 (77.0)	151 (85.8)	**<0.01**
SAMA	2 (0.1)	1 (0.6)	**0.02**	5 (0.2)	1 (0.6)	0.20	9 (0.3)	1 (0.6)	0.47	21(0.6)	2 (1.1)	0.42	285(8.6)	21 (11.9)	0.12
LTRA	100 (3.0)	11 (6.3)	**0.02**	130 (3.9)	11 (6.3)	0.12	166(5.0)	13 (7.4)	0.16	235(7.1)	23 (13.1)	**<0.01**	428 (12.9)	32 (11.2)	**0.04**
Systemic corticosteroid	19 (0.6)	3 (1.7)	0.06	36 (1.1)	7 (4.0)	**<0.01**	64 (1.9)	11 (6.3)	**<0.01**	162 (4.9)	18 (10.2)	**<0.01**	674 (20.3)	40 (22.7)	0.43
History of (or current) comorbidities (Yes; n[%])															
Obesity	0 (0)	0 (0)	0.93	2 (0.1)	1 (0.6)	0.92	7 (0.2)	1 (0.6)	0.54	32 (1.0)	2 (1.1)	0.82	95 (2.9)	4 (2.3)	0.65
Gastrointestinal reflux disease	1 (0)	0 (0)	0.82	1 (0)	0 (0)	0.82	2 (0.1)	0 (0)	0.74	10 (0.3)	0 (0)	0.47	58 (1.7)	3 (1.7)	0.97
Anxiety	0 (0)	0 (0)	0.82	5 (0.2)	0 (0)	0.61	9 (0.3)	0 (0)	0.49	18 (0.5)	0 (0)	0.33	52 (1.6)	4 (2.3)	0.47
Lower respiratory tract disease	0 (0)	0 (0)	0.82	0 (0)	0 (0)	0.02	0 (0)	0 (0)	0.40	0 (0)	0 (0)	0.96	0 (0)	0 (0)	0.35
History (or															

concommitant use) of other drugs (Yes; n [%])															
Antacids	0 (0)	0 (0)	0.93	1 (0)	0 (0)	0.82	6 (0.2)	1 (0.6)	0.26	7 (0.2)	0(0)	0.54	33 (1.0)	0 (0)	0.18
Hypnotics	14 (0.4)	2 (1.1)	0.17	23 (0.7)	2 (1.1)	0.50	36 (1.1)	3 (1.7)	0.44	67 (2.0)	3 (1.7)	0.77	115 (3.5)	8 (4.6)	0.45
Anxiolytics	8 (0.2)	0 (0)	0.51	14 (0.4)	0 (0)	0.39	14 (0.4)	0 (0)	0.39	28 (0.8)	2 (1.1)	0.68	125 (3.8)	6 (3.4)	0.81
Antidepressants	7 (0.2)	0 (0)	0.54	8 (0.2)	0 (0)	0.51	10 (0.3)	0 (0)	0.47	16 (0.5)	2 (1.1)	0.24	26 (0.8)	3 (1.7)	0.19
Antihistamines	304 (9.2)	24 (13.6)	0.05	400 (12.0)	32 (18.2)	**0.02**	489 (14.7)	31 (17.6)	0.29	943 (28.4)	58 (33.0)	0.19	2,015 (60.6)	117 (66.5)	0.12
Antibiotics	94 (2.8)	4 (2.3)	0.66	149(4.5)	13 (7.4)	0.07	250(7.5)	16 (9.1)	0.44	734 (22.1)	50 (28.4)	0.05	2,764 (83.2)	147 (83.5)	0.90
Nasal preparations	284 (8.5)	25 (14.2)	**<0.01**	328 (9.9)	27 (15.3)	**0.02**	453 (13.6)	37 (21.0)	**<0.01**	847 (25.5)	61 (34.7)	**<0.01**	1,816 (54.6)	110 (62.5)	0..04
Aspirin	0 (0)	0 (0)	0.66	0 (0)	0 (0)	0.07	0 (0)	0 (0)	0.44	1 (0)	0 (0)	0.82	0 (0)	0 (0)	0.89

[a] Inhalational corticosteroids + Long-acting beta-adrenoceptor agonists (fixed combination); [b] Inhalational corticosteroids + Long-acting beta-adrenoceptor agonists (loose combination)

As could be expected; using longer look back periods increased the prevalence of the risk factors substantially. Compared to children receiving ICS+LABA fixed, significantly more (p-value < 0.01) of those receiving the loose combination had severe asthma; and this was observed across all the investigated periods. Significantly more (p-value < 0.01) of the children receiving the loose combination had received SABA. In contrast, few children were prescribed SAMA or LTRA. Of note, children in both exposure groups were similar in the comorbidities they experienced, including obesity, gastrointestinal reflux disease, anxiety and lower respiratory treat disease. Also, children in both exposure groups were similar in their use of drugs (whether in the past or together with the studied drugs), except for nasal preparations. Figure 3 shows that for all the investigated periods, the PS distribution for children receiving ICS+LABA fixed versus loose, overlapped considerably.

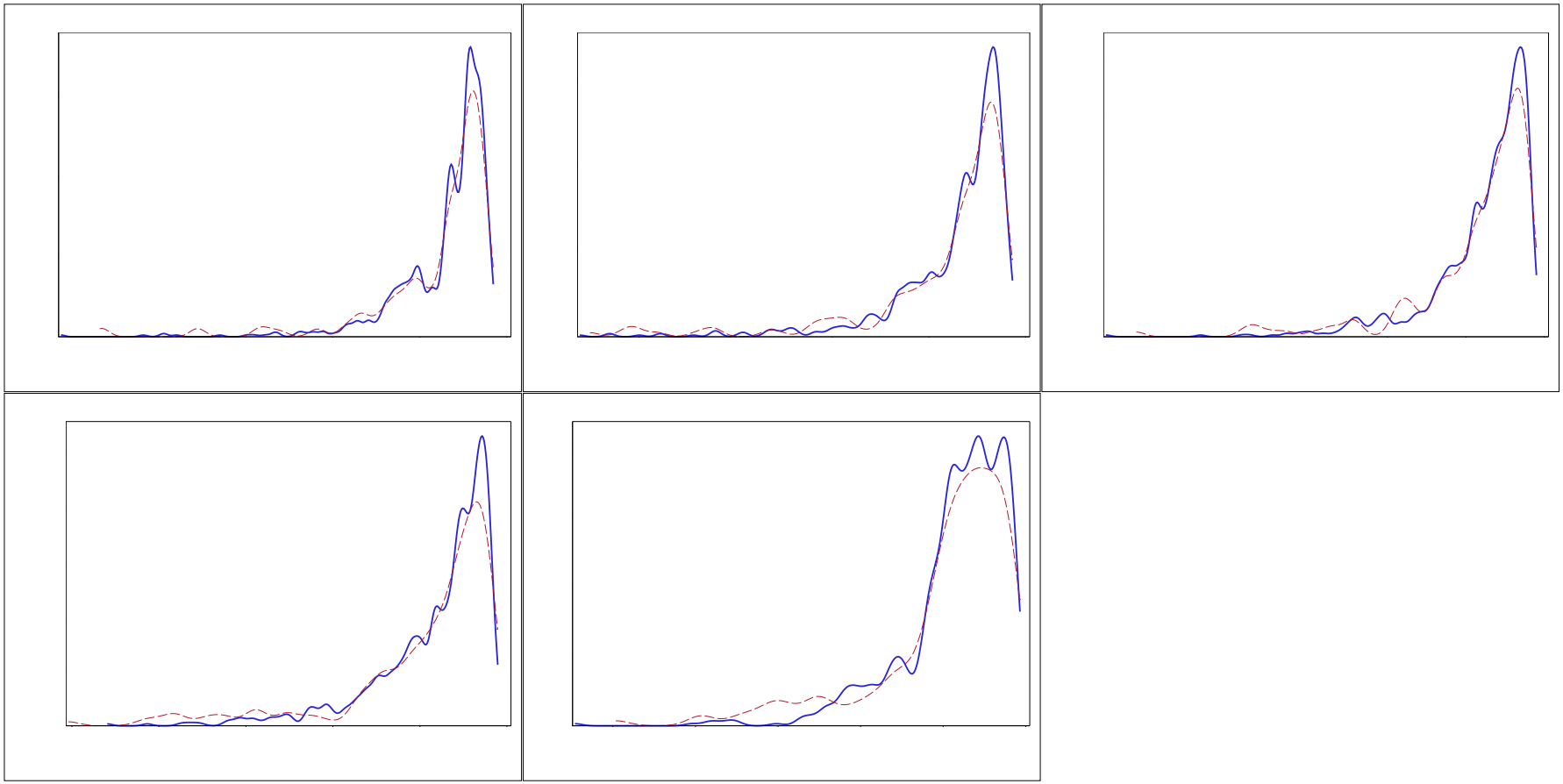


Figure 3: Distribution of propensity scores and overlap between the exposure groups, according to the investigated periods

After matching on propensity scores (for each period), the initially observed differences between the exposure groups were no longer present (table 2).

Table 2: Characteristics of the study populations after propensity scores matching, according to the investigated periods

	Matched sets based on propensity model using different history periods														
Look back-period		1 week			1 month			3 months			1 year			Full history	
Characteristics	**Fixed[a] (838)**	**Loose[b] (175)**	**p-val[c]**	**Fixed (824)**	**Loose (173)**	**p-val.**	**Fixed (828)**	**Loose (172)**	**p-val.**	**Fixed (819)**	**Loose (172)**	**p-val.**	**Fixed (811)**	**Loose (171)**	**p-val.**
Number of events (incidence [per 100 personyears])	30 (9.3)	13 (15.2)	0.14	25 (8)	11 (13.5)	0.14	31 (9.9)	13 (15.3)	0.19	31 (10)	12 (14.7)	0.26	26 (8.2)	11 (13.5)	0.16
History of severe asthma (Yes; n [%])	33(3.9)	11 (6.3)	0.17	58 (7.0)	17 (9.8)	0.21	93 (11.2)	23 (13.4)	0.43	158 (19.3)	40 (23.3)	0.24	423 (52.2)	90 (52.6)	0.91
History of use of specific anti-asthma drugs (Yes; n [%])															
SABA	257 (30.7)	62 (35.4	0.22	293 (35.6)	66 (38.2)	0.52	344 (41.6)	74 (43.0)	0.72	464 (56.7)	102 (59.3)	0.52	687 (84.7)	146 (85.4)	0.82
SAMA	2 (0.2)	0 (0)	0.52	1 (0.1)	0 (0)	0.65	1 (0.1)	0 (0)	0.65	7 (0.9)	1 (0.6)	0.72	93 (11.5)	20 (11.7)	0.93
LTRA	47 (5.6)	10 (5.7)	0.96	47 (5.7)	10 (5.8)	0.97	55 (6.6)	12 (7.0)	0.87	92 (11.2)	22 (12.8)	0.56	144 (17.8)	31 (18.1)	0.91
Prescence of comorbidities (Yes; n[%])															
Obesity	0 (0)	0 (0)	0.92	2 (0.2)	1 (0.6)	046	0 (0)	0 (0)	0.24	23 (2.8)	3 (1.7)	0.43	18 (2.2)	4 (2.3)	0.92
Concommitant drug use (Yes; n [%])															
Antacids	0 (0)	0 (0)	0.92	0 (0)	0 (0)	0.46	5 (0.6)	1 (0.6)	0.97	0 (0)	0 (0)	0.72	0 (0)	0 (0)	0.92
Hypnotics	9 (1.1)	2 (1.1)	0.94	8 (1.0)	1 (0.6)	0.62	13 (1.6)	3 (1.7)	0.87	12 (1.5)	3 (1.7)	0.79	35 (4.3)	7 (4.1)	0.90
Anxiolytics	0 (0)	0 (0)	0.91	0 (0)	0 (0)	0.41	0 (0)	0 (0)	0.72	8 (1.0)	2 (1.2)	0.82	32 (4)	6 (3.5)	0.79
Antidepressants	0 (0)	0 (0)	0.94	0 (0)	0 (0)	0.62	0 (0)	0 (0)	0.87	7 (0.9)	1 (0.6)	0.72	6 (0.7)	2 (1.2)	0.57

	93	24 (13.7)	0.32	107	27	0.36	148	31	0.96	278	57	0.84	547 (67.5)	114	0.84
Antihistaminies	(11.1)			(13.0)	(15.6)		(17.9)	(18.0)		(33.9)	(33.1)			(66.7)	
Antibiotics	18 (2.2)	4 (2.3)	0.91	44 (5.3)	12 (6.9)	0.41	70 (8.5)	16 (7.3)	0.72	221 (27)	48 (27.9)	0.80	677 (83.5)	142 (83)	0.89
Nasal	87	25 (14.3)	0.13	112	26	0.62	175	36	0.95	267	59	0.67	258 (31.8)	57	0.70
preparations	(10.4)			(13.6)	(15.0)		(21.1)	(20.9)		(32.6)	(34.3)			(33.3)	
Aspirin	0 (0)	0 (0)	0.91	0 (0)	0 (0)	0.41	0 (0)	0 (0)	0.72	0 (0)	0 (0)	0.80	0 (0)	0 (0)	0.68

[a] Inhalational corticosteroids + Long-acting beta-adrenoceptor agonists (fixed combination); [b] Inhalational corticosteroids + Long-acting beta-adrenoceptor agonists (loose combination)

Within the fixed cohort, 73 children experienced a moderate to severe asthma exacerbation resulting in an incidence of 6.3/100 person years. In the loose cohort, the incidence rate of moderate to severe asthma exacerbations was 15.1/100 person years (13 children with exacerbations). Crude and adjusted HRs (comparing the effect of ICS+LABA fixed versus loose) are provided in figure 4 for different ways of adjustment.

The crude HR on the risk of asthma exacerbations following use of ICS+LABA as fixed combination vs. ICS+LABA as loose combination was 0.366 (95% CI: 0.202; 0.664). With regard to the effect of PS on the change in estimate, PS-matching had the most pronounced impact on the change in estimate – in the 3 month look back period, the HR changed from 0.366 to 0.699 and was no longer statistically significant. See figures 4 and 5 for further details.

Time	Analysis	HazardRatio	95 % Hazard Ratio Confidence Limits
	Crude	0.366	(0.202 ; 0.664)
1 Week	Multivariate	0.406	(0.221 ; 0.745)
	PS-matching	0.480	(0.222 ; 1.306)
	PS-IPTW	0.381	(0.196 ; 0.742)
	PS-adjustment	0.433	(0.231 ; 0.811)
1 Month	Multivariate	0.468	(0.250 ; 0.877)
	PS-matching	0.601	(0.262 ; 1.375)
	PS-IPTW	0.408	(0.207 ; 0.806)
	PS-adjustment	0.565	(0.287 ; 1.112)
3 Months	Multivariate	0.533	(0.282 ; 1.008)
	PS-matching	0.699	(0.311 ; 1.571)
	PS-IPTW	0.428	(0.209 ; 0.878)
	PS-adjustment	0.564	(0.290 ; 1.097)
1 Year	Multivariate	0.552	(0.296 ; 1.030)
	PS-matching	0.561	(0.253 ; 1.244)
	PS-IPTW	0.452	(0.207 ; 0.988)
	PS-adjustment	0.608	(0.315 ; 1.174)
Full History	Multivariate	0.477	(0.259 ; 0.880)
	PS-matching	0.575	(0.242 ; 1.364)
	PS-IPTW	0.384	(0.166 ; 0.887)
	PS-adjustment	0.525	(0.282 ; 0.978)

Figure 4: Forest plot showing crude and adjusted hazard ratios (HRs) for the average effect of ICS+LABA fixed versus loose, according to the different look back periods

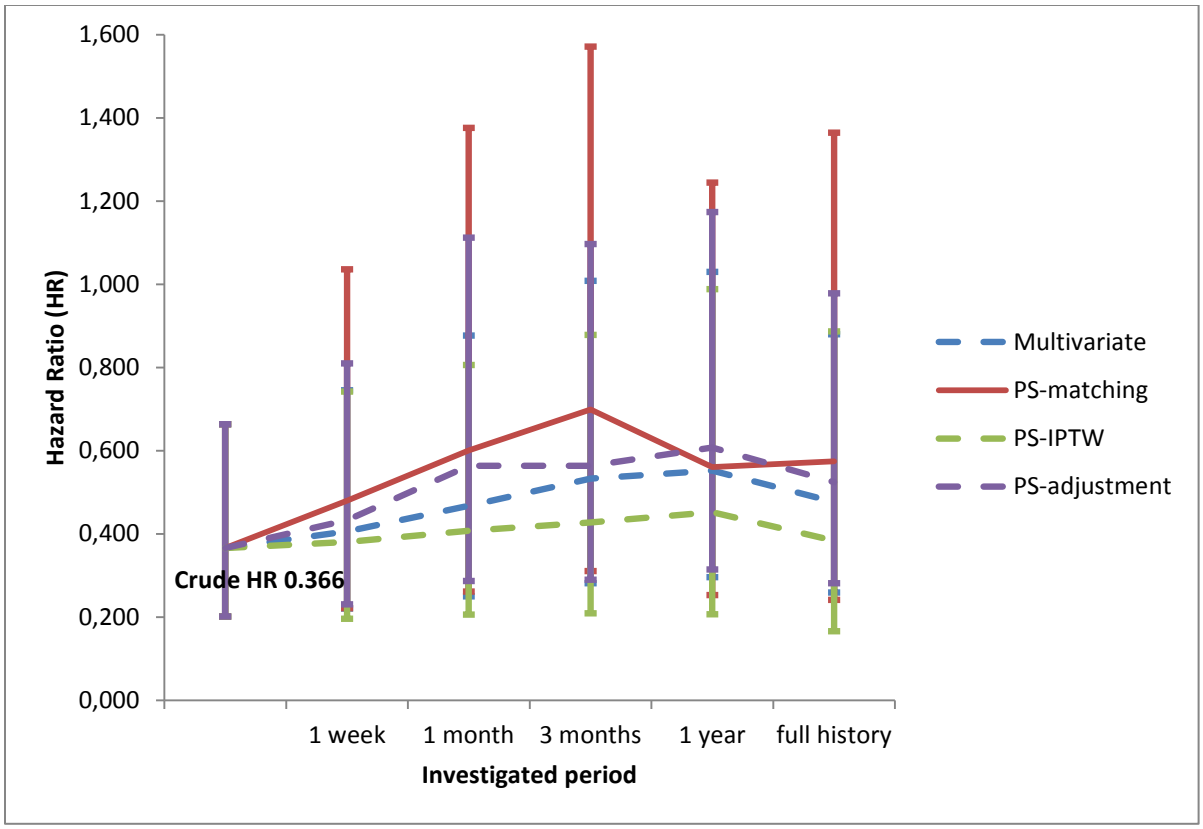


Figure 5: Hazard ratios comparing ICS+LABA fixed versus ICS+LABA loose, according to method used to control confounding and the investigated period

(Multivariate=conventional multivariate modelling; PS=propensity scores; IPTW=Inverse probability of treatment weighting)

Discussion

This study aimed to explore the impact of different look back periods on the estimation of the propensity score to deal with confounding by indication in pediatric comparative effectiveness studies. Based on a case study on the effects of fixed and loose ICS+LABA combinations we learned that the time period over which the PS is estimated makes quite some difference, as well as how the PS is used. Compared to other PS methods, matching on PS resulted in the largest changes in the point estimate. Regarding the investigated periods, controlling for characteristics that occurred during the 3 months before study entry resulted in the largest adjustment of the crude HR. The study demonstrated that children receiving the loose combination had more severe asthma but matching on the propensity score balanced the covariates in the different groups, as expected. Using a fixed combination reduced the risk of exacerbation in comparison to loose combination in most models, however not in the PS-matched analysis, in which a non-significant reduction was observed.

The usefulness of PS for controlling confounding in comparative effectiveness studies has been demonstrated multiple times [279,280]. To ensure that the PS is efficient, covariates related to the outcome (irrespective of the exposure) should always be included [265,266,281]. Crucial to achieving this is to know the most relevant period (before drug exposure) for identifying such covariates. In asthma, it is plausible that the factors predisposing to exacerbation and resulting in treatment step-up will occur just before such step-up [282]. Our results show that including covariates that occurred during the few months before treatment start resulted in the biggest change of estimate. This is not surprising; in asthmatic children specifically, respiratory tract infections can quickly trigger exacerbations[274,283]. Meanwhile a physician will most likely step-up treatment based on the current situation and not necessarily considering events that occurred further off in the past. The beneficial effects of the fixed combination of ICS+LABA compared to the loose combination has been confirmed in RCTs where the fixed combination had a larger effect on peak flow[284]. A recent observational study using data from the CPRD and the Optimum Patient Care Research Database also reported that fixed combinations of ICS+LABA are more effective in the prevention of asthma exacerbations[285]. Fixed combinations guarantee

use of ICS, which are crucial for asthma control. In addition, it is suggested that treatment adherence is higher in fixed combinations vs loose combinations.

Before implementing PS, the distributions of the PS should be checked to ensure there is sufficient overlap. We demonstrated reasonable overlap leading to little loss of matched pairs with increasing look back periods. There are various approaches to implementing PSs [276,281]. Among these, matching is the most common and has been extensively investigated [263,281,286,287]. Ali et al. 2015 stated that the choice of PS method should be dictated by the objective of the research. Since our primary objective was not to estimate treatment effect we decided to explore all methods and applied PS matching in addition to other methods. Austin 2014 concluded that calliper matching tended to yield estimates of treatment effect with less bias compared with optimal and nearest neighbor matching even though the latter two methods resulted in treatment estimates with negligibly less variability. Moreover, matching with replacement offered no advantage over matching without replacement. Perhaps these explain two of our findings. First, matching yielded effect estimates that are similar to results from RCTs although the investigated outcome in the RCTs was peak flow[284]. Secondly, the confidence interval for PS-matched HRs were wider (reflecting greater variability around the point estimates) when compared to the other PS methods that we applied. For matching, we applied a calliper (maximum distance) width of 0.2 of the standard deviation of the logit of the PS, recommended by Austin 2011 based on simulation studies[278]. Consequently, both exposure groups had similar characteristics irrespective of the look-back period. Of note, the proportions of patients that had experienced severe asthma in both groups was the same. Nearest neighbour matching without specifying a calliper can result in bad matches since the nearest neighbour can be very far away [288]. Therefore calliper matching helps to minimize bias in treatment effect [277]. The benefits of regression adjustment for the PS (PS-adjustment) are less clear because it involves modelling the outcome in addition to the PS [289]. Although the use and interest of PS-IPTW has increased in recent years, Austin and Stuart 2015 observed that most researchers did not check whether weighting balanced measured covariates between the

exposure groups [290]. The authors attributed this to lack of suitable methods. We recommend further research into these alternative methods.

Conclusion

PS models should be used to control for confounding in pediatric comparative (drug) effectiveness studies. The impact of different look back periods and the choice of the way to implement the PS are important. The results on a matched analysis are comparable to clinical trial data on the comparison between fixed and loose ICS+LABA combinations in preventing worsening of asthma.

Appendix 1: World Health Organization-Anatomic Therapeutic Chemical (WHO-ATC) codes used to identify anti-asthma drugs

- Inhaled corticosteroids (ICS): R03BA
- Short acting β2 agonists (SABA): R03AC02, R03AC03,R03AC04, R03AC05, R03AC06, R03AC07, R03AC08, R03AC09, R03AC10, R03AC15, R03AC16, R03AC17
- Long acting β2 agonists (LABA): R03AC11, R03AC12, R03AC13, R03AC14, R03AC18, R03AC19
- Fixed combination of ICS and LABA: R03AK06, R03AK07, R03AK08, R03AK09, R03AK10, R03AK11
- Leukotriene modifier (LTRA): R03DC01, R03DC02, R03DC03, R03DC04
- Short acting muscarinic antagonist (SAMA): R03BB01, R03BB02
- Fixed combination of SABA and SAMA: R03AL01, R03AL02, R03AK03, R03AK04
- Theophyllines: R03DA, R03DB
- Systemic glucocorticosteroids for the treatment of asthma: H02AB
- Anti-IgE treatment: R03DX05

Chapter 6 Other considerations

Chapter 6.1 Reference set for performance testing of pediatric vaccine safety signal detection methods and systems

Abstract

Background: Safety signal detection in spontaneous reporting system databases and electronic health-care records is key to detection of previously unknown adverse events following immunization. Various statistical methods for signal detection in these different datasources have been developed, however none are geared to the pediatric population and none specifically to vaccines. A reference set comprising pediatric vaccine-adverse event pairs is required for reliable performance testing of statistical methods within and across data sources.

Methods: The study was conducted within the context of the Global Research in Paediatrics (GRiP) project, as part of the seventh framework programme (FP7) of the European Commission. Criteria for the selection of vaccines considered in the reference set were routine and global use in the pediatric population. Adverse events were primarily selected based on importance. Outcome based systematic literature searches were performed for all identified vaccine-adverse event pairs and complemented by expert committee reports, evidence based decision support systems (e.g. Micromedex), and summaries of product characteristics. Classification into positive (PC) and negative control (NC) pairs was performed by two independent reviewers according to a pre-defined algorithm and discussed for consensus in case of disagreement.

Results: We selected 13 vaccines and 14 adverse events to be included in the reference set. From a total of 182 vaccine-adverse event pairs, we classified 18 as PC, 113 as NC and 51 as unclassifiable. Most classifications (91) were based on literature review, 45 were based on expert committee reports, and for 46 vaccine-adverse event pairs, an underlying pathomechanism was not plausible classifying the association as NC.

Conclusion: A reference set of vaccine-adverse event pairs was developed. We propose its use for com-paring signal detection methods and systems in the pediatric population.

Introduction

Every year, more infants, children, and adolescents are protected from illness, disability and death by virtue of global immunization programs [291]. Robust systems for monitoring benefits and risks of these programs and the vaccines administered are pivotal for program sustainability, the safety of the mostly healthy vaccine recipients and for maintaining public confidence in the vaccine[292]. This requires the ability to reliably detect safety signals in the pediatric population in a globally harmonized approach.

Today, various definitions of what constitutes a signal exist including definitions by WHO and CIOMS. The latter defined safety signal as follows: 'Information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of suffi-cient likelihood to justify verificatory action' [293,294]. Further, various methods for signal detection in spontaneous reporting system (SRS) databases and electronic healthcare records (EHR) have been developed for drugs[295]. Approaches to test their performance within systems and to compare systems are based on reference sets com-prising drug/vaccine-adverse event pairs with a high likelihood for a strong association (positive controls [PC]) and an absence of any association (negative controls [NC]). A reference set allows assessing if statistical methods can detect expected positive or no associations between events and vaccines. Previous approaches to develop such standards for drugs included consulting reference books such as the Physicians Drug Reference or Martindale[296], considering label changes[297], combining information from summary of product characteristics (SPC) and the literature as in two recent initiatives, the 'Observational Medical Outcomes Partner-ship (OMOP)' and the 'EU-ADR project' [298,299]. Work on validating approaches for the pediatric population is in progress [149].

However, to the best of our knowledge no such reference sets are available for vaccines. The aim of the current study was to develop such a reference set applicable in SRS databases and EHR around the globe to test performance of statistical methods for signal detection and the systems in general.

Methods

The study was conducted within the context of the Global Research in Paediatrics (GRiP) project, funded under the seventh framework programme (FP7) of the European Commission. FP7 is a funding program of the European Union for Research and Innovation. The main goal of GRiP is to establish a network of excellence to improve the development and safe use of medicines in children (www.grip- network.org).

Selection of vaccines

As the GRiP project focuses on the performance testing of sta-tistical methods for signal detection of pediatric vaccines, we only considered vaccines which are used in children for the construc-tion of the reference set. Vaccines also had to be routinely used for several years to ascertain adequate exposure and to allow detec-tion of associations with potentially rare adverse events of interest. As GRiP is an international project, most of the included vaccines should also have global utility and applicability. These criteria resulted in the inclusion of 13 commonly used vaccines: Bacil-lus Calmette–Guérin (BCG), diphtheria-tetanus-acellular pertussis (DTaP), diphtheria-tetanus-whole cell pertussis (DTPw), hepatitis A (HAV), hepatitis B (HBV), haemophilus influenzae type B (Hib), influenza (any type), pneumococcal (PV), meningococcal (MV), measles-mumps-rubella (MMR), oral polio (OPV), rotavirus (RV) and varicella zoster virus (VZV) vaccine.

Selection of adverse events

Given the expectation that few PCs might be found, adverse events were first selected based on their likelihood of being PCs for at least one vaccine based on literature review or their previous formal evaluation in an official report. The list was then narrowed down based on the specificity and importance of the event [300]. Thus, we selected clearly defined clinical entities to increase the likelihood of comprehensive literature searches and comparable data sets for performance testing. Adverse events generally considered to be “important” in the European and North American routine immunization programs were prioritized, because their reporting is generally required in most member states of these regions regardless of the available

knowledge on their causal association with specific vaccines. A total of 14 adverse events were included: anaphylaxis, arthritis, Bell's palsy, convulsions, insulin-dependent diabetes mellitus (IDDM), disseminated BCG-itis, encephalitis, disseminated Oka VZV, Guillain-Barré Syndrome (GBS), hypotonic hyporesponsive episode (HHE), intussuscep-tion, thrombocytopenia, vaccine-associated paralytic poliomyelitis (VAPP), and wheezing (reactive airway disease). This resulted in a total of 182 vaccine-adverse event pairs which needed to be clas-sified into PC or NC, or unclassifiable [UC].

Literature search and included studies

We performed literature searches until end of 2012 in MedLine through OvidSP (from 1946), Embase (all years) and the Cochrane Library and extracted the references to EndnoteX7. Table 1 exemplifies a search algorithm in Medline. All other search strategies are available from the authors on request. To maximize the number of potentially relevant studies, we performed the searches by outcome instead of specific searches by vaccine-event pair. An exception was made for anaphylaxis, where we performed a specific vaccine-event pair search for unknown associations (i.e. associations between anaphylaxis and OPV, RV, Hib, BCG and PV) to reduce the size of the highly sensitive search result. We focused on English literature with no age restrictions and reviewed the search result of vaccine-event pairs that were not previously reviewed and classified by the Institute of Medicine (IOM, 2011 report on 'Adverse effects of vaccines – Evidence and Causality', 2004 report on 'Influenza Vaccines and neurological complications') [300], or included in WHO information sheets or in the Vaccine Injury Table (VIT) [16] (91 in total). For each vaccine-event pair of inter-st, we included all relevant studies by title or abstract in the first instance, and by full text, if the title or abstract did not provide sufficient information. As in the IOM report, review papers, letters and editorials were not included. However, we checked these publications for any additional relevant references of original data.

Table 1: Search algorithm for Bell's palsy as an adverse event following immunization – an example

Medline	#1	exp Vaccines/ (Mesh)
	#2	exp Vaccination/ (Mesh)
	#3	exp Immunization/ (Mesh)
	#4	(vaccin$ OR immuni$ OR inoculat$).tw.
	#5	or/1-4
	#6	exp Bell Palsy/ (Mesh)
	#7	exp Facial Paralysis/ (Mesh)
	#8	(bell$ palsy OR facial$ paralys$ OR facial diplegia OR facial nerve paralys$ OR facial nerve palsy OR facial nerve paresis OR facial palsy OR facial paresis OR prosopoplegia OR facioplegia OR facial weakness OR facial synkinesis OR facial neuropath$).tw.
	#9	((seventh cranial nerve OR 7th cranial nerve) adj (palsy OR paralys$ OR paresis OR neuropath$)).tw.
	#10	((seventh nerve OR 7th nerve) adj (palsy OR paralys$ OR paresis OR neuropath$)).tw.
	#11	(face adj (paralys$ OR palsy OR paresis OR neuropath$)).tw.
	#12	or/6-11
	#13	5 and 12
	#14	limit 13 to (english language and humans)

We extracted study identifiers (author, title, publication year), details on type of study, vaccine of interest, sample size, age category of the study population, number of cases with the adverse event of interest and risk measure(s) by using a standard data extraction form (available from the authors upon request). A first extraction of relevant articles was performed individually by CN, MP and YB. Subsequent classification of vaccine-adverse event pairs based on the extracted literature (described below) was done by two reviewers (from the list of authors) in parallel and then dis-cussed for consensus with a third arbitrator (JB or TV) in case of uncertainties. The quality of the extraction process of relevant arti-cles was randomly double-checked.

Classification of vaccine-adverse event pairs

If a vaccine-adverse event pair had been evaluated by the IOM, WHO or VIT sources, we accepted this classification. Vaccine-adverse event associations, which were pathophysiologically unlikely (e.g. disseminated Oka VZV following HBV vaccine) were classified as NC. For all other vaccine-adverse event pairs, a lit-erature review was performed and the

algorithm as shown in Table 2 was applied. “Evidence” was defined as at least one ran-domized controlled trial or meta-analysis (level I) OR at least one controlled observational study (cohort/case–control/case-cross over/self-controlled case series) (level II). Surveillance studies counting events observed in spontaneous reporting (e.g. evaluation of number of reports to the US Vaccine Adverse Event Reporting System [VAERS]) and clinical trials reporting only the rates of the events of interest were not considered for classification. Fig. 1 displays our classification method graphically.

Table 2: Definitions of positive and negative control exposure-outcome pairs for performance testing of signal detection methods and systems

Positive control (PC)	Negative control (NC)	Unclassifiable (UC)
Evidence [*] **in favour** **AND** **Any additional information in favour** **AND** **Not enough evidence not in favour**	Absence of any *evidence* in our Pubmed searches and Micromedex AND No listing in SPC OR *Evidence* against an association AND No *evidence* in favour of the association	Neither fits the definitions of negative nor positive control
Explanations		
Enough evidence: at least one evidence of the same weight of evidence in favour	For case reports evidence is in favour if at least three independent case reports from different sources and concerning different patients OR less than three case reports but at least one with proven mechanism	

[a] Evidence: at least one properly designed randomized controlled trial or meta-analysis (level I) OR at least one controlled observational study (cohort/case-control/case-cross over/self-controlled case series) (level II);SPC – summary of product characteristics

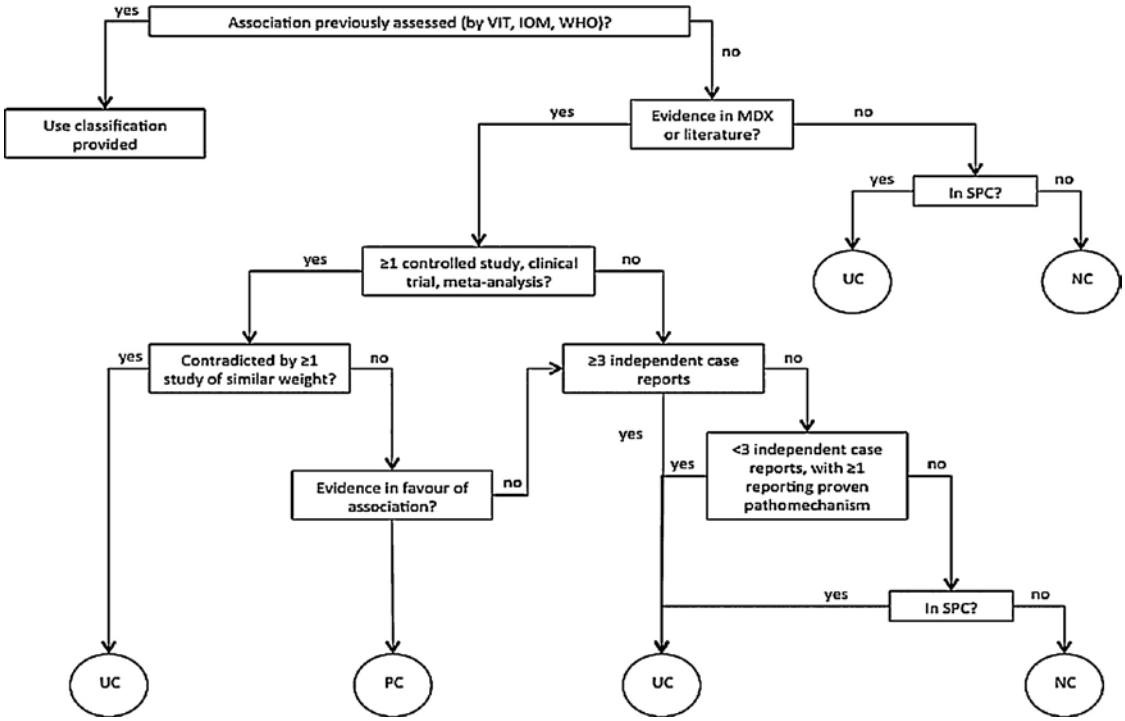


Fig. 1. Classification algorithm for development of the reference set for performance testing of signal detection methods and systems (considers pathophysiologically possiblevaccine-adverse event associations only) VIT, vaccine injury table; IOM, reports of the Institute of Medicine; MDX, micromedex; SPC, summary of product characteristics;UC, unclassifiable; PC, positive control; NC, negative control.

We have classified the exposure event pairs based on target dis-ease rather than on specific products. Thus, one exposure type may comprise different products immunizing against the same target disease. Therefore, this simplification will not allow for product level signal detection.

For the purpose of developing a reference set for performance testing of signal detection methods, the NC category was designed to comprise the following three subsets of evidence for the vaccine-adverse event pairs that have been classified by literature review: vaccine-adverse event pairs with evidence of absence of an association, those with absence of evidence and those with an unlikely pathomechanism for an association.

To identify any associations that may not be published in the scientific literature, but known to the industry or the regulators, we also checked the product labeling for vaccine-adverse event pairs classified as NC based on literature and Micromedex review. We could not check the labels for all vaccine brands and from all countries as there is a lack of a central resource for such information. Hence, we decided to focus on the Summary of Product Character-istics (SPC) of

European centrally authorized products based on a table created in the frame of the IMI project PROTECT [301]. If not available, then the UK SPC was used as it is in English or the WHO information leaflets.

Results

Literature search and included studies

The literature search resulted in a total of 42803 publications including 2871 for anaphylaxis, 8975 for arthritis, 340 for Bell's palsy, 3097 for convulsions, 6369 for diabetes mellitus, 6265 for encephalitis, 2578 for GBS, 3804 for HHE, 532 for intussusception, 4932 for thrombocytopenia and 3040 for wheezing. Of these pub-lications, 119 references of case reports, controlled observational studies, and meta-analyses were retained for classification of the 91 pathophysiologically possible vaccine-adverse event associations that had not been classified by other sources, i.e. IOM, WHO or VIT. For more than half of the associations, we did not find any relevant literature. Table 3 exemplifies the classification table for the event thrombocytopenia. A table referencing all studies considered for classification of each vaccine-adverse event pair is available from the authors upon request. Although we did not specifically focus on case reports or studies in children, the majority of the publications focused on children or on children and adults. Only for the outcome arthritis, most of the considered studies included only adults.

Table 3:Classification table for the event thrombocytopenia – an example

Type of publication	**Case report/Case series**		**Meta-analysis**		**Clinical trial**		**Controlled epidemiological study**		**Events in clinical trials or from sur-veillance studies***	**In MDX?**	**In SPC?**	**Classi-fication**
Evidence in favour?	*Yes / possible*	*no / unknown*	*Yes / possible*	*no / unknown*	*Yes / possible*	*no / unknown*	*Yes / possible*	*no / unknown*	*N/A*			
Vaccine												
BCG										no	no	NC
DTaP	1[C]**						1[C]		5 (A/C)	yes	yes	PC
DTPw	2[C], 1 [C]							1[A]		no	yes	UC
HAV							1[C]			yes	no	UC
HBV	1[A], 2[A/C] , 1 [C], 3 [C], 5 [C], 12 [C], 7 [C], 3 [C]						1 [A/C], 1 [A/C]		263 [A/C]	yes	yes	PC
PV	1 [A], 1 [A], 1[C]						1[A], not controlled		6[A/C]	yes	no	UC
Influenza	1[A], 1[A], 1[C]	1[A]					1[A]	1[A]	8[A/C]	yes	yes	UC
MV								1 [C]		no	no	NC
MMR												PC based on VIT
VZV												UC based on IOM
OPV	1[A]									no	no	NC
RV									1[A/C]	yes (PI)	no	NC

Hib	yes (1 report to FDA)	no	NC

[C], children; [A], adults; [A/C], children and adults; MDX, micromedex; PI, product information: if reference in Micromedex refers to product information, this was not considered as listed in SPC;
PC, positive control; NC, negative control; UC, unclassifiable; * not considered for classification; ** one entry refers to one publication
BCG, Bacillus Calmette–Guérin; DTaP, Diphteria-Tetanus-acellular Pertussis; DTPw, Diphteria-Tetanus-whole cell Pertussis; HAV, Hepatitis A Virus; HBV, Hepatitis B Virus; PV, Pneumococcal Virus; MV, Meningococcal Virus; MMR, Measles-Mumps-Rubella; VZV, Varicella Zoster Virus; OPV, Oral Polio Virus; RV, Rotavirus; Hib, Haemophilus Influenza Virus

Classification of vaccine-adverse event pairs

The reference table resulting from the vaccine-adverse event pair classifications is shown in Table 4. Forty-five vaccine-adverse event pairs were previously classified by the IOM, WHO and VIT, of which 14 were considered PC, 4 NC and 27 UC. The events of disseminated BCG-itis, VAPP and disseminated Oka strain VZV are specific to the respective vaccines and cannot be related to any other vaccination. Of the 91 vaccine-adverse event pairs, for which we did a literature review, only 4 could be classified as PC, 63 as NC, and 24 were UC. Overall, we identified 18 PC and 113 NC, respectively. Review of the literature showed that the number of controlled epidemiological studies on vaccine-adverse event pairs not already classified by expert committee reports was limited. Furthermore, we found only few published clinical trials specifically investigating any of the included vaccine-adverse event pairs and only three meta-analyses[302-304]. While the NC category comprises three quite different types of evidence, Table 5 specifies these sub-categories for transparency.

Table 4: Reference table of positive and negative controls for vaccine-adverse event pairs.

Vaccines	Anaphylaxis	Thrombo-cytopenia	Convulsions	Disseminated BCG-itis	HHE	Encephalitis	Intussus-ception	VAPP	Disseminated Oka VZV	Arthritis	GBS	Wheezing / Reactive Airway disease	IDDM	Bell's Palsy
BCG	UC (1)	NC (1)	NC (1)	WHO	NC (1)	NC (1)	NM	NM	NM	NC (1)	UC (2)	NC (2)	NC (2)	NC (2)
DTaP	IOM (1)	PC	IOM (1)	NM	MG	IOM (1), VIT	NM	NM	NM	IOM (1)	IOM (1)	NC (2)	IOM (1)	IOM (1)
DTPw	VIT	UC (1)	UC (1)	NM	MG	VIT	NM	NM	NM	IOM (1)	NC (2)	NC (2)	NC (2)	NC (1)
HAV	IOM (1)	UC (3)	NC (1)	NM	NC (1)	NC (1)	NM	NM	NM	NC (2)	IOM (1)	UC (2)	NC (1)	IOM (1)
HBV	IOM (1)	PC	IOM (1)	NM	NC (1)	IOM (1)	NM	NM	NM	IOM (1)	IOM (1)	UC (2)	NC (2)	UC (2)
PV	UC (2)	UC (3)	UC (2)	NM	UC (2)	NC (1)	NM	NM	NM	NC (2)	NC (1)	WHO	NC (1)	NC (1)
Influenza (any)	IOM (1)	UC (1)	IOM (1)	NM	NC (1)	IOM (1)	NM	NM	NM	IOM (1)	IOM (2)	IOM (1)**	NC (1)	IOM (1)
MV	IOM (1)	NC (2)	UC (2)	NM	UC (2)	IOM (1)	NM	NM	NM	NC (2)	IOM (1)	NC (2)	NC (1)	NC (1)
MMR	IOM (1)	VIT	IOM (1)*	NM	NC (1)	IOM (1)	NM	NM	NM	IOM (1)	IOM (1)	UC (1)	IOM (1)	NC (1)
VZV	IOM (1)	IOM (1)	IOM (1)	NM	NC (1)	IOM (1)	NM	NM	IOM (1)	IOM (1)	IOM (1)	UC (2)	NC (2)	UC (2)
OPV	NC (1)	NC (1)	NC (1)	NM	NC (1)	NC (1)	NC (2)	VIT	NM	NC (1)	UC (1)	NC (2)	NC (2)	NC (1)
RV	NC (1)	NC (1)	NC (2)	NM	NC (1)	NC (2)	UC (1)	NM	NM	NC (1)	NC (1)	NC (2)	NC (1)	NC (1)
Hib	UC (2)	NC (1)	UC (2)	NM	UC (2)	NC (1)	NC (1)	NM	NM	NC (1)	UC (2)	NC (2)	NC (2)	NC (1)

Detailed information about basis for classification; association classified by:

1) Literature review:
   - PC = positive control

- NC (1) = negative control - absence of evidence, NC (2) = negative control - evidence against
- UC (1) conflicting evidence, UC (2) absence of evidence or evidence of absence and ≥3 independent case reports/case series or proven pathomechanism or in SPC, UC (3) some evidence but not enough for positive control
- NM = pathomechanism not possible
- MG = review: Gold MS. Hypotonic-hyporesponsive episodes following pertussis vaccination: a cause for concern? Drug Saf. 2002;25(2):85-90. Review.[305]

2) Official report:

IOM (1) = Reports of the Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality (2011)[306]
IOM (2) = Reports of the Institute of Medicine, Influenza Vaccines and neurological complications (2004)[307]
VIT = Vaccine Injury Table (July 2011)[308]
WHO = WHO, World Health Organisation, vaccine reaction rates information sheets[309]

BCG, Bacillus Calmette–Guérin; DTaP, Diphteria-Tetanus-acellular Pertussis; DTPw, Diphteria-Tetanus-whole cell Pertussis; HAV, Hepatitis A Virus; HBV, Hepatitis B Virus; PV, Pneumococcal Virus; MV, Meningococcal Virus; MMR, Measles-Mumps-Rubella; VZV, Varicella Zoster Virus; OPV, Oral Polio Virus; RV, Rotavirus; Hib, Haemophilus Influenza Virus;

HHE, Hypotonic-Hyporesponsive Episode; VAPP, Vaccine-associated paralytic poliomyelitis; GBS, Guillain-Barré Syndrome; IDDM, type I Diabetes Mellitus

* = for febrile seizure
** = unclassifiable for children <5 years

	Positive control
	Negative control
	Unclassifiable

Table 5: Subcategories of negative control category

Evidence of absence	Absence of evidence	Pathomechanism unlikely
Thrombocytopenia	*Anaphylaxis*	*Disseminated BCG-it is*
MV	OPV, RV	DTaP, DTPw, HAV, HBV, PV, Influenza, MV, MMR, VZV, OPV, RV, Hib
Convulsion	*Thrombocytopenia*	
RV	BCG, OPV, RV, Hib	*Intussusception*
Encephalitis	*Convulsions*	BCG, DTaP, DTPw, HAV, HBV, PV, Influenza, MV, MMR, VZV
RV	BCG, HAV, OPV	
Intussuception	*HHE*	*Vaccine-associated paralytic poliomyelitis*
OPV	BCG, HAV, HBV, Influenza, MMR, VZV, OPV, RV	BCG, DTaP, DTPw, HAV, HBV, PV, Influenza, MV, MMR, VZV, RV, Hib
Arthritis	*Encephalitis*	
HAV, PV, MV	BCG, HAV, PV, OPV, Hib	Disseminated Oka VZV
Guillain-Barré Syndrome	*Intussusception*	BCG, DTaP, DTPw, HAV, HBV, PV, Influenza, MV, MMR, OPV, RV, Hib
DTPw,	Hib	
Wheezing, reactive airway disease	*Arthritis*	
BCG, DTaP, DTPw, MV, OPV, RV, Hib, Influenza*	BCG, OPV, RV, Hib	
Type 1 diabetes mellitus	*Guillain-Barré Syndrome*	
BCG, DTPw, HBV, VZV, OPV, Hib, DTaP*, MMR*	PV, RV	
Bell's palsy	*Type 1 diabetes mellitus*	
BCG, Influenza*	HAV, PV, Influenza, MV, RV	
	Bell's palsy	
	DTPw, PV, MV, MMR, RV, Hib	

*associations evaluated by IOM report

BCG, Bacillus Calmette–Guérin; DTaP, Diphteria-Tetanus-acellular Pertussis; DTPw, Diphteria-Tetanus-whole cell Pertussis; HAV, Hepatitis A Virus; HBV, Hepatitis B Virus; PV, Pneumococcal Virus; MV, Meningococcal Virus; MMR, Measles-Mumps-Rubella; VZV, Varicella Zoster Virus; OPV, Oral Polio Virus; RV, Rotavirus; Hib, Haemophilus Influenza Virus

Discussion

In this study, we presented our approach to create a reference set for performance testing of signal detection methods for vaccines in SRS databases and EHR and for functional performance testing across signal detection systems. To our knowledge, this is the first structured approach in this direction. We decided to apply an outcome driven approach to search the published literature due to the variability of antigen composition in the various products for the same target disease and the various combination vaccines addressing different selections of target disease. This resulted in a high number of references identified in the literature, but a relatively low number of articles used in the end for classification of vaccine-event pairs. In addition, only controlled studies and case reports were used for classification. From 182 vaccine-adverse event pairs, we classified 18 as PC, 113 as NC and 51 as unclassifiable.

In a study on performance testing of vaccine safety signal detection algorithms, van Holle L et al. have used information in the product label of vaccines as a proxy for true safety signals [310]. However, as vaccine coverage is usually high in the healthy and non-healthy population, the probability for case reports to emerge is high, and lists of adverse events in product labels tend to be long for multiple medical and legal reasons. Hence, we considered the listing of an adverse event in the SPC of vaccines not as evidence of an association but only as evidence against a negative association.

Our reference set of 18 (10%) positive, and 113 (62%) negative controls was similar with regards to the frequency of PC and NC in the reference set developed by OMOP with 17% PC and 83% NC for performance testing of eight analytic methods in ten observational healthcare databases [298]. The official sources (mainly the IOM report [300]) classified the majority of the vaccine-adverse event pairs as UC ('Evidence is inadequate to accept or reject a causal relationship') and only very few pairs as NC. In contrast, in our review, we classified more than two thirds of the pairs as NC and less than one third as UC. This difference may be explained by the different aim of the IOM committee evaluating causality. Therefore, the IOM committee did not consider absence of evidence to reject a causal association. The IOM Committee only rejected a causal relationship in presence of strong and convincing evidence against a causal

relationship. Furthermore, evidence they found had to be strong and the studies of good methodological quality for favoring acceptance or rejection of a causal association. Our classification system is established for a different purpose. We did not set out to verify a causal association but to establish a reference set for signal detection methods. Thus, the findings of the IOM report inform our purpose, while our findings may not be interpreted as an extension of the IOM table. Our reference table classifies absence of evidence and evidence of absence as NC. This is because most of the vaccines in our reference set have been on the market for quite some time, and we assumed that at least some case reports could have been expected.

However, the influence of the unequal distribution of few PC in our reference set as compared with NC needs to be evaluated in the frame of the performance measurement of statistical methods and if necessary, additional PC need to be identified.

As mentioned in the methodology section, we focused on clearly defined adverse events. The example of arthritis showed us that this is particularly important. Initially, we had chosen arthralgia as event of interest. Upon review of the literature, we noticed that there were no studies investigating an association between vaccines and arthralgia. Furthermore, arthralgia is not a disease entity, but a symptom with various underlying causes, and it is a frequently observed event in clinical trials. We hence decided to focus on various forms of arthritis as clear disease entities.

The authors acknowledge that the published evidence for classification as positive or negative control pair includes data obtained in adults. As all selected vaccines are given in the pediatric population, and all events can be observed in the pediatric population, we do not consider this a weakness of the method applied. If we assess unexpected results though when testing the performance of signal detection methods using events rather seen in adults (e.g. arthritis), we will evaluate the findings.

We limited our literature search to English literature only. Furthermore, for non-Mesh terms used in the search algorithms, we only searched in title, abstract, and keywords. With these limitations, we may have missed some articles. However, we do not think that availability of such articles would have changed the final classification as our search was already quite broad. For a recent systematic review on the safety of vaccines used for routine immunization of US

children [311], the authors updated the search in the IOM report from 2011 and included additional vaccines. No additional studies relevant for our work were identified in this review article which could have influenced our reference set.

As in the IOM report, we did not differentiate by age, vaccine antigen or time of publication when classifying the vaccine-adverse event pairs based on the literature. While we collected this information for each reference in our literature review, we do not have this information extracted consistently from the publications referenced in the IOM report and may have to go back to the original literature should the evaluation of the performance of statistical methods for signal detection in databases make this necessary.

Independent of the reference set, another important issue that needs to be evaluated in performance evaluation of statistical methods for signal detection is the influence of the database characteristics on the methods. The amount of reports to a SRS is dependent on various factors, such as the time since market introduction of a new product, seriousness of the report, media attention and availability of compensation programs. EHR are less influenced by those factors, however, completeness of the data may have an influence in this case. Since we used events that are likely to be reported, we may introduce a bias in the comparison for methods between SRS and EHR.

We wish to highlight that the proposed reference set is based on knowledge accumulated up to the point of the literature review, i.e. until end of 2012. If we had closed the search of evidence at any different point in time, the reference set may be different, e.g. vaccine-adverse event pairs classified as NC or UC may become PC over time because of potential accumulation of evidence. This time-dependency is shown in Fig. 2 and needs to be considered and evaluated in the performance testing of the signal detection methods and highlights the need for cyclical revision. Furthermore, it precludes the reference set to be used outside the purpose of evaluating signal detection methods.

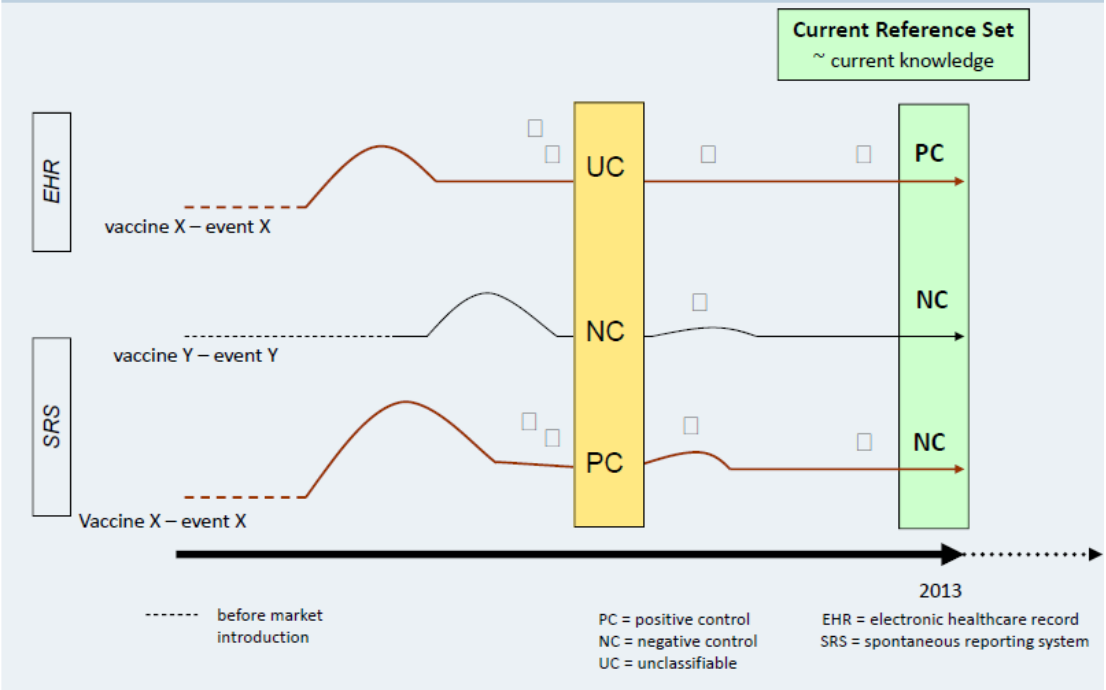


Fig. 2. Time-dependency of reference set validity.

Well-tested statistical methods for safety signal detection of pediatric vaccines and well-tested signal detection systems are a precondition for optimization of methods and systems as well as meaningful interpretation of results. A reference set is a necessary condition for such improvements. For example, performance testing of pediatric vaccine signal detection methods and systems with the help of this reference set will be done as a next step. Thus, we trust that our work contributes to the improvement of vaccine pharmacovigilance in children.

Conclusion

Following a systematic approach, we have developed a reference set for performance testing of pediatric vaccine safety signal detection methods and systems. The method and established database allow for regular update of this reference set pending new evidence and field testing.

Chapter 6.2 Current needs in pediatric pharmacoepidemiology

Abstract

Purpose: We report on a needs assessment conducted by the International Society of Pharmacoepidemiology (ISPE) Pediatric Special Interest Group (SIG) to identify critical needs in pediatric pharmacoepidemiology and directions for future activities.

Methods: A mixed methods survey using a structured interview was conducted in the SIG and ISPE membership to elicit information about current activities in pediatric pharmacoepidemiology and identify critical methodologic issues. The interviews were conducted in two phases over 2013 and 2014, beginning with interviews of SIG members, and expanding to the wider ISPE membership. Members of the SIG conducted the interviews and summarized the responses.

Results: Twenty-nine ISPE members participated in the needs assessment The respondents reported working with a total of 59 distinct databases, with only 8 databases used by more than one respondent.. Seventeen respondents (57%) reported issues of limited sample sizes, noting that the problem intensifies when studying age sub-groups or specific genetic populations. Missing data elements were a problem in three main areas: lack of detailed medication information, inability to link to parental data, and lack of detailed information about age. Respondents reported the need for data elements not typically required in studies of adults, such as birthweight and current height and weight, as well as school performance and mental health status.

Conclusions: Our needs assessment describes a preliminary picture of the emerging sub-specialty of pediatric pharmacoepidemiology encompassing a range of age sub-groups, disease areas and medical specialties. The assessment also documents a body of methodologic challenges unique to pharmacoepidemiologic research in children.

Background

This report summarizes the results of a needs assessment conducted by the International Society for Pharmacoepidemiology (ISPE) Pediatric Special Interest Group (SIG) to identify key issues in the emerging sub-specialty of pediatric pharmacoepidemiology. Pediatric pharmacoepidemiology has grown out of the historic exclusion of children from clinical trials, a practice that was meant to protect children from the risks inherent in participating in clinical trials [312] [313,314]. As a result of decades of this policy, and despite efforts to reverse the policy, clinical trial data about efficacy and safety of medications in children are not available for many widely used medications. This has led, in turn, to a general lack of pediatric labeling for many drugs and the widespread off-label use of medications in children [315-318]. Other factors include limitations in extrapolating data from studies conducted in adults to children because of the many differences between adults and children with regard to organ development, metabolism, absorption, pharmacokinetics and pharmacodynamics [319,320], and the increase in the numbers of medications used by children, as well as the numbers of children using medications on a regular basis.

Pediatric pharmacoepidemiology relies on general methods developed to study all age groups. However, challenges unique to pediatric populations have led to the emergence of a separate sub-specialty within pharmacoepidemiology. ISPE, as the sole professional organization dedicated to pharmacoepidemiology, has a unique role in fostering the development of methods and best practices in pediatric pharmacoepidemiology. The ISPE Pediatric SIG undertook the needs assessment reported below to identify the critical scientific and educational issues in the emergence of pediatric pharmacoepidemiology as a sub-specialty.

Methods

A mixed methods approach was used with a two-phased series of qualitative interviews conducted in 2013 to identify critical needs in pediatric pharmacoepidemiology and directions for future activities of the ISPE Pediatric SIG, followed by quantitative descriptive analysis. An interview form was developed by a subgroup of SIG members and covered four domains: Research and Scientific Needs, Educational Needs, SIG Communications/Organizational Needs,

and participant Demographics. The expected time to provide verbal answers to all questions by each interviewee was approximately 15 minutes. No compensation for the interviewee's time was provided. The instrument was piloted with two interviews, and the pilot data were included along with data collected from subsequent interviews. The first phase of interviews targeted Pediatric SIG members and was conducted in June and July of 2013. Volunteers from the SIG with survey expertise conducted interviews, and all members of the SIG were invited to participate. The survey was conducted by telephone interview, and when telephone interview was not possible respondents were offered the opportunity to respond by email. We also allowed the interviewer to send the instrument to the respondent to allow time for the respondent to consider the questions. For telephone interviews, we agreed that the interviewer need not follow the survey wording verbatim, but should consider the script as a guide. Interviewers were encouraged to use judgment with probes and comments. When asking about additional comments interviewers encouraged open-ended responses (more information) rather than placing narrow restrictions on responses to ensure the needs assessment encompassed concepts we might not have anticipated.

A second phase was conducted in December 2013 - January 2014 targeting the wider ISPE membership. Respondents for Phase II were identified by soliciting suggestions from other SIG chairs and from Phase I respondents. The identical interview instrument was used except questions about internal SIG communications/operations were eliminated. For both phases, responses were collated manually, and synthesized in a narrative form, as well as simple coding and categorization for descriptive summaries. Responses from the two phases were summarized separately and then combined after reviewing the characteristics of respondents in each phase of the needs assessment. Descriptive analysis was then performed to generate summary data.

Results

Twenty-nine ISPE members participated in the needs assessment with sixteen in Phase I and thirteen in Phase II (see Table 1). This constituted approximately 50% of SIG members, and 2.2% of ISPE membership. The majority of respondents were at a higher level of seniority with

19 (66%) having 10 or years experience after receipt of their terminal degree. The largest number reported working in academia (11/29 or 38%) followed by industry (7/29 or 24%). The countries of respondents reflected the diversity of ISPE membership, and the largest number of respondents were from the United States (19/29, 66%), followed by two each from Canada, the Netherlands and Taiwan.

Table 1: Research, scientific and educational needs.

Survey Question	Response n (%) Total: 29 respondents
Research and Scientific Needs	
Which databases do you use most frequently ?	28 (96%) provided 59 distinct databases, with almost no overlap between respondents
What types of databases do you use†?	
National or government sponsored	16 (55%)
Insurance claims	14 (48%)
Registry	11 (38%)
Outpatient	10 (34%)
Inpatient	4 (14%)
Adverse Event	2 (7%)
Pediatric Network	2 (7%)
Have there been times in your research when the ability to answer questions in pediatric pharmacoepidemiology was limited because of an absence of data sources or adequate sample sizes, a problem especially likely to occur in pediatric research? What kind of data elements have you found to be missing or problematic? If data or adequate sample sizes weren't available, how did you address the study questions?	
Sample size challenges encountered	17 (57%)
Sample size not an issue	3 (10%)
No comment on sample size	9 (31%)
Other issues/themes identified:	**Inadequate medication information -** lack of : dose, defined daily dose for pediatrics, time of administration, indication for treatment, reasons for changes to dose or therapy **Inadequate clinical information** - lack of current height or weight, laboratory results, access to relevant parental clinical or behavioral information such as smoking, achievement of developmental milestones **Inadequate demographic or other information -** lack of: gestational age at birth, birthweight/length, small for gestational age status, specific date of birth (rather than just birth year), school performance, mental health status
How small sample size addressed:	**Multiples approach:** combine databases or studies; triangulate results
How missing data addressed:	Imputation; limit analysis to subset with available data; bridging strategy for common elements of a comparative analysis

What do you think are the most pressing clinical questions that need to be addressed by pediatric pharmacoepidemiology*?"	
Disease Area	Psychiatry/Mental Health (n=9) Infectious Disease (n=7) Asthma (n=4) Oncology (n=4) Sedation/Pain (n=4) Diabetes (n=3) Rheumatology (n=3) Other: Critical care, dermatology, ophthalmology, rare disease (n=1 each)
Drug Category	Vaccines (n=4) Antiretrovirals (n=3) Antibiotics (n=3) Other: Analgesics, anti-depressants, anti-convulsives, growth hormone, over-the-counter medications (n=1 each)
Pediatric Subpopulations	Preterm babies; neonates; genetic variations; global variations in pediatric diseases and health; socioeconomic groups such as foster children
Methodologic	Pediatric treatment effectiveness measures; defining pediatric laboratory test norms; long term effects on growth or development; changing type and/or susceptibility to adverse drug reactions during growth and maturation

Educational Needs

Are you aware of training programs specifically dedicated to pediatric pharmacoepidemiology? What are they?	10 programs identified: • 3 specific to Pediatric Pharmacoepidemiology: 2 medical school fellowships, 1 graduate level at college of pharmacy • 6 with Pediatric Pharmacoepdemiology content: Schools of public health, medical school department of pharmacology, colleges of pharmacy
What other resources are most needed to further educate people about pediatric pharmacoepidemiology†?	
ISPE Course	18 (62%)
Online Webinar	15 (52%)
Continuing Education for pediatricians	14 (48%)
Other (please provide)	10 (34%)
Suggestions:	Presentations at scientific congresses; whitepaper/peer reviewed journal article (n=3); add to pharmacoepidemiology curricula; add to ISPE or other relevant scientific organizations' learning resources

†Respondents could provide multiple categories and thus results are >100%

* Respondents varied in their interpretation of the question, often including a focus on what issues or themes on which they were currently working.

The survey assessed research, scientific and educational needs; the results are shown in Table 1. The vast majority (28 of 29) of respondents reported working with secondary databases such as insurance claims, primary care, pharmacy, or hospital databases. There was almost no overlap in the databases used by respondents with only eight databases mentioned by more

than one respondent. Seventeen respondents (57%) reported an issue of limited sample sizes, noting that the problem intensifies when studying age sub-groups or specific genetic populations. The question about missing data elements elicited discussion in three main areas: lack of detailed medication information, inability to link to parental data, and lack of detailed information about age, especially for newborns and infants.

Discussion

To our knowledge, this needs assessment is the first to address the emerging discipline of pediatric pharmacoepidemiology. It drew on expertise from the leading professional organization committed to pharmacoepidemiology, and solicited feedback from members with an interest in pediatric pharmacoepidemiology. It serves as a starting point for a thoughtful discussion of the current needs in pediatric pharmacoepidemiology.

A striking finding was that respondents reported working with a total of 59 distinct databases of various types, and that only eight databases were mentioned by more than one respondent. This expands the information obtained from an earlier survey which identified 25 datasources from 12 European countries as suitable for pediatric pharmacoepidemiology [321]. Our methodology went beyond a survey of databases by asking professionals to indicate the databases they were using, and we did not restrict our search to Europe. Both methods resulted in a large number of databases that can be used for pediatric pharmacoepidemiology, and it seems likely that our combined lists do not cover all the potential databases. It is also not clear how the pattern seen in our sample (many databases with few being used by more than one investigator) compares to the use of databases in other branches of pharmacoepidemiology. The pattern we observed seems to suggest diverse activities perhaps reflecting the wide range of disease areas investigated, or the large number (16) of respondents using national databases. If researchers in different countries rely on their national databases to conduct pediatric pharmacoepidemiology, it follows that an international group of researchers will not be using the same databases. The implications for developing an international body of knowledge about medications in children is unclear, as is the validity of

extrapolating from a national database to a global context. It may suggest that pediatric studies are less likely to be conducted across international boundaries than are adult studies.

With regard to methodologic issues, 57% of respondents expressed concern about sample sizes, but the remainder did not. Respondents raised the issue of a lack of information about medication dosing, noting its particular importance because dosing guidelines are often unavailable for children, and dosing variation can have a big impact on efficacy and safety in children. A third area of methodologic concern were the problems in linking children's records to the mother's record, family information or school performance, although recent efforts have demonstrated some success in creating mother-baby linkages [322]. Finally, respondents noted the need for gestational age and more detailed age information especially in younger age groups where age in days or weeks is of importance, but extending up to older age groups where age in months or even years may be missing.

Psychiatry and mental health were the areas mentioned most frequently by respondents, followed by infectious disease, and a range of conditions including asthma, oncology, and sedation. It is not clear whether this distribution reflects the priorities of pediatric pharmacoepidemiology outside of ISPE respondents, or some other factors. The increasing use of psychotropic medications in children has been well documented and the cluster of survey respondents working in this disease area may reflect the growing use of these medications [323-326].

A preliminary picture of the emerging sub-specialty of pediatric pharmacoepidemiology encompasses a range of age sub-groups, disease areas and medical specialties. This diversity of activities may pose a challenge as the field begins to coalesce. We also identified distinct methodologic issues that are of critical importance in pediatric pharmacoepidemiology and merit further discussion. These center around sample sizes, data availability, and data linkage. Finally, we identified the need for greater educational efforts in a range of venues including graduate and professional training. The ISPE Pediatric SIG has incorporated the information in planning its future activities, and offered the first pre-conference course in Pediatric Pharmacoepidemiology at the annual ICPE conference in 2015. The SIG will continue to serve as a platform for ongoing development of the sub-specialty of pediatric pharmacoepidemiology.

Chapter 7 Summary and general discussion

Chapter 7.1 Summary and general discussion

Disease occurrence and the effects of drug use in children: the need for valid evidence

Licensed drugs have limited or no direct evidence of safety and effectiveness in children and have resulted in high levels of unlicensed and off-label drug use[18-22]. To address this unfairness, evidence on safety and effectiveness should be generated using 'real-world' data in children. Methods need to be made 'child-proof'. In this thesis, we study and develop methods for assessing the occurrence of disease, and drug safety and effectiveness in children. Based on our findings, we make appropriate recommendations.

Accurately estimating the occurrence of diseases in children: a necessity

In order to license drugs, valid estimates of disease occurrence are required but often lacking. Such estimates can be easily obtained from population-based healthcare data like electronic health records (EHRs), but specific attention should be paid to the peculiarities of the databases themselves and those of childhood diseases.

Electronic health care databases usually contain only 'snapshots' of a person's life time. Entry may depend on healthcare system, age, insurance, residency, employment status, and exit may depend on the same factors as well as death. Following a new-born from birth till death is not possible, also because computerization of health care is relatively novel. In spite of these limitations, we can regard information in health care databases as dynamic populations applying a person-time denominator rather than fixed person cohort, however we will always need to account for the fact that we have right and left censoring. Another challenge of real world data is that it reflects real world patient behaviour, which means that we cannot estimate the duration of disease (patients typically visit the physician when they have complaints and not when such complaints are cured). Therefore assumptions need to be made on the duration of disease episodes for non-chronic conditions, and this may have impact on the disease occurrence measures.

In this thesis we tried to demonstrate that disease occurrence can be estimated from electronic health care databases, using the Integrated Primary Care Information database, a longitudinal electronic medical record database. Also, we demonstrated that there is an impact of left censoring and the choice of episode duration assumptions. We showed that for the common and recurrent diseases like acute otitis media (AOM), increasing the assumed length of an episode decreases the incidence but increases the prevalence estimates of disease in children. *We recommend that researchers measuring the incidence of common recurrent childhood diseases explore the impact of applying different assumptions regarding episode duration*. *To determine the correct episode duration for different common recurrent diseases, we recommend that a a 'new' (relative to start of the study) birth cohort of children can be followed to determine (from electronic health care databases) their first contact with the general practitioner for such diseases; then surveys may be conducted to determine (from their caregivers) when disease symptoms resolve*. For chronic childhood diseases, increasing the length of the run-in period prior to start of follow-up decreases the incidence rate with negligible effect on the prevalence. Of note, the length of the run-in period impacts both common and rare diseases. *We recommend that when estimating the incidence of chronic diseases, researchers should apply the longest feasible run-in. Linkage across systems, which would allow a patient to be followed over life should be recommended.*

Detecting drug safety signals from pediatric spontaneous reporting data: crucial for routine safety surveillance

Following the marketing of approved drugs, adverse events that were not identified during randomized clinical trials (RCTs) will be detected since more patients, and patients in unstudied populations (such as children/pregnant women, elderly) will use the drugs[76]. Healthcare professionals and patients (in some drug regulatory jurisdictions) should/can report suspected adverse drug reactions to the marketing authorization holders or national (i.e. US Federal Drug Administration - FDA) or international (European Medicines Agency - EMA, and WHO collaborating center for international drug monitoring) pharmacovigilance centers. Databases containing such spontaneous reports (i.e. FAERS (FDA), EUDRAVIGILANCE (EMA), and

VIGIBASE (WHO)) need to be screened to detect new signals, this is often done using statistical signal detection algorithms (SDAs) such as Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), Information Component (IC) and Empirical Bayes Geometric Mean (EBGM)[327-330]. For a long time, child-specific SDAs were lacking and children were analysed together with adults. Recently this has changed and WHO and EMA recommend that children be analysed separately[331-333]. Even if children are now separated from adults, children are still not a homogeneous group. Organ development and maturation may predispose certain age categories to different susceptibilities of adverse events[334,335]. In this thesis[336] we verified whether further age stratification amongst children would have an impact on signal detection and whether this differed for different SDAs. In order to compare the performance of different SDAs on pediatric data specifically, a pediatric-specific reference set of drug-event combinations (DEC) was required as a first step.

Creating a pediatric-specific drug-adverse event reference set

We created a reference set comprising 37 known (positive controls - PC) and 90 'unknown' (negative controls - NC) DECs. The reference set was based on drugs that are routinely used in pediatrics, in both outpatient and inpatient settings. In order to test (and develop SDAs that can be applied to) databases that exist in low and middle-income countries (LMIC), we included drugs that are used in such countries. Adverse events were selected considering both outpatient (i.e. frequent events) versus inpatient (i.e. rare and potentially life-threatening events) settings. Therefore, the reference set can be applied to databases existing in various contexts. As proof that a pediatric-specific reference set is welcome we would like to point out that there is limited overlap between our reference set and the ones created within the context of other projects like OMOP, EU-ADR and PROTECT [83,95-97]. Drugs were not selected independently of adverse events in OMOP and EU-ADR [83,84]. Since our (GRIP) reference set was intended for testing both spontaneous reporting system (SRS) and EHR databases, selecting drugs independently of adverse events was necessary to avoid any bias. To ensure validity of the positive and negative controls, we conducted extensive literature reviews. To confirm the positive controls, we applied a specific literature search algorithm and therefore retrieved

publications that reported on the event and drug in the context of drug safety in children or adults, an approach similar to that adopted by the EU-ADR project[83]. Positive controls with evidence from only adults were not considered for testing signal detection algorithms. The downside of applying a specific literature search algorithm may be that there was no or inadequate evidence to confirm some well-known associations in children (just because papers/studies were not available, or reported through means other than the peer-reviewed literature). *We recommend that for creating a reference set, other drug regulatory documents should be consulted in addition to SPCs and peer-reviewed literature*. With regard to confirmation of positive controls, we searched for evidence in children specifically and in addition searched for pharmacological (in addition to epidemiological) evidence to further strengthen the association. However we were able to find pharmacological evidence for only 13 out of the 37 PCs. The limited pharmacological evidence for most of the PCs may reflect the current gap of knowledge and understanding of adverse drug reactions.

Confirming a negative control required absolute certainty that the drug cannot cause the adverse event and both adult as well as pediatric data was used. The status of negative controls may change over time (if new evidence emerges), therefore *we recommend regular update of their status*. For the positive controls it is important to know at which point in time the association was in the public domain as this may lead to changes in reporting behaviour to spontaneous reporting databases and to changes in clinical care. Those changes may have an impact on the ability to detect associations (i.e. in spontaneous reporting databases it may increase the association whereas it may decrease such association in electronic health record databases) [121-123].

Assessing the performance of SDAs when applied to pediatric data specifically

Using the reference set that we created, we tested two routinely applied SDAs - the proportional reporting ratio (PRR) and Empirical Bayes Geometric Mean (EBGM) - on the pediatric dataset of FAERS (the FDA database on spontaneous reports in the USA comprising non-vaccine products only), and we stratified by age categories to investigate the impact of effect modification by age. We showed that the type of SDAs did not matter a lot. As reported in the PROTECT project[146], the PRR and EBGM showed good performance overall, although the

results were slightly lower than results reported on other (not pediatric-specific) reference sets [155,156]. Age-stratified analysis in children revealed some drug-event combinations that were masked when data on the entire pediatric population was analysed. Conversely, some drug-event combinations that were initially observed for the entire pediatric population were observed only in some but not all pediatric age groups. Such effect modification may result from differences in drug use[126,154], susceptibility to adverse events across pediatric age groups and power issues. *We recommend that when conducting drug safety surveillance in the pediatric population, age-stratified analysis should be performed to avoid masking.* We also strongly recommend complete and detailed recording of age information in pediatric spontaneous adverse drug event reports, many subjects had empty/ zero age, and it was not clear whether age was missing or truly zero.

Pediatric pharmacoepidemiological safety studies: current status and recommendations for improvement

When drug safety signals are detected, further evaluation is required to quantify risk[336]. This is often achieved by conducting pharmacoepidemiological studies. While such studies are conducted frequently in adults with progressively better methods, the same cannot be said of children. In order to assess the state of the art and potentially make recommendations, we conducted a systematic review to assess the characteristics of pediatric pharmacoepidemiological safety studies that were published over 34 years.

As main findings, we discovered that the absolute number of pediatric pharmacoepidemiological safety studies is low and the studies are almost exclusively conducted in high income countries and receive limited funding from pharmaceutical companies and other private sources. Designs differed a lot between drug and vaccine studies. Focus in these studies was only on a small fraction of registered drugs and mainly intermediate outcomes (signs/symptoms) were studied. *We recommend the conduct of more and better studies in LMICs, interaction between the drug safety and vaccine safety world to improve methodology and apply designs more broadly, better funding, particularly for under prioritized safety issues i.e. long term effects of drugs, and*

collaboration across institutes. Sharing existing databases will enlarge sample size to study the rarer and potentially more serious safety issues.

Although the pediatric legislations that have been introduced globally were primarily aimed at stimulating clinical trials, this also affected the conduct of pharmacoepidemiological studies. For example under the 'Best Pharmaceuticals for children's Act' (BPCA)[26], the US National Institutes of Health sponsored several pharmacoepidemiological studies in children[182]. These legislations may explain why most studies were conducted in the US and EU. Yet many children live in LIMCs. According to the United Nations Children's Emergency Fund (UNICEF), between 2010 and 2025, the child population of sub-Saharan Africa will rise by 130 million. From around 2030, sub-Saharan Africa will be the single region with the greatest number of children under 18 years. By 2050, almost 1 in every 3 children under 18 years will be African. Also according to UNICEF, half of the world's 6.6 million under-five deaths occur in Africa with pneumonia, malaria and diarrhea accounting for 40% of the deaths. These diseases are mostly treated with drugs. *It is important to further build on a worldwide pharmacoepidemiological capacity with regard to knowledge and information technology (IT) infrastructure to monitor the safety of these drugs. More effort should be focused on applying personal smart phone based methods (for collecting data on drug use and health outcomes) that may be more suitable for for LIMCs.*

Even if the right data and methods are available for pediatric studies, there may be a need to prioritize the drug classes to be studied based on their frequency of use in children. In our review, we found that almost half of the evaluated drugs belonged to only 3 classes namely anti-infectives, psychoanaleptics and psycholeptics. Unlike anti-infectives, psychoanaleptics and psycholeptics represent a minority of drug exposure in children[85]. *We recommend that pediatric pharmacoepidemiological safety studies should be focused on drugs that are commonly used in pediatrics and where required evidence is still missing. In LMICs, effort should be focused on studying the effects of drugs that are used in treating the aforementioned infectious diseases.*

There were few studies of rare drug exposures in our review. The effects of such exposures may better be studied using case-only designs i.e. self-controlled case series[192]. Case-only designs are particularly suited for the drug utilization patterns and characteristics of outcomes in children[193,194]. Case-only designs are particularly useful for studies in children since such

designs are much more efficient in terms of costs and data collection. Multi-site data pooling should be promoted to acquire adequate power to study rarer events in children[77,195]. International collaboration on a global scale may be required; which is one of the main aims of the Global Research in Pediatrics (GRIP) project.

Quality of pediatric pharmacoepidemiological safety studies: implications for evidence based pediatrics

Knowledge about the safety and efficacy (effectiveness in real life) of drugs allows clinicians to make better treatment decisions, a process termed evidence-based medicine (EBM)[196]. Successful practice of EBM is largely dependent on the ability to critically appraise and interpret research evidence. The US National Cancer Institute initiated a programme to address the use of epidemiology in knowledge integration which itself was defined as 'the methodological process of selecting, storing, collating, analyzing, integrating, and disseminating information within and across disciplines for the benefit of population health'[337]. Central to this programme is the ability to know which information is valid. Many clinicians do not yet have the knowledge on research methodology to properly appraise study results[338]. Meanwhile, the peculiar challenges of pediatric pharmacoepidemiological studies make the appraisal of such studies particularly difficult. For adequate assessment of pediatric studies specifically, detailed information about various characteristics is required including specific date of birth (rather than just birth year), gestational age at birth, birthweight/length, small for gestational age status, school performance, and mental health status [199]. Also, detailed information about drug doses, concomitant medication, indication for treatment and reasons for changes to dose or therapy is required. Finally, defining the optimal risk window to observe outcomes resulting from chronic drug exposures and the investigation of transient versus recurrent outcomes, which frequently occur in children, might be a burden in pediatric pharmacoepidemiology.

We systematically assessed the quality of published pediatric pharmacoepidemiological safety studies. Our aim was to identify the likely sources of bias and other pediatric-specific study characteristics. As main findings, studies which scored the highest on quality were: published from 2010, SCCS studies of vaccines, and studies conducted in North America and Europe

based on retrospectively collected secondary data. Vaccine-only studies, which were better than drug-only studies, applied only SCCS design perhaps accounting for their higher quality because of better control of potential confounding factors. *We recommend that where feasible, the SCCS and other case-only designs should be applied to more studies, and not only for vaccine studies.*

Cohort studies were most likely to be biased because historical time prior to study start was not considered for the identification of prevalent cases of the outcome of interest and because follow-up time after study start was not long enough to observe occurrence of the outcome(s). Case control studies were most likely to be of poor quality because of differences in non-response rate (regarding ascertainment of the exposure) between the cases and controls, and because the authors did not specifically report that the controls did not experience the outcome of interest. The majority of studies utilizing retrospectively collected secondary data showed good quality possibly because most of them were published from the year 2000, a period during which extensive research effort has been focused on improving the quality and utilization of such data [237-240]. Detailed patient information is now recorded in many healthcare databases especially EHRs, thereby improving the utility of secondary data. Inadequate reporting may explain why despite this improvement, the quality of many pediatric pharmacoepidemiological studies still scored low. The impact of reporting on quality (assessment) of research has been emphasized[197,241,242]. Recently the RECORD statement was introduced, aimed at encouraging better reporting of studies based on EHR specifically [233].

The use of an appropriate tool is crucial for an adequate assessment of study quality. Many available tools do not include critical assessment elements (i.e. confounding by indication) that are relevant to pharmacoepidemiological safety studies generally and pediatric studies specifically[197]. *We recommend further research to develop a tool that can easily be utilized to evaluate pediatric studies specifically.*

Comparative drug effectiveness studies in children: recommendations for improvement

Efficacy evidence, upon which drug approval is based, may not translate into drug effectiveness following approval and routine clinical use. Comparative effectiveness research (CER) can yield 'real-world' evidence about the benefits of a drug and therefore improve its prescribing [339]. Especially for effectiveness research, the validity of such evidence is dependent on the ability to correct for bias and confounding in particular confounding by (contra)indication. In recent years, a lot of research has been focused on refining methods for CER research in adults however with no focus on children specifically.

We conducted a systematic review to identify the weaknesses of published drug effectiveness studies in children and to make recommendations for improvement. We found that studies were few, mainly conducted in North America and Europe and mainly based on public funding. Comparative effectiveness studies in newborns were rare. With regard to study design, the cohort design was the most commonly applied, probably also because it allows to study multiple outcomes. With regard to outcome, intermediate outcomes were often used. Use of intermediate outcomes is frequently observed in RCTs because of short trial duration. *In CER however, where duration of follow-up should not necessarily be an issue, we recommend the use of clinical outcomes.* The investigated drugs did not always reflect routine drug utilization in paediatrics. Although commonly utilized, analgesics (WHO-ATC NO2), drugs for obstructive airway diseases (WHO-ATC R03), and anti-inflammatory and antirheumatic drugs (WHO-ATC M01) and nasal preparations (WHO-ATC R01) were seldom studied. In contrast, although seldom utilized, antineoplastic agents (WHO-ATC L01) and immunosuppressants (WHO-ATC L04) were frequently studied.

Most studies that we reviewed applied traditional methods to control for confounding by indication; including multivariate modelling analysis, matching and restriction. Propensity scores adjustment was seldom applied even though it is particularly suited for controlling confounding by indication[247,254].

In addition, dose-effect studies were seldom conducted, representing a missed opportunity[250]. Few studies used EHRs, even though their great potential for pediatric research has been demonstrated[253].

Based on quality assessment with the NOS, cohort studies had higher scores than case control studies and therefore may be viewed as better even though there is no established threshold to label studies as having low or high risk of bias[206]. Studies on analgesics and immunosuppressants had the lowest median scores. The low scores for studies investigating analgesics, a frequently utilized drug class, may be explained by the specific challenges in pain studies. First, it is difficult to define pain as an outcome, resulting in misclassification. Secondly, it is difficult to assess the use of over-the-counter medications and medications that are used as needed in various doses[257]. *As recommendation, we propose the development of tools to better quantify pain and other outcomes that are difficult to measure.*

Comparing drug effectiveness in children using propensity scores

Propensity scores (PS) adjustment is one of the methods to better control for confounding by indication in comparative effectiveness studies. In this thesis we applied this in pediatrics, and we looked at the most optimal period (prior to drug exposure) during which potential confounders should be assessed for the calculation of PS using a case study in children with asthma. We compared the effectiveness of new users of ICS+LABA (fixed dose combination versus administration via 2 different inhalers) for the prevention of moderate to severe asthma exacerbations. We derived the PSs by modelling (logistic regression) confounding patient characteristics that were identified during six distinct periods before incident prescription of the fixed combination of ICS+LABA: 1 week, 1 month, 3 months, 6 months, 1 year and full history. Compared to the loose combination, ICS+LABA fixed protected against exacerbation. Calliper matching without replacement resulted in the largest adjustments of the crude hazard ratio (HR) especially in the 1 month prior to treatment start. The results of different ways to deal with propensity scores made a big impact. *We recommend further research into use of PS methods in comparative effectiveness research in childhood. Since PSs can only be applied to control for measured confounders, other methods that can account for unmeasured confounders (i.e.. instrumental variable analysis) should be investigated.*

Current needs in pediatric pharmacoepidemiology: added value of a survey

The needs assessment drew on the expertise of the leading professional organization committed to pharmacoepidemiology – ISPE (International Society of Pharmacoepidemiology. We solicited feedback - through phone or face-to-face interviews - from ISPE members with an interest in pediatric pharmacoepidemiology, with regard to current needs in pediatric pharmaco-epidemiology.

Of note, respondents reported working with 59 distinct databases of various types, and only 8 databases were mentioned by more than one respondent. This complements an earlier survey that identified 25 data sources from 12 European countries[321]; more so because we did not restrict our search to Europe.

Our finding that few databases are used by more than one researcher may reflect the wide range of disease areas investigated or the large number (16) of respondents using national databases. If researchers in different countries rely on their national databases to conduct pediatric pharmacoepidemiological studies, the implications for developing an international body of knowledge about medications in children is unclear, as is the validity of extrapolating from a national database to a global context. This highlights the need for global efforts aimed at identifying all existing databases that can be used for pediatric pharmacoepidemiological studies.

Regarding the disease areas covered by the databases, psychiatry and mental health were the areas mentioned most frequently by respondents, followed by infectious disease, and a range of conditions including asthma, oncology, and sedation. It is not clear whether this distribution reflects the priorities of pediatric pharmacoepidemiology outside of ISPE respondents. The increasing use of psychotropic medications in children has been well documented and the cluster of survey respondents working in this disease area may reflect the growing use of these medications[323-326].

Conclusions and future perspectives

This thesis was focused on disease occurrence, safety signal detection and methods for comparative outcome studies. Across all of these areas, it is evident that methods are required that are better suited for children.

From the perspective of disease occurrence estimation, our methods should be verified in a wider realm of databases, in this thesis we focused on medical records from GPs, but the impact of different run in periods and disease episode durations should be systematically verified also in claims databases and systems with high turnover (short follow-up).

Regarding signal detection continuous refinement of signal detection algorithms is required. Where age-specific drug use is known or suspected, age-stratified safety monitoring should be conducted. Since the number of reports in newborns cannot be estimated well, since age may be put at 0 because of missingness, we would recommend complete recording of age in spontaneous reporting databases. In addition we would recommend that systems be developed where data from various international databases can be pooled since the power to detect in small age strata, remains low. We built a common data model for spontaneous reporting data which captured FAERS, EUDRAVIGILANCE and VAERS and the usefulness of that pooling should be verified. To maintain the usefulness of the drug-adverse event reference set for performance testing of signal detection algorithms, the status of the associations especially the negative controls should be quickly updated based on new evidence. This process can be facilitated if screening of the following data sources/types is automated: pharmacokinetic and pharmacodynamics data, summary of product characteristics and other regulatory documents, as well as published literature. *Such automated approaches should be developed*. Since screening of electronic health records can yield important complementary evidence to support drug safety monitoring in children, *different methods should be tested to determine their suitability for such screening*. Social media represents a potential source of information for suspected adverse drug reactions in children. In LMICs, the widespread use of mobile phones represents an opportunity to improve reporting of suspected adverse drug reactions; *this should be further explored.* In many LMICs, many people are religious. The leaders of religious groups usually exert enormous influence over their members. *Researchers may liaise with such leaders and healthcare practitioners that are members of such groups to improve reporting of*

suspected adverse drug reactions. In neonatal intensive care units (ICUs), there is often co-adiministration of drugs which increases the possibility of occurrence of adverse drug reactions (ADRs) but which may however not be adequately reported. *Methods for stimulating reporting of such suspected ADRs should be investigated*; *compared to other neonates and children, the number of neonates admitted in ICUs is usually much fewer and therefore it may be possible to evaluate every medical occurrence as a possible ADR.* Also there should be more focus on methods dealing with drug drug interactions.

From the quantity of studies, pediatric pharmacoepidemiology is an underdeveloped field. More researchers with specific training in this field are required. Also, more funding of studies is needed; although there has been a time when the European Commission focused on children the shift now seems to be to healthy ageing, we recommend that children stay in the picture. Similarly, it is relevant to develop methods and systems that would allow to monitor long term effects of drugs in children. More and better data is required to conduct studies that can provide answers to the most pressing clinical questions. Better methods for controlling confounding and bias are required.

In this thesis we found that the limited pediatric pharmacoepidemiological studies that are conducted, do not include low-and-middle-income countries (LMICs). However the largest number of children live in those regions and the impact of adequate drug treatments on child health is highest there. Knowledge and/or competence in pharmacoepidemiological methods should be developed by providing scholarship for e-learning such as done in EU2P and GRIP. There are reputable health-related non governmental organizations (NGOs) that can serve as a platform for collaboration between *researchers in LMICs and their colleagues in high-income countries; such collaboration should be encouraged and explored. In LMICs where collection and/or recording of medical records is still inadequate, the added benefit of surveys in collecting information on drug use and health outcomes should be explored to increase the internal validity of pharmacoepidemiological safety and effectiveness studies. Generally, more effort should be focused on the effects of prenatal drug exposures and maternal immunizations.*

To overcome the limitations of clinical trials and to fill the knowledge gaps on the effects of drugs in children, we should increase secondary use of health care databases. However, there are challenges such as the ability to account for measured and unmeasured confounders. This is crucial to obtain valid results from pharmacoepidemiological studies. In addition to propensity scores, t*he utility of other modern methods like marginal structural models for controlling measured confounders should be investigated*. *Generally, more and better effort through global collaboration is required to identify and develop suitable methods that can be applied to adequately answer the most pressing and clinically relevant questions regarding the use and effects of drug in children worldwide.*

Chapter 8 Summary/Samenvatting

Chapter 8.1 Netherlands Samenvatting

Geneesmiddelen worden bij kinderen vaak gebruikt ondanks het feit dat de veiligheid en werkzaamheid bij kinderen niet getest werd aan de hand van klinische studies. Om die reden is het van belang de veiligheid en effectiviteit te onderzoeken aan de hand van gegevens uit de dagelijkse praktijk, die er in overvloed zijn.

In dit proefschrift bestudeerden methoden om het vóórkomen van ziekten en bestuderen van de effecten van geneesmiddelen in kinderen te schatten, gebruikmakend van routine zorg data uit de dagelijkse praktijk, dit maakte deel uit van het GRIP netwerk dat werd gefinancierd door de Europese Commissie en het EVIPED project dat werd gefinancierd door ZONMW.

Geldige schattingen van het vóórkomen van ziekten in kinderen zijn een noodzakelijk onderdeel van het verlenen van een licentie, maar gegevens ontbreken vaak. Dergelijke schattingen zouden relatief gemakkelijk verkregen kunnen worden door gebruik te maken van gezondheidszorg gegevens op bevolkingsniveau maar deze bestanden hebben beperkingen omdat ze niet voor onderzoek worden vastgelegd maar voor routine zorg, en vaak een beperkte periode van het 'leven' van een persoon beslaan, omdat personen veranderen van zorgverleners. In hoofdstuk 2.1 onderzochten we het effect van een aanname over de duur van ziekte-episodes op de nauwkeurigheid van de incidentie- en prevalentiemeting.

Bij veelvoorkomende en terugkerende ziektes, zoals middenoorontsteking zorgde het verlengen van de aangenomen duur van een ziekte-episode voor een verlaagde incidentie, maar een verhoogde prevalentie. Om de effecten te schatten van het feit dat we niet de hele voorgeschiedenis hebben werd gekeken naar het effect van een verlenging van de inloopperiode (minimale follow-up periode die nodig is vooraleer de gegevens van de patiënt kunnen gebruikt worden). Bij een langere inloopperiode daalde de incidentie, maar was er slechts een verwaarloosbaar effect op de prevalentie.

In de routine farmacovigilantie staat het rapporteren van bijwerkingen centraal. Hierdoor kunnen na het op de markt brengen van nieuwe geneesmiddelen nieuwe bijwerkingen aan het

licht komen. Databases met spontane meldingen van zorgverleners en patiënten worden regelmatig geanalyseerd met statistische detectie algoritmes (SDA's), zoals de Proportional Reporting Ratio (PRR) en de Empirical Bayes Geometric Mean (EBGM) on ongekende bijwerkingen zo snel mogelijk op te pikken. Helaas wordt er vaak niet specifiek naar signalen in kinderen gekeken. In het kader van GRIP wilden we onderzoeken hoe we signaaldetectie bij kinderen kunnen verbeteren. Om dit te doen was in eerste instantie een geneesmiddel-bijwerking referentieset nodig. In hoofdstuk 3.1 beschrijven we een dergelijke referentieset bestaande uit 37 bekende (positieve controles - PC) en 90 'onbekende' (negatieve controles - NC) geneesmiddel-bijwerking combinaties (GBC`s). Deze referentieset bevat geneesmiddelen die vaak gebruikt worden bij kinderen en bijwerkingen die optreden in de ambulante zorg of tijdens hospitalisatie. Om de validiteit van de PC`s en de NC`s te waarborgen werd een uitgebreide literatuurstudie gedaan. In hoofdstuk 3.2 hebben we dit referentieset gebruikt om de prestatie van de PRR en de EGBM te testen in de FDA spontane rapportage database (FAERS). Dit onderzoek liet zien dat het type SDA niet veel uitmaakte voor signaaldetectie maar dat het belangrijk is om te stratificeren omdat sommige signalen anders verborgen blijven.

Als er nieuwe signalen van mogelijke bijwerkingen gedetecteerd worden, dan is verdere evaluatie nodig om de associatie te kwantificeren. Dit wordt vaak gerealiseerd aan de hand van hypothese toetsende farmaco-epidemiologische studies. In hoofdstuk 4.1 beschrijven we een systematische literatuurstudie naar de kenmerken van farmaco-epidemiologische "safety studies" die gepubliceerd werden in de afgelopen 34 jaar. De voornaamste bevindingen waren dat we ontdekten dat het aantal studies laag is, dat studies bijna uitsluitend in ontwikkelde landen werden uitgevoerd zijn en dat financiering beperkt was. Er waren grote verschillen in studieopzet tussen geneesmiddelen- en vaccinatiestudies. In de geneesmiddelenstudies lag de focus op een klein deel van de geregistreerde geneesmiddelen, en werden voornamelijk intermediaire uitkomsten (tekenen en symptomen) bestudeerd. Wij pleiten voor meer en betere studies in de toekomst waarbij ook gegevens gebruikt worden van lagere en middeninkomenlanden. Extra financiering is noodzakelijk zodat ook onderzoek kan gebeuren naar de langetermijneffecten van geneesmiddelen en geneesmiddelen die minder vaak worden

gebruikt. Tevens dient onderzoek gedaante worden naar optimalisatie van study designs zoals bijvoorbeeld self-controlled case series (SCCS). In hoofdstuk 4.2 keken we naar de kwaliteit van de studies. De voornaamste bevindingen waren als volgt: de studies met de hoogste kwaliteitscore waren recentelijk gepubliceerd (2010 en later), waren vaak vaccin-studies met SCCS als studieopzet, en gebruikten voornamelijk gegevens uit Europa en Noord-Amerika. Bij cohort studies merkten we op dat de tijd vóór het begin van de studie vaak niet in overweging was genomen. Dit kan tot misclassificatie van prevalente gevallen leiden. Daarnaast was de duur van de follow-up tijd in cohort studies vaak onvoldoende lang om de beoogde uitkomst(en) te meten. Case-control studies waren veelal van slechte kwaliteit door de verschillen in non-respons (met betrekking tot het vaststellen van de bloostelling) tussen patiënten en controlepersonen, en omdat de auteurs niet specifiek rapporteerden dat de controlepersonen de beoogde uitkomst niet ontwikkelden.

Werkzaamheid van een geneesmiddel vertaalt zich na goedkeuring en bij “real-life” gebruik niet altijd in effectiviteit. Vergelijkend effectiviteitsonderzoek kan bewijs geven van de voordelen van een geneesmiddel in “real life”. In hoofdstuk 5.1 beschreven we, aan de hand van een systematisch literatuuronderzoek de methoden die toegepast worden om studies naar de effectiviteit van geneesmiddelen uit te voeren bij kinderen. Het aantal studies was klein, met name met publieke gelden gefinancierd en voornamelijk uitgevoerd in Europa en Noord-Amerika. Effectiviteitsonderzoek bij pasgeborenen was zeldzaam. Wat betreft de gebruikte methodes, werd voornamelijk gebruik gemaakt van cohort studies, waarschijnlijk omdat daarmee meerdere uitkomsten onderzocht kunnen worden. Er werden vaak intermediaire uitkomsten gebruikt. Het gebruik van intermediaire uitkomsten ziet men vaak bij gerandomiseerde klinische studies vanwege de korte duur van het onderzoek. Daarentegen raden wij aan klinische uitkomsten te gebruiken voor effectiviteitsonderzoek, gezien de duur van de follow-up geen probleem hoeft te zijn. De onderzochte geneesmiddelen waren niet altijd representatief voor het geneesmiddelen gebruik bij kinderen. Traditionele methodes werden toegepast om te adjusteren voor confounding zoals matchen, restrictie en multivariaat analyse. Adjusteren of matchen op propensity scores werd nauwelijks toegepast. Het effect van dosering

werd zelden onderzocht, wat een gemiste kans is. Slechts een klein aantal onderzoeken maakte gebruik van elektronische patiëntendossiers.

In hoofdstuk 5.2 onderzochten we het gebruik van propensity scores om te adjusteren voor confounding. We vergeleken de effectiviteit van geïnhaleerde corticosteroiden (ICS's) en langwerkende beta-2 agonisten (LABA's), hetzij als vaste combinatie hetzij als twee losse inhalers, in de preventie van matige tot ernstige astma-exacerbaties. Wij kozen voor astma omdat het een veelvoorkomende en chronische aandoening in kinderen is. De propensity scores werden berekend aan de hand van een logistische regressie. Propensity scores werden berekend aan de hand van patiënten karakteristieken, vastgesteld in zes specifieke periodes voorafgaande aan het eerste (incident) voorschrijven van de vaste combinatie van ICS's met LABA's. De specifieke periodes waren één week, één maand, drie maanden, zes maanden, één jaar en de volledige geschiedenis voorafgaand aan het eerste voorschrift van een ICS+LABA. In de ongeadjusteerde analyse zagen we een verlaagd risico op matige tot ernstige astma exacerbaties bij het gebruik van een vaste combinatie van ICS's met LABA's . "Caliper matchen" op de propensity scores, zonder vervanging, resulteerde in de grootste aanpassing van de hazard ratio (HR), met name in de eerste maand vóór het begin van de behandeling. Verder onderzoek is nodig naar het gebruik van propensity scores in vergelijkend doelmatigheidsonderzoek bij kinderen.

Overige onderzoeken die van belang zijn om farmacoepidemiologisch onderzoek bij kinderen te verbeteren zijn opgenomen in hoofdstuk 6.

In hoofdstuk 6.1 ontwikkelden we een vaccinatie-bijwerking referentieset. Dit referentieset kan gebruikt worden om de prestaties van verschillende SDA' s te testen voor het monitoren van de vaccinveiligheid. In hoofdstuk 6.2 presenteren we de resultaten van een enquête (telefonische of face-to-face interviews) onder leden (experts) van dé toonaangevende professionele organisatie gericht op farmaco-epidemiologie: ISPE (International Society of Pharmacoepidemiology). Dit om nader inzicht te krijgen in de behoeften van de kinder farmaco-epidemiologie. Opvallend was dat 59 aparte databases werden vermeld, en dat maar acht

databases meer dan eens genoemd werden. Onze bevinding dat een gering aantal databases door meer dan één onderzoeker gebruikt wordt, kan een afspiegeling zijn van de grote verscheidenheid aan deelgebieden van ziektes die onderzocht wordt, of van het grote aantal (16) onderzoekers die nationale databases gebruiken. Dit accentueert de noodzaak tot het inventariseren van alle bestaande databases die gebruikt kunnen worden voor farmaco-epidemiologische studies bij kinderen.

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ADR	Adverse Drug Reactions
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AKI	Acute Kidney Injury
ALI	Acute Liver Injury
AOM	Acute Otitis Media
APN	Acute Pyelonephritis
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Receiver Operating Characteristics Curve
BCG	Bacille-Calmette-Guerin
BMJ	British Medical Journal
BPCA	Best Pharmaceuticals for Children Act
CER	Comparative Effectiveness Research
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CNODES	Canadian Network for Observational Drug Effect Studies
DEC	Drug-Event Combination
DM	Diabetes Mellitus
DVT	Deep Venous Thrombosis
EBGM	Empirical Bayes Geometric Mean
EBM	Evidence Based Medicine
EC	European Commission
ECG	Electrocardiogram
EHR	Electronic Health Records
EM	Erythema Multiforme
EMA	European Medicines Agency
EMR	Electronic Medical Records
EU	European Union
FAERS	US FDA Adverse Event Reporting System
FDA	Federal Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	US FDA Modernization Act
FDE	Fixed Drug Eruption

GBS	Gullain-Barre Syndrome
GFR	Glomerular Filtration Rate
GINA	Global Initiative for Asthma
GP	General Practitioner
GRIP	Global Research In Paediatrics
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HG	High Level Group Term
HHE	Hypotonic Hyporesponsive Episode
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HT	High Level Term
LMIC	Low-and-Middle-Income Countries
IC	Information Component
ICD	International Classification of Diseases
ICH	International Conference on Harmonization
ICPC	International Classification of Primary Care
ICPE	International Conference On Pharmacoepidemiology and Therapeutic Risk Management
ICS	Inhaled Corticosteroids
IDDM	Insulin-Dependent Diabetes Mellitus
IOM	Institute Of Medicine
IPCI	Integrated Primary Care Information
IQR	Interquartile Range
IPTW	Inverse Probability of Treatment Weighting
IR	Incidence Rate
IRR	Incidence Rate Ratio
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
KWH	Kruskal-Wallis H
LABA	Long-Acting Beta-2-Agonists
LGPS	Longitudinal Gamma Poisson Shrinker
LT	Lower Level Term
LTRA	Leukotriene Receptor Antagonist
MA	Marketing Authorization
MDX	Micromedex
MHRA	Medicines and Healthcare products Regulatory Agency

MMR	Measles-Mumps-Rubella
MV	Meningococcal Vaccine
MWU	Mann-Whitney U
NC	Negative Control
NCCHD	National Center for Child Health and Development
NICHD	National Institutes of Child Health and Development
NIH	National Institutes of Health
NLM	National Library of Medicine
NOS	Newcastle Ottawa Scale
NPV	Negative Predictive Value
OL	Non-current Lower Level Term
OMOP	Observational Medical Outcomes Partnership
OPV	Oral Polio Vaccine
OTC	Over The Counter
PC	Positive Control
PDCO	Paediatric Committee
PE	Pulmonary Embolism
PIP	Pediatric Investigation Plan
PPV	Positive Predictive Value
PREA	Pediatric Research Equity Act
PRR	Prevalence Rate Ratio
PRR	Proportional Reporting Ratio
PS	Propensity Scores
PT	Preferred Term
PUMA	Paediatric Use Marketing Authorization
PV	Pneumococcal Vaccine
PY	Person-Years
RECORD	Reporting Guidelines for Pharmacoepidemiology and other Observational Research Using Routinely-collected Health Data
ROBINS	Risk Of Bias In Non-randomized Studies Of Interventions
ROC	Receiver Operating Characteristics
ROR	Reporting Odds Ratio
RR	Relative Risk
RV	Rotavirus Vaccine
SABA	Short-acting Beta-2-Agonist
SAMA	Short-acting Muscarinic Antagonist

SCCS	Self-Controlled Case Series
SCD	Sudden Cardiac Death
SDR	Signal of Disproportionate Reporting
SIDS	Sudden Infant Death Syndrome
SIG	Special Interest Group
SJS	Stevens-Johnson Syndrome
SMQ	Standardized MedDRA Query
SPC	Summary of Product Characteristics
SRS	Spontaneous Reporting System
TEN	Toxic Epidermal Necrolitis
UC	Unclassifiable
UK	United Kingdom
UNICEF	United Nations Children's Emergency Fund
US	United States
UTI	Urinary Tract Infection
VA	Verbal Autopsy
VAERS	US Vaccine Adverse Event Reporting System
VAPP	Vaccine-Associated Paralytic Poliomyelitis
VF	Ventricular Fibrillation
VIT	Vaccine Injury Table
VZV	Varicella Zoster Virus
WHO	World Health Organization

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2014	International English Language Testing System (IELTS), Academic version, British Council, Amsterdam.
2013	English Biomedical Writing and Communication. Erasmus University Medical Center, Rotterdam.
2011-2013	European Joint Master of Science in Pharmacovigilance and Pharmacoepidemiology (EU2P) coordinated by Universite Bordeaux 1, Bordeaux (France).

Oral Presentation

Drug safety in children: Performance of Signal Detection Algorithms and Impact of Age Stratification

- *ISPE's 9th Asian Conference on Pharmacoepidemiology, Bangkok, Thailand 2015*

Poster Presentations

Evaluating Adverse Drug Effects In Children: A Systematic Review

- *ISPE's 9th Asian Conference on Pharmacoepidemiology, Bangkok, Thailand 2015*

Comparing Drug Effectiveness In Children: A Systematic Review

- *ISPE's 9th Asian Conference on Pharmacoepidemiology, Bangkok, Thailand 2015*

Performance Of Signal Detection Algorithms in the pediatric dataset of the publicly-available US FDA Adverse Event Reporting System (FAERS)

- *International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Boston, USA 2015*

Creating a reference set for comparing data mining methods and evaluating database performance in children – The GRiP Project

- *International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada 2013*

Lecturing

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Peer reviews
British Journal Of Clinical Pharmacology
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Pharmacological Research
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Co-coordination of the Global Research In Pediatrcis specifically collection of information on databases on a global scale and monitoring distributed studies, 2012-2016

Teaching

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2015	Course, Data Analysis, NIHES, Rotterdam
2014-2015	Julijana Dukanovic, MSc student, 'Systematic review of drug comparative effectiveness studies in children'

List of Publications

Manuscripts related to this thesis

1. **Chapter 2.1**

   Osemeke U Osokogu, Alexandra Pacurariu, Mees Mosseveld, Peter Rijnbeek, Daniel Weibel, Katia Verhamme, Miriam C J M Sturkenboom
   Impact of different assumptions on estimates of pediatric disease occurrence from health care data: A retrospective cohort study
   Submitted

2. **Chapter 3.1**

   Osemeke U. Osokogu, Federica Fregonese, Carmen Ferrajolo, Katia Verhamme, Sandra de Bie, Geert 't Jong, Mariana Catapano, Daniel Weibel, Florentia Kaguelidou, Wichor M. Bramer, Yingfen Hsia, Ian C. K. Wong, Madlen Gazarian, Jan Bonhoeffer, Miriam Sturkenboom on behalf of the Global Research in Paediatrics (GRiP) - Network of Excellence
   Pediatric drug safety signal detection: A new drug-event reference set for performance testing of data-mining methods and systems
   Drug safety 38.2 (2015): 207-217

3. **Chapter 3.2**

   Osemeke U Osokogu, Caitlin Dodd, Alexandra Pacurariu, Florentia Kaguelidou, Daniel Weibel, Miriam C J M Sturkenboom
   Drug safety monitoring in children: Performance of signal detection algorithms and impact of age stratification
   Drug safety (2016): 1-9

4. **Chapter 4.1**

   Osemeke U Osokogu, Julijana Dukanovic, Carmen Ferrajolo, Caitlin Dodd, Alexandra C Pacurariu, Wichor M Bramer, Geert t'Jong, Daniel Weibel, Miriam C J M Sturkenboom, Florentia Kaguelidou
   Pharmacoepidemiological Safety Studies in Children: A Systematic Review
   Pharmacoepidemiology and drug safety (2016).

5. **Chapter 4.2**

   Osemeke U Osokogu, Carmen Ferrajolo, Julijana Dukanovic, Daniel Weibel, Katia Verhamme, Florentia Kaguelidou, Miriam C J M Sturkenboom
   Quality of published pediatric pharmacoepidemiological safety studies: Implications for evidence-based drug prescribing in pediatrics
   Submitted

6. **Chapter 5.1**

   Julijana Dukanovic, **Osemeke U Osokogu**, Krupa Patel, Carmen Ferrajolo, Daniel Weibel, Miriam CJM *Sturkenboom*
   Comparing drug effectiveness in children: A Systematic Review
   Submitted

7. **Chapter 5.2**

   Osemeke U. Osokogu, Javeed Khan, Swabra Nakato, Daniel Weibel, Maria de Ridder, Miriam C.J.M. Sturkenboom, Katia Verhamme
   Comparing drug effectiveness in children using propensity scores based on different durations of patient history: a retrospective cohort study
   Submitted

Other publications

8. Chapter 6.1

Yolanda Brauchli Pernus**,** Cassandra Nan, Thomas Verstraeten, Mariia Pedenko, **Osemeke U. Osokogu**, Daniel Weibel, Miriam Sturkenboom, Jan Bonhoeffer, on behalf of the GRIP consortium.
Reference set for performance testing of pediatric vaccine safety signal detection methods and systems
Vaccine (2015).

9. Chapter 6.2

Tamar Lasky, Al Artaman, Angela S. Czaja, Sonia S. Maruti, **Osemeke U. Osokogu**, Katia Verhamme, Rachel E. Sobel
Current needs in pediatric pharmacoepidemiology
Pharmacoepidemiology and drug safety (2016).

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When I left home to start my secondary education, I was 12 years old. Since then, I have never lived at home completely. I met a lot of interesting people during my secondary education. One of such people was the principal (headteacher) of my school, Mr. D.O. Akintola. I remember a particular advice he kept repeating over and over again: 'whatever you do, be the best at it'. This advice impacted me early on and influenced my vision of the man I wanted to be. Mrs. Ogunro, my Economics teacher, taught me the value of communicating effectively, a skill I am still learning. She taught her subject (Economics) so well that I fell in love with the subject especially 'the law of diminishing returns'. Her method of teaching has helped me understand the value of truly listening when communicating. Also, I remember Lanre Iyinolakan, a fellow student, with whom I became very close, shared wonderful moments and who went on to also train as a medical doctor and is now completing his training as an ophthalmologist. During my time in secondary school, I was introduced to leadership by being appointed as the 'captain' of one of the halls of residence. I learnt that integral to leading, is not to be aggressive or passive but rather assertive, a trait I am still perfecting. When it was time for me to decide what I wanted to study in the university, I found myself torn between my first love - Medicine - and Engineering. One beautiful evening after the day's work, my father invited me so that we could have a discussion. He succeeded in convincing me to study Medicine.

When it was time for me to commence my university education, I had to choose between attending two institutions: one located about 100 kilometers from where we lived and the second, located about 500 kilometers away. I chose the later because deep down in me I relished the prospect of adventure. Getting into medical school was a rude awakening for me; I realized that I needed to put in more effort and be better at time management. After struggling for a while, I eventually adapted. I met many good people with whom I am still friends. Of

note, I met Uzoho Chinaka, a good man, who helped me in ways that I can't start to recount. I can't fail to mention my former teacher, Ambrose Isah, a physician and Professor of Clinical Pharmacology, who ignited in me, an interest in the effects of drugs in humans. To you sir, I am grateful for the good foundation that has helped me to pursue my PhD studies. I can't fail to mention Oslo Omo-Ikhile, a very loving uncle who accommodated me during part of my medical education.

After graduating from medical school, I was not sure about the clinical specialty that I wanted to major in. Initially, I considered Obstetrics and Gynecology but after a while I became 'scared' at the propect of 'living my life in a hospital'. Over time, I became increasingly interested in Public Health, believing that it not only combined all the other specialties of Medicine but provided the opportunity for me to (more broadly) retain a connection with the 'real-world', even as a medical doctor. Therefore I migrated to Europe, first to Belgium then Netherlands, to broaden my horizon, studying Statistics, Public Heath and Pharmacovigilance (and Pharmacoepidemiology) in that order. I must mention some people that were crucial to my migration and studies: Clarkson Umelo, who facilitated my study visa, and Ngozi Umelo, his wife. Also, I will like to thank Kenneth and Becky Ashion as well as Gibson Ehijene and Fred Ikhile. I met wonderful friends in the course of my studies in Belgium; specifically, I will like to mention Daniel Atwine, with whom I forged a great friendship that has endured. We reminded each other that every success requires hardwork. Also, I will like to thank Ayo and Jumoke, both of whom supported me emotionally and in other ways, when I first arrived in the Netherlands to start my PhD studies. I remain grateful to you.

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I will end by quoting from a poem by Robert Frost: 'Two roads diverged in a wood, and I, I took the one less travelled by, And that has made all the difference'. At the time I commenced my PhD studies, I could have returned to Nigeria to a potentially rewarding job BUT I decided to take up the challenge of following a PhD trajectory and here I am about 5 years later; I am a much better man, not simply because I finished my studies but because of all the beautiful people I met along the way.

About the Author

Osemeke Uwarihu Osokogu was born in Ilorin, Nigeria. He attended Cherubim and Seraphim College, Ilorin (Nigeria) for his secondary education from where he graduated in 1993. He acquired his medical education at at the University of Benin, Benin (Nigeria), graduating in 2003. From 2003 to 2004, he completed one-year medical internship at the Lagos University Teaching Hospital (LUTH), Lagos (Nigeria) during which he completed rotations in Internal Medicine, Surgery, Obstetrics and Gynecology, and Pediatrics. From 2004 to 2005, he completed one year of compulsory Nigerian National Service, during which he provided medical care to an underserved (rural) population with limited access to healthcare. Over the next three years, he worked in private medical practice, in various clinical specialties including Pediatrics. Because of his quest for knowledge, he studied statistics at the Univeristy of Hasselt, Diepenbeek (Belgium) between 2008 and 2009 after which he proceeded to the Universite Libre de Bruxelles (ULB), Brussels (Belgium) where he completed a Master in Public Health Methodology (Epidemiology and Biostatistics), graduating in 2010 as the second best student.

In 2011, he started his PhD studies as described in this thesis. Osemeke was tutored by Prof. dr. Miriam Sturkenboom, Dr. Katia Verhamme and Dr. Daniel Weibel. During his PhD studies he obtained an European Joint Master of Science degree in Pharmacovigilance and Pharmacoepidemiology, coordinated by Universite Bordeaux 1, Bordeaux (France). Also, he has performed teaching activities.

Osemeke has also been involved in other scientific, educational and volunteering activities. In 2014, he co-founded a non-governmental organization (NGO) in Mbarara (Uganda) with the main aim of stimulating African students to pursue a career in research while collaborating with foreign NGOs and other organizations to conduct health-related research (including pharmacoepidemiology) in Africa.

In January 2017, he commenced a procedure to be accredited as a Public Health Physician by the Faculty of Public Health, Royal College Of Physicans, United Kingdom.

Osemeke has a wonderful son, Noah.

As hobbies, he enjoys watching detective (TV) series, travelling and hiking.