GRiP

Global Research in Paediatrics

Network of Excellence

HEALTH-F5-2010-261060

Start date
01/01/2011

Duration
5 years

Project Coordinator
Dr. Carlo GIAQUINTO

Azienda Ospedaliera di Padova (AOPD)

Deliverable number D2.7

"Report on methods of safety signal generation in paediatrics from pharmacovigilance databases"

Lead Beneficiary
EMC

Author(s)

Caitlin Dodd, Osemeke Osokogu, Federica Fregonese, Florentia Kaguelidou, Carmen Ferrajolo, Yolanda Brauchli, Cassandra Nan, Thomas Verstraeten, Jan Bonhoeffer, Miriam Sturkenboom

Revision date
22-7-2014

Dissemination Level

Public	**PU**

Reference WP
WP2 – Integrated infrastructure for epidemiological and post marketing studies

Reference Activity
Task 2.06 – Define methods for Signal detection

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n. 261060

Index

1. List of Authors

Name	Institution
Caitlin Dodd	EMC
Osemeke Osokogu	EMC
Federica Fregonese	AOPD
Florentia Kaguelidou	EMC
Carmen Ferrajolo	EMC
Yolanda Brauchli	BCF
Cassandra Nan	P95
Thomas Verstraeten	P95
Jan Bonhoeffer	BCF
Miriam Sturkenboom	EMC

2. Abstract

This deliverable is based on the need to develop and test methods for safety signal detection in children. Signal detection is the mainstay of detecting safety issues, but so far very few groups have specifically looked at children. We developed reference sets for positive and negative drug-event combinations and vaccine-event combinations by a systematic literature review on all combinations. We retrieved the FDA AERS database, the CDC VAERS database and EUDRAVIGILANCE database. In order to analyse the datasets we had a stepwise approach from extraction of data, cleaning (e.g. mapping MedDRA and ATC codes) and transformation into a a common data model that we defined for the spontaneous reporting databases. A statistical analysis plan was created for the testing of methods and we provided some descriptive analyses of the FAERS data. Next steps will be to complete the analyses.

3. Abbreviations used in this document

ADR	Adverse Drug Reaction
AEFI	Adverse Events Following Immunization
AERS	Adverse Event Reporting System
AKI	Acute Kidney Injury
ALI	Acute Liver Injury
AUC	Area Under the ROC Curve
BCG	Bacillus Calmette–Guérin
CDC	Centers for Disease Control
CIOMS	Council for International Organizations of Medical Sciences
COSTART	FDA's Coding Symbols for a Thesaurus of Adverse Reaction Terms
DHHS	U.S. Department of Health and Human Services
DILI	Drug-Induced Liver Injury
DTaP	Diphtheria-Tetanus-acellular Pertussis
DTwP	Diphtheria-Tetanus-whole cell Pertussis
EHR	Electronic Healthcare Records
EM	Erythema Multiforme
EMA	European Medicines Agency
EMC	Erasmus Medical Center
eMC	electronic Medicines Compendium
EU-ADR	European Adverse Drug Reaction
FDA	Federal Drug Administration
FDE	Fixed Drug Eruption
GBS	Guillain-Barré Syndrome
GPS	Gamma Poisson Shrinker
GRiP	Global Research in Paediatrics
HAV	Hepatitis A Virus

HBV	Hepatitis B Virus
HHE	Hypotonic Hyporesponsive Episode
Hib	Haemophilus influenzae type B
IC	Bayesian Information Component
ICSR	Individual Case Safety Reports
IDDM	Insulin Dependent Diabetes Mellitues
IOM	Institute of Medicine
LGPS	Longitudinal Gamma Poisson Shrinker
MHRA	Medicines and Healthcare products Regulatory Agency
MMR	Measles-Mumps-Rubella
MSAEFI	Monitoring System for Adverse Events Following Immunization
MV	Meningococcal Virus
NC	Negative Control
NCVIA	National Childhood Vaccine Injury Act
NLM	National Library of Medicine
NPV	Negative Predictive Value
OMOP	Observational Medical Outcomes Partnership
OPV	Oral Polio Virus
OTC	Over The Counter
PC	Positive Control
PV	Pneumococcal Virus
PRR	Proportional Reporting Ratio
ROR	Reporting Odds Ratio
PPV	Positive Predictive Value
RR	Relative Risk
RV	Rotavirus
SIDS	Sudden Infant Death Syndrome

SJS	Stevens-Johnson Syndrome
SPC	Summary of Product Characteristics
SRS	Spontaneous Reporting Systems
TEN	Toxic Epidermal Necrolysis
UC	Unclassifiable
VZV	Varicella Zoster Virus
VAERS	Vaccine Adverse Event Reporting System
VAPP	Vaccine-Associated Paralytic Poliomyelitis
VIT	Vaccine Injury Table
WHO	World Health Organization

4. Introduction

In this deliverable we describe the creation of a reference set as a first step in the comparison of different methods in the evaluation of database performance for signal detection in children. Subsequently we describe the spontaneous reporting datasets that will be utilized, the transformation of these datasets into a common data model, the statistical analysis plan and some initial results.

5.1 Drug safety monitoring:

In the last 50 years, drug safety monitoring has assumed an increasingly more important role in the preservation of public health in most parts of the world [1-3]. This started with the recognition that medicines can cause very serious adverse reactions that present a huge challenge to the health of the population, typified by the thalidomide disaster which led to the withdrawal of the drug in 1961. At the global level, the World Health Organization (WHO) initiated and has maintained a systematic collection of information on serious adverse drug reactions observed during the post-marketing period of drug development since the 1960's [4].

5.2 Drug safety monitoring in children:

While there has been remarkable progress with respect to drug safety monitoring in adults, the same cannot be said of children. It has been shown that the worldwide incidence of unlicensed/off-label drug use in children is 11% - 18% generally and 16% - 62% in paediatric wards.[5] In Europe, unlicensed and off-label use of drugs in children in paediatric wards is as high as 46%.[6] In fact, recognition of the lack of information on the efficacy and safety of drugs in children has led to various forms of legislation, first in the USA, then in Europe and progressively in other parts of the world.[7-8] These legislations are aimed at encouraging collection of evidence with respect to efficacy and safety of drugs in this vulnerable segment of the population.[9-10] All these legislations emphasize the need for children to be included in clinical trials, which is clearly a deviation from what was done in the past.

5.3 Signal detection

5.3.1 Signal detection in spontaneous reports databases:

Spontaneously reported adverse drug reactions (ADRs) are currently the most important source for identifying drug safety signals and studies have shown that method development is necessary for adequate signal detection on spontaneous reporting databases for the paediatric age [11-12].

For efficient signal-detection, data mining methods have been developed that are mostly based on measures of disproportionality. Although useful, data mining methods are subject to bias and confounding. The phenomenon of clusters of reports of a specific group of drugs may jeopardize

the assumption that reporting should be non-differential in order to guarantee unbiased estimates of measures of disproportionality.[12] This is observed very clearly in paediatric safety signal-detection. Within national compilations of paediatric ICSRs, vaccines make up 45-69% of the suspected drugs within the ADR reports.[11-12] ADRs reported for vaccines differ from non-vaccines with respect to seriousness and type of ADRs. The potential influence of vaccines on safety signal-detection for drugs was recently raised in the report of the CIOMS working group VIII.[13] The working group proposed that it may be appropriate to undertake automatic signal-detection using both medicines and vaccines, and some analysis using vaccines only. De Bie et al. recently reported on the methodological aspects of signal detection within paediatric ADR data where the prevalence of vaccine-related ADRs is high.[12] It was concluded that the most inclusive and sensitive signal detection method would be the combination of a crude and subgroup-based data mining approach, based on the ratio between the proportion of vaccines within the ADR of interest and within all other ADRs.

5.4 Signal detection and reference set

One of the objectives of the GRiP project is to improve signal detection methods for paediatrics on spontaneous reports and on electronic healthcare databases.

Development of new methods for signal detection and comparison of methods and database performance requires the creation and use of a ‘gold standard’ set of drug-adverse event associations for the paediatric population. This gold standard is needed to define the positive and negative predictive value of different methods with respect to safety signal detection. As it was not readily available, in this study we describe how a ‘reference set’ as alloyed gold standard has been created.

6 Objectives

The objective of this deliverable was

1) to create a set of drug/vaccine event combinations which, based on evidence in the literature, can be considered positive association or negative association. This has been done both for events upon exposure of small molecules (ADRs) and adverse events following immunization (AEFI);

2) To develop and test methods for signal detection on spontaneous reports from the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Centers for Disease Control (CDC) (FAERS, Eudravigilance and VAERS).

7 Signal detection in children: A new drug reference set for performance testing of data-mining methods and systems

Authors: Osemeke U. Osokogu[1], Federica Fregonese[2,3], Carmen Ferrajolo[1,4], Katia Verhamme[1], Sandra de Bie[1], Geert 't Jong[1,5], Mariana Catapano[6], Daniel Weibel[1], Florentia Kaguelidou[1], Wichor M Bramer[7], Yingfen Hsia[8,9], Ian C K Wong[8,10], Madlen Gazarian[11], Jan Bonhoeffer[12,13], Miriam Sturkenboom[1] on behalf of the GRiP consortium.

[1]Department of Medical Informatics, Erasmus MC - University Medical Center, Rotterdam, The Netherlands; [2]Azienda Ospedaliera di Padova, University of Padua, Italy; [3]CRCHUM, Université de Montreal, Canada; [4]Campania Regional Centre of Pharmacovigilance and Pharmacoepidemiology, Department of Experimental Medicine, Pharmacology Division, Second University of Naples, Italy; [5]Department of Paediatrics and Child Health, University of Manitoba, Winnipeg, Canada; [6]Gruppo Italiano per gli Studi di Farmacoeconomia (GISF), Pavia, Italy; [7]Medical Library, Erasmus MC - University Medical Center Rotterdam, The Netherlands; [8]Centre of Paediatric Pharmacy Research, UCL School of Pharmacy, Department of Practice and Policy, London, United Kingdom;[9]Paediatric Infectious Diseases Research Group, St. Georges University of London, United Kingdom; [10]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, University of Hong Kong, China; [11]School of Medical Sciences, University of New South Wales, Sydney, Australia; [12]Department of Paediatric Infectious diseases and vaccines, University Children's Hospital, Basel, Switzerland; [13]Brighton Collaboration Foundation, Basel, Switzerland.

Correspondence to: Dr Osemeke U. Osokogu. Department of Medical Informatics, Erasmus Medical Center, Postbus 2040, 3000 CA, Rotterdam, the Netherlands. Telephone: +31 10 7044481. Fax: +31 10 7044722. Email: o.osokogu@erasmusmc.nl

7.1 Abstract

Background: Better utilization of spontaneous reporting systems and electronic health records (EHR) may improve paediatric pharmacovigilance. However application of paediatric-specific signal detection methods is required. The Global Research in Paediatrics (GRiP) – Network of excellence aims to develop such methods by comparing the performance of already existing methods on paediatric data. A reference set of known and 'unknown' drug-adverse event associations (*positive* and *negative control)* is required.

Objective: To develop a reference set of known and 'unknown' drug-adverse event associations for comparing signal detection methods and evaluating system performance in children.

Methods: Sixteen drugs and 16 adverse events were utilized. Selected drugs: were frequently and/or globally used in children; had age and/or healthcare-setting specific use. Selected adverse events: had been reported for children within the World Health Organization Vigibase system; are serious (in terms of pharmacovigilance) and specific. A cross-table of unique drug-adverse event pairs was created, and each pair was defined as *positive* or *negative control*: first, the drug's Summary of Product Characteristics, and Micromedex were reviewed. Concordant pairs were further evaluated, based on published literature retrieved from Embase.com and Medline (via Ovid SP).

Results: Altogether, *127* drug-adverse event associations constituted the reference set: *37 positive* and *90 negative control pairs*. The drugs are flucloxacillin, clarithromycin, doxycycline, lopinavir, isoniazid, praziquantel, mebendazole, quinine, fluticasone, montelukast, loperamide, domperidone, ibuprofen, methylphenidate, isotretinoin and cyproterone/ethinylestradiol. The events are bullous eruption, aplastic anaemia, agranulocytosis, thrombocytopaenia, psychosis, suicide, ventricular arrhythmia, sudden death, QT prolongation, thromboembolism, anaphylaxis, seizure, acute kidney injury, acute liver Injury, sepsis, and sudden infant death syndrome (SIDS). Four *positive control* pairs - *clarithromycin-thrombocytopaenia, montelukast-psychosis, montelukast-suicide* AND *methylphenidate-psychosis* - had supporting evidence reported only in children.

Conclusion: We have proposed a reference set that can be used to compare signal detection methods and evaluate system performance in children.

7.2 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 [1-3]. This evolution has

focused on the adult population more than on children. However, paediatric drug safety monitoring is of particular importance, because children are usually underrepresented in pre-licensure safety studies. Suboptimal monitoring methods may leave this vulnerable population inadequately observed for adverse events. 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 [4-8].

Globally, specific regulations are being implemented to generate better evidence on safety and efficacy of paediatric medicines particularly through clinical trials [9, 10]. 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 [11]. This shortcoming may be addressed by tailored analyses of already existing data from spontaneous reporting systems (SRS) and electronic health record (EHR) databases to yield important safety evidence rapidly [12-14], from signal detection, to signal verification and hypothesis testing [15, 16]

Although analysis of spontaneous reports is currently the most commonly used method for identifying safety signals, specific approaches to surveillance of the paediatric population are limited. The Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII recently advocated for an increased paediatric focus in signal detection using SRS [17]. CIOMS also suggested methods to control for confounding in vaccines safety assessment, an issue specific to the paediatric population, and de Bie et. al proposed further refinement of these methods[18]

Safety signal detection using SRS databases may be complemented by longitudinal data derived from 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 [14, 19, 20]. Although newly developed methods i.e. Longitudinal Gamma Poisson Shrinker (LGPS) show promising results on paediatric data [21], 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 children; 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 paediatric 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 paediatric drug-adverse event pairs serving as *positive* and *negative control*, is required to calculate baseline performance statistics. Coloma et al. recently described the methodology for creation of a reference set used to test methods in the EU-ADR project [22]. Similarly, Ryan et. al. established a reference set for testing methods in the OMOP project [23]. However, both were not specific to the paediatric population and comprise many drugs infrequently prescribed to children, and events that rarely (or never) occur in children.

In this paper we describe how we created a proposed reference set for comparing the performance of different methods in detecting signals in the paediatric population: in a given database and across SRS and EHR databases.

7.3 METHODS

The first step in creating the reference set was to select a list of drugs to be utilized. Four primary lists of drugs were created: those frequently prescribed for children on outpatient basis in high income countries (as per papers and reports of use) [24, 25]; drugs used in hospitalized children or by specialists [25]; drugs frequently used in low/middle income countries (as per list of essential medicines of the WHO)[26]; and drugs used in specific paediatric age groups (for example - adolescents) [25].

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 the drug that had the oldest initial marketing authorization worldwide. This was done based on the assumption that we were more likely to find reported evidence of existing and/or documented drug-adverse event associations. 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[27], and minocycline in 1972[28]. Secondly, we preferentially selected drugs that appeared in the highest number of lists, for example a drug appearing on 3 of 4 primary lists would be retained instead of another drug appearing on only 2 lists.

Adverse events were chosen following the same aim of generating a set applicable to different databases; both rare and common adverse drug events were included. The consecutively applied criteria for selection were: (1) ADRs reported for children aged 0-18 years of age in the WHO global monitoring system (Vigibase), in order to ensure that such events have the possibility of occurring as a result of drug use[29, 30] (2) serious adverse event (according to the WHO definition) [31]; and (3) the event was highly specific and identifiable, whenever possible by objective measures, to avoid misclassification. For a few adverse events, we applied specific restrictive criteria in defining them as a means of making them more easily identifiable across different data sources. For example, psychosis referred to only cases of substance-induced psychosis [32]. We generated the list of events independent of the identified drugs.

All the adverse events were defined in reference to case definitions provided in standard resources (i.e. medical textbooks, uptodate.com and scientific societies such as CIOMS) to increase the likelihood of comprehensive literature searches and comparable data sets for performance testing. Medical textbooks were accessed through the medical library of Erasmus Medical Center (EMC), Rotterdam. Uptodate.com is an evidence-based knowledge system, its content is written and edited by a global community of >5000 physicians who are world-renowned experts in their fields of specialization. Among its content are definitions of clinical events based on the most current literature review and with appropriate references. CIOMS (http://www.cioms.ch/) is an international, non-governmental, non-profit organization that represents a substantial proportion of the biomedical scientific community. Among other activities, CIOMS develops precise definitions of specific adverse drug events, for example Drug-Induced Liver Injury (DILI).

The reference set was generated by cross tabulating the final lists of drugs and adverse events which led to a matrix of unique drug-adverse event pairs. In order to classify each unique drug-event pair as a 'positive', 'negative' or 'unclassifiable' association, previously reported medical evidence was reviewed in 2 sequential steps:

1) Review of Summary of Product Characteristics (SPC) and Micromedex

First, we reviewed each drug's SPC to ascertain that a specific event (for example aplastic anaemia) 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) for the 'electronic Medicines Compendium (eMC)' [33]. DailyMed (the 'Contraindications, Warnings, Precautions and/or 'Adverse Reactions' section) was consulted only if a drug was not listed in eMC [34]. 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, we 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 SPC and Micromedex, drug-adverse 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-adverse event pair was further evaluated (figure 1).

2) Review of published literature

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

For each **'potential positive control'**, the search algorithm was modified to include *only controlled vocabulary for the drug*. Free text was retained (in addition to controlled vocabulary) for the adverse event. In addition, *controlled vocabulary was also 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 [22]. We only considered articles published in English.

The type of publication was considered in assessing evidence regarding unique drug-adverse event pairs. 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.

Based on data extracted from retrieved publications, unique drug-adverse event pairs were classified according to the criteria outlined in **table 1**, modified from previous processes [22]. For example, **level I** evidence – 'evidence from at least one (properly designed) randomized controlled trial or meta-analysis'-qualified a specific drug-adverse event pair as a positive association (*positive control)*, 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-adverse 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-adverse event pair.

Whereas confirmation of negative control pairs required lack of association for either adults or children, positive control pairs were assessed for availability of evidence pertaining to children. However, such evidence was not mandatory for classification as positive control, due to the acknowledged lack of studies specific to children [35].

7.4 RESULTS

7.4.1 Selected drugs

We included 16 drugs (*unique WHO-ATC codes, 5th level chemical substance*) in the reference set**.** These include 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).

7.4.2 Selected adverse events

We defined 16 adverse events including bullous eruption (comprising fixed drug eruption [FDE], erythema multiforme [EM], Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]), aplastic anaemia, agranulocytosis, thrombocytopaenia, 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**).

7.4.3 Cross table of drugs and adverse events

As shown in **figure 1***,* following discontinued assessment of *34* unclassifiable drug-adverse event pairs, literature search generated *17,685 hits* for *222* potential positive (*7745 hits*) or negative (*9940 hits*) associations, based on which *127* associations were confirmed as **positive control** (*37 pairs*) or **negative control** (*90 pairs*) (**tables 2 and 3**). In confirming the *positive control* pairs, evidence from only 171 relevant publications (out of 7745 hits) was utilized, comprising *14* biological studies, *10* clinical trials, *23* observational studies, *34* reviews, and *90* case reports/series. The association between *quinine and thrombocytopaenia* had the single 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-thrombocytopaenia* and *clarithromycin-bullous eruption* were established. For the

complete evaluation of all positive drug-adverse event associations, please refer to the **appendix.**

Of *37* positive associations that we found, only *4* (*clarithromycin-thrombocytopaenia*, *montelukast-psychosis, montelukast-suicide AND methylphenidate-psychosis*) were supported by evidence generated exclusively in children, while 20 had supporting evidence that was found only in adults. Thirteen associations were supported by evidence generated from both children and adults.

7.4.4 Comparison between GRiP, EU-ADR and OMOP reference sets

In **table 5**, we compare the reference set we have created with those created within EU-ADR and OMOP. Out of 16 drugs selected within GRiP, only 4 were similarly included in EU-ADR and/or OMOP: fluticasone, ibuprofen, isoniazid and mebendazole. Ibuprofen was found to be associated with acute kidney injury (AKI) across the 3 studies; while the same drug was found to be associated with acute liver injury (ALI) within only GRiP and EU-ADR. Meanwhile isoniazid was associated with ALI, as found in both GRiP and OMOP; on the contrary, both projects did not reveal evidence for association between mebendazole and AKI, as well as between fluticasone and ALI.

7.5 DISCUSSION

We describe a pragmatic approach for creating a reference set of paediatric drug-adverse event associations that may be used for testing the performance of different signal detection methods within individual SRS and EHR databases, and for functional performance testing across signal detection systems. To our knowledge, this is the first structured approach to creating a reference set that is specific to paediatric safety outcomes. This approach yielded *37* positive and *90* negative drug-adverse event associations.

Other projects like OMOP and EU-ADR have also created reference sets, but none of them is specific to paediatrics and the reference set proposed here was based on a different approach [22, 36-38]. In the current project, drugs were selected independent of adverse events, unlike EU-ADR and OMOP where adverse events were pre-selected before identification of drugs that could cause such events based on reported evidence[22, 23]. Still, the EU-ADR network restricted the list of drugs for possible inclusion in the reference set, based on the amounts 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-adverse event associations could actually be identified if indeed they occurred within the network. Similar calculations were not done for the current project although only drugs that are frequently used in children (based on reported evidence in the literature) were considered. Further, the reference set resulting from the current project will be applied to SRS databases (in addition to EHRs) for which such calculations are irrelevant, since population-based data on drug use are usually not available in SRS databases[14].

Unlike EU-ADR, the current project considered the need for diversity of selected drugs as equally important as the need to have strong, well substantiated drug-adverse event associations, given

the intended application of this reference set to global databases with varying drug use profiles. Sets with drugs for inpatient use may favour SRS databases[39], while sets utilizing drugs prescribed for outpatient treatments may favour EHR databases[40]. Moreover we preferentially selected drugs with longer licence status. Therefore we were more likely to find reported evidence on their safety.

In selecting adverse events, we prioritized 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 [22]. Such events may be reported more often than common, multifactorial events because they are easier to identify. Given that the composition of the lists of drugs and adverse events to be tested may have an extensive impact on performance assessment [41], we ensured 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 both positive and negative evidence. 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. This was considered necessary to increase the probability of retrieving relevant publications (i.e. publications that reported on clinical event and drug in the context of drug safety), an approach similar to that adopted by the EU-ADR project[22].

Whereas the negative drug-adverse event associations required lack of association for adults or children, the positive drug-adverse event associations were specifically (or primarily) assessed for availability of evidence pertaining to children. However, only 4 associations (*clarithromycin-thrombocytopaenia, montelukast-psychosis, montelukast-suicide AND methylphenidate-psychosis*) were supported by evidence generated exclusively in children: a case-control study for *clarithromycin-thrombocytopaenia* [42]; case reports (more than 3) for *montelukast-psychosis [43]*; review of spontaneous reports for *montelukast-suicide [44];* and *clinical trial as well as case series for methylphenidate-psychosis[45].* The scarcity and quality of child-specific data further highlightthe difficulties in generating safety evidence in the paediatric population, thereby underlining the importance of developing a tool to define appropriate signal detection methods in childen.

We chose to classify all pairs with inconsistent evidence as unclassifiable, to limit to well documented drug-adverse event association pairs that would allow us to compare methods. Therefore the reference set that has been created in this project does not include all known drug-adverse event associations but those associations for which adequate reported evidence, as defined in this study, was found. We searched for biological (in addition to epidemiological) evidence to further strenghthen retrieved evidence for positive control pairs. However we were only able to find such evidence for *13* out of 37 positive associations: *quinine-aplastic anaemia[46]; quinine-agranulocytosis[47]; quinine-thrombocytopaenia[48*]; *isotretinoin-psychosis[49, 50]*; *methylphenidate-psychosis [51, 52]; isotretinion-suicide[49, 50]; domperidone-ventricular arrhythmia[53]; domperidone-sudden death[54]; clarithromycin-QT prolongation[55]; quinine-QT prolongation[56, 57]; ibuprofen-anaphylaxis[58]; isoniazid-seizure[59]; and ibuprofen-acute kidney injury[60].* Of these, *quinine-thrombocytopaenia* 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[61]; 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. Out of 16 drugs considered in GRiP, only 4 were similarly considered 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.

Many *potential positive control* pairs established on the basis of SPC and Micromedex contents were not supported by evidence in the peer-reviewed literature, for example *domperidone-QT prolongation* and *cyproterone/ethinylestradiol-venous thromboembolism,* both of which have been well investigated. The search query we used to retrieve the publications may have been too specific. For other uncomfirmed *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).

Although the reference set we have proposed may be utilized for testing different methods both within and across signal detection systems, generalizing the results of such performance assessments to other systems may not be valid. Various unknown database-specific factors may limit such generalizability.

This reference set may be viewed as dynamic. The status of drug-adverse event associations may change over time. For example negative or unclassifiable associations may become positive associations if evidence supporting such becomes available. Therefore periodic review is advised.

Nevertheless, well tested statistical methods for safety signal detection of paediatric drugs and well tested signal detection systems are a precondition (prerequisite) for optimization of methods and systems as well as meaningful interpretation of results. A reference set is a necessary condition for such improvements.

7.6 CONCLUSION

We have generated a paediatric-specific reference set that can be applied to both SRS and EHR databases. It is designed for comparing signal detection methods and evaluating system performance.

7.7 REFERENCES

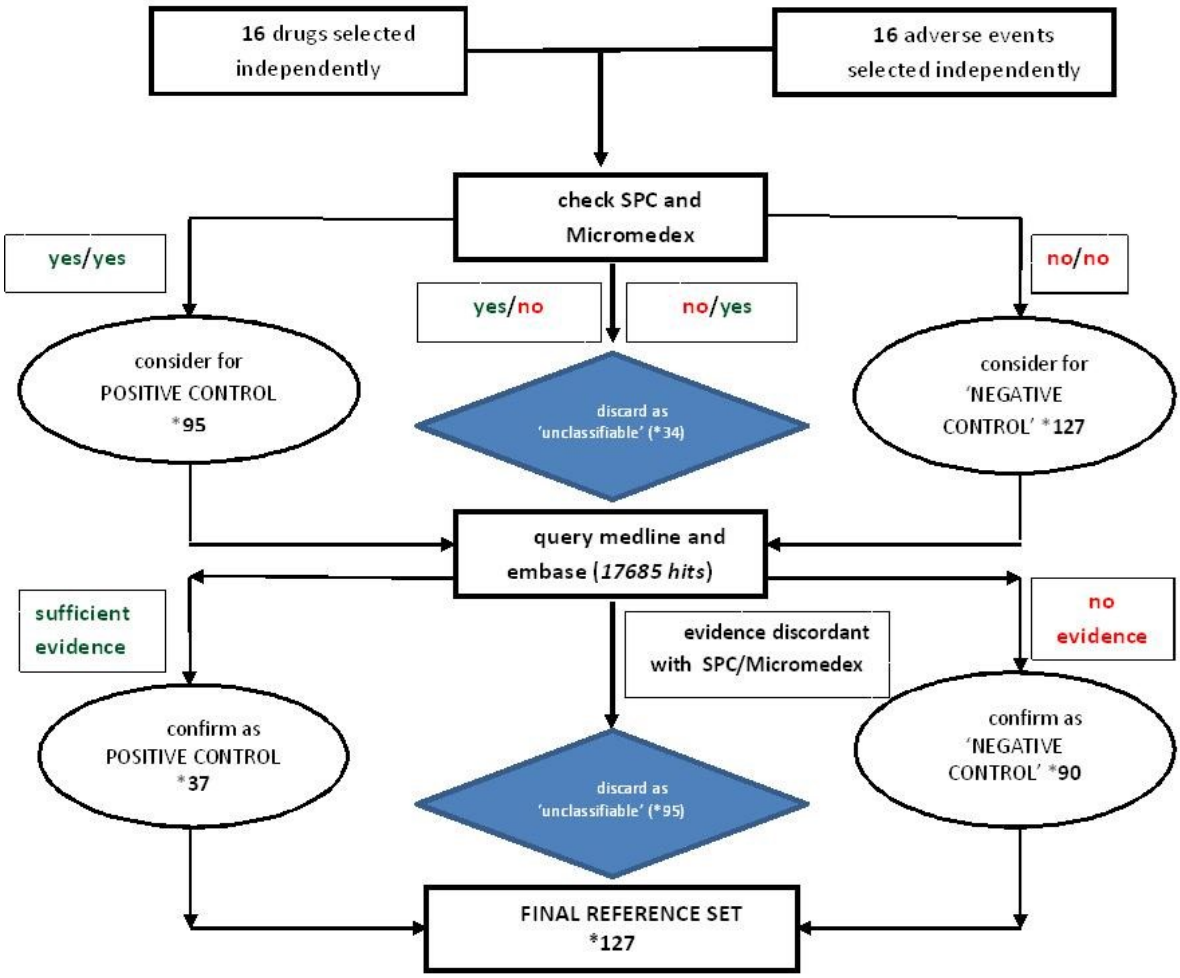
1. Scurti V, Romero M, Tognoni G. A plea for a more epidemiological and patient-oriented pharmacovigilance. Germany: Department of Clinical Pharmacology and Epidemiology, Centro Studi SIFO, Consorzio Mario Negri Sud, Via Nazionale 8/a, 66030, S. Maria Imbaro, Italy. scurti@negrisud.it; 2012 [cited 68 en4, 1256165]; 1:[11-9]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21773732.
2. Meyboom RHB. Pharmacovigilance in a changing world. Klinicka Farmakologie a Farmacie. 2011;25(3):102-11.
3. Van Grootheest K. The dawn of pharmacovigilance: An historical Perspective. International Journal of Pharmaceutical Medicine. 2003;17(5-6):195-200.
4. Vlahovic-Palcevski V, Mentzer D. Postmarketing surveillance. Germany: Department for Clinical Pharmacology, University of Rijeka Medical School, University Hospital Center Rijeka, Kresimirova 42, 51000 Rijeka, Croatia. vvlahovic@inet.hr; 2011 [cited 205 7902231]; 339-51].

Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21882120.
5. Autret-Leca E, Marchand MS, Cissoko H, Beau-Salinas F, Jonville-Bera AP. [Pharmacovigilance in children]. France: Service de pharmacologie clinique, centre regional de pharmacovigilance et d'information sur le medicament, CHRU de Tours, 2, boulevard Tonnelle, 37044 Tours cedex 9, France. autret-leca@med.univ-tours.fr; 2012 [cited 19 9421356, bwh]; 8:[848-55]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22748689.
6. Phan H, Leder M, Fishley M, Moeller M, Nahata M. Off-label and unlicensed medication use and associated adverse drug events in a pediatric emergency department. Pediatric Emergency Care. 2010;26(6):424-30.
7. Conroy S. Unlicensed and off-label drug use: Issues and recommendations. Pediatric Drugs. 2002;4(6):353-9.
8. Knellwolf AL, Bauzon S, Alberighi ODC, Lutsar I, Bacsy E, Alfarez D, et al. Framework conditions facilitating paediatric clinical research. Italian Journal of Pediatrics. 2011;37(1).
9. United States Of America. Pediatric Research Equity Act. 2003 [3 Sep 2013]; Available from: www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm077853.pdf.
10. Agency EM. Paediatric Regulation. 2006 [3 Sep 2013]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp.
11. Pincus T. Limitations of randomized clinical trials to recognize possible advantages of combination therapies in rheumatic diseases. UNITED STATES: Division of Rheumatology and Immunology, Vanderbilt University School of Medicine, Nashville, TN 37232-2681.; 1993 [cited 23 1306053, umv]; 2 Suppl 1:[2-10]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8278816.
12. de Almeida Vieira Lima LM, Nunes NGSC, da Silva Dias PGP, Marques FJB. Implemented data mining and signal management systems on spontaneous reporting systems' databases and their availability to the scientific community - a systematic review. United Arab Emirates: University of Coimbra, Portugal. miguelvlima@gmail.com; 2012 [cited 7 101270895]; 2:[170-5]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22873501.
13. Jacquot J, Gony M, Baudrin D, Chastel X, Montastruc J-L, Bagheri H. [Could we improve notification of adverse drugs reactions in hospital? Assessment of 5 years of network PharmacoMIP's activities]. France: Service de Pharmacologie Clinique, Centre Midi-Pyrenees de Pharmacovigilance, de Pharmacoepidemiologie et d'Informations sur le Medicament, Equipe de Recherche de Pharmacoepidemiologie INSERM U1027, Centre Hospitalier Universitaire, Toulouse, France.; 2012 [cited 67 vq6, 0420544]; 3:[231-6]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22874489.
14. Coloma PM, Trifiro G, Schuemie MJ, Gini R, Herings R, Hippisley-Cox J, et al. Electronic healthcare databases for active drug safety surveillance: Is there enough leverage? Pharmacoepidemiology and Drug Safety. 2012;21(6):611-21.
15. Ball R, Horne D, Izurieta H, Sutherland A, Walderhaug M, Hsu H. Statistical, epidemiological, and risk-assessment approaches to evaluating safety of vaccines throughout the life cycle at the Food and Drug Administration. Pediatrics. 2011;127(SUPPL. 1):S31-S8.
16. Valkhoff VE, Schade R, t Jong GW, Romio S, Schuemie MJ, Arfe A, et al. Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries in the SOS project: What size of data platforms and which study designs do we need to assess safety issues? BMC Pediatrics. 2013;13(1).
17. CIOMS, editor. Practical Aspects of Signal Detection in Pharmacovigilance.Report of CIOMS Working Group VIII.
18. de Bie S, Verhamme KMC, Straus SMJM, Stricker BHC, Sturkenboom MCJM. Vaccine-based subgroup analysis in VigiBase: effect on sensitivity in paediatric signal detection. 2012;35(ahq, 9002928):335-46. Epub 4.

19. Schuemie MJ, Coloma PM, Straatman H, Herings RM, Trifiro G, Matthews JN, et al. Using electronic healthcare records for drug safety signal detection: A comparative evaluation of statistical methods. Pharmacoepidemiology and Drug Safety. 2012;21:342.
20. De Bie S, Coloma P, Ferrajolo C, Trifiro G, Verhamme K, Schuemie M, et al. The power of electronic healthcare databases for active drug safety surveillance in children and adolescents: An EUADR study. Pharmacoepidemiology and Drug Safety. 2012;21:329-30.
21. Ferrajolo C, Coloma Pm Fau - Verhamme KMC, Verhamme Km Fau - Schuemie MJ, Schuemie Mj Fau - de Bie S, de Bie S Fau - Gini R, Gini R Fau - Herings R, et al. Signal detection of potentially drug-induced acute liver injury in children using a multi-country healthcare database network. (0114-5916 (Print)).
22. Coloma PM, Avillach P, Salvo F, Schuemie MJ, Ferrajolo C, Pariente A, et al. A reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases. New Zealand: Department of Medical Informatics, Erasmus Medical Center, Postbus 2040, 3000, CA, Rotterdam, The Netherlands. p.coloma@erasmusmc.nl; 2013 [cited 36 ahq, 9002928]; 1:[13-23]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=23315292.
23. Ryan PB, Schuemie MJ, Welebob E, Duke J, Valentine S, Hartzema AG. Defining a reference set to support methodological research in drug safety. Drug safety : an international journal of medical toxicology and drug experience. 2013;36 Suppl 1(ahq, 9002928):S33-47.
24. Sturkenboom MCJM, Verhamme KMC, Nicolosi A, Murray ML, Neubert A, Caudri D, et al. Drug use in children: Cohort study in three European countries. BMJ. 2008;337(7682):1338-41.
25. European Medicines Agency. Report on the survey of all paediatric uses of medicinal products in Europe. 2010; Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500101006.
26. WHO. WHO Model Lists of Essential Medicines. 2011.
27. Alexander J. Doxycycline MedKit Regulatory Background. 2012 [cited 2014 16th June]; Available from: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm299210.pdf.
28. Lawrenson RA, Seaman HE, Sundstrom A, Williams TJ, Farmer RDT. Liver damage associated with minocycline use in acne: A systematic review of the published literature and pharmacovigilance data. Drug Safety. 2000;23(4):333-49.
29. World Health Organization. Promoting safety of medicines for children. 2007 [cited 2014 16th June]; Available from: http://www.who.int/iris/handle/10665/43697#sthash.bXlIM3UL.dpuf.
30. Star K, Noren GN, Nordin K, Edwards IR. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. New Zealand: Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. kristina.star@who-umc.org; 2011 [cited 34 ahq, 9002928]; 5:[415-28]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21513364.
31. World Health Organization. Quality Assurance and Safety of Medicines Team. Safety of medicines : a guide to detecting and reporting adverse drug reactions : why health professionals need to take action. 2002 [cited 2014 16th June]; Available from: http://www.who.int/iris/handle/10665/67378.
32. Niemi-Pynttari JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola SP. Substance-induced psychoses converting into schizophrenia: A register-based study of 18,478 finnish inpatient cases. Journal of Clinical Psychiatry. 2013;74(1):e94-e9.
33. Limited DC. Electronic Medicines Compendium.
34. Medicine NLO. DailyMed.
35. Choonara I. Unlicensed and off-label drug use in children: Implications for safety. Expert Opinion on Drug Safety. 2004;3(2):81-3.
36. Hochberg AM, Hauben M, Pearson RK, O'Hara DJ, Reisinger SJ, Goldsmith DI, et al. An evaluation of three signal-detection algorithms using a highly inclusive reference event database. New Zealand: ProSanos Corporation, Harrisburg, Pennsylvania 17102, USA.

alan.hochberg@prosanos.com; 2009 [cited 32 ahq, 9002928]; 6:[509-25]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19459718.
37. Hauben M, Reich L, Chung S. Postmarketing surveillance of potentially fatal reactions to oncology drugs: potential utility of two signal-detection algorithms. Germany: Pfizer Inc, 150 E. 42nd Street, New York, NY 10017, USA.; 2004 [cited 60 en4, 1256165]; 10:[747-50]. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15619136.
38. Lindquist M, Stahl M, Bate A, Edwards IR, Meyboom RHB. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. Drug Safety. 2000;23(6):533-42.
39. Ahmad SR. Adverse drug event monitoring at the food and drug administration: Your report can make a difference. Journal of General Internal Medicine. 2003;18(1):57-60.
40. Pearson JF, Brownstein CA, Brownstein JS. Potential for electronic health records and online social networking to redefine medical research. Clinical Chemistry. 2011;57(2):196-204.
41. Zhou X-H, Obuchowski N, McClish D. Statistical methods in diagnostic medicine: John Wiley & Sons; 2011.
42. Bertuola F, Morando C, Menniti-Ippolito F, Da Cas R, Capuano A, Perilongo G, et al. Association between drug and vaccine use and acute immune thrombocytopenia in childhood: A case-control study in Italy. Drug Safety. 2010;33(1):65-72.
43. Wallerstedt SM, Brunlof G, Sundstrom A, Eriksson AL. Montelukast and psychiatric disorders in children. Pharmacoepidemiology and Drug Safety. 2009;18(9):858-64.
44. Bygdell M, Brunlof G, Wallerstedt SM, Kindblom JM. Psychiatric adverse drug reactions reported during a 10-year period in the Swedish pediatric population. Pharmacoepidemiology and Drug Safety. 2012;21(1):79-86.
45. Shibib S, Chalhoub N. Stimulant induced psychosis. Child and Adolescent Mental Health. 2009;14(1):20-3.
46. Maguire RB, Stroncek DF, Campbell AC. Recurrent pancytopenia, coagulopathy, and renal failure associated with multiple quinine-dependent antibodies. Annals of Internal Medicine. 1993;119(3):215-7.
47. Sutherland R, Vincent PC, Raik E, Burgess K, Sutherland R, Vincent PC, et al. Quinine-induced agranulocytosis: toxic effect of quinine bisulphate on bone marrow cultures in vitro. British Medical Journal. 1977;1(6061):605-7.
48. Peterson JA, Nelson TN, Kanack AJ, Aster RH. Fine specificity of drug-dependent antibodies reactive with a restricted domain of platelet GPIIIA. Blood. 2008;111(3):1234-9.
49. Bremner JD, Shearer K, McCaffery P. Retinoic acid and affective disorders: The evidence for an association. Neuropsychopharmacology. 2010;35:S115.
50. Bremner JD, McCaffery P. The neurobiology of retinoic acid in affective disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2008;32(2):315-31.
51. Pliszka SR. Pharmacologic treatment of attention-deficit/hyperactivity disorder: Efficacy, safety and mechanisms of action. Neuropsychology Review. 2007;17(1):61-72.
52. Ross RG. Psychotic and manic-like symptoms during stimulant treatment of attention deficit hyperactivity disorder. American Journal of Psychiatry. 2006;163(7):1149-52.
53. Claassen S, Zunkler BJ. Comparison of the effects of metoclopramide and domperidone on HERG channels. Pharmacology. 2005;74(1):31-6.
54. Stork D, Timin EN, Berjukow S, Huber C, Hohaus A, Auer M, et al. State dependent dissociation of HERG channel inhibitors. British Journal of Pharmacology. 2007;151(8):1368-76.
55. Stanat SJC, Carlton CG, Crumb Jr WJ, Agrawal KC, Clarkson CW. Characterization of the inhibitory effects of erythromycin and clarithromycin on the HERG potassium channel. Molecular and Cellular Biochemistry. 2003;254(1-2):1-7.
56. Sheldon R, Duff H, Koshman ML. Antiarrhythmic activity of quinine in humans. Circulation. 1995;92(10):2944-50.
57. White NJ, Looareesuwan S, Warrell DA. Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. Journal of cardiovascular pharmacology. 1983;5(2):173-5. Epub 1983/03/01.

58. Nanau RM, Neuman MG. Ibuprofen-induced hypersensitivity syndrome. Translational Research. 2010;155(6):275-93.
59. Wood JD, Peesker SJ. A correlation between changes in GABA metabolism and isonicotinic acid hydrazide-induced seizures. Brain research. 1972;45(2):489-98.
60. Carmichael J, Shankel SW. Effects of nonsteroidal anti-inflammatory drugs on prostaglandins and renal function. American Journal of Medicine. 1985;78(6 I):992-1000.
61. Brinker AD, Beitz J. Spontaneous reports of thrombocytopenia in association with quinine: Clinical attributes and timing related to regulatory action. American Journal of Hematology. 2002;70(4):313-7.



* number of drug-adverse event pairs

Figure 1: Flow-chart showing procedure adopted for the construction of the reference set

Table 1: Evaluation and grading of unique drug-adverse 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 [properly designed] randomized controlled trial or meta-analysis)	*Proven* for causal association	Evidence from at least 1 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 1 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 1 publication explaining mechanistic pathway	**NC1**
			Plausible against causal association	No published evidence	**NC2**

SPC - summary of product characteristics

Table 2: Classification of unique drug-adverse event pairs as positive control (green - *comprising PC1 and PC2*) or negative control (red - *all of which are NC2*)

		selected adverse events															
		bullous eruption	aplastic anaemia	agranulocytosis	thrombocytopaenia	psychosis	suicide	vent. arrhythmia	sudden death	QT prolongation	thromboembolism	anaphylaxis	seizure	acute kidney injury	acute liver injury	sepsis	SIDS
selected drugs	flucloxacillin																
	clarithromycin																
	doxycycline																
	lopinavir																
	isoniazid																
	praziquantel																
	mebendazole																
	quinine																
	fluticasone																
	montelukast																
	isotretinoin																
	loperamide																
	domperidone																
	methylphenidate																
	ibuprofen																
	cyproterone/ethinylestradiol																

Table 3: Positive drug-adverse event associations

Event	Positive associations					
	ATC code	Name	Level of *epi. Evidence	#Population $(A / B / C)	Biological evidence &(Pr/Pl)	^Grade
~bullous eruption	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	iIbuprofen	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

~includes fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis *** Epidemiological - Levels I and II are as defined in table 1**

 # Population in which epidemiological evidence was found; $ Adults/Both/Children

^ As defined in table 1

& Pr – Proven biological evidence; Pl – Plausible biological evidence

As presented in **table 3,** 13 (out of 37) positive associations were supported by proven biological evidence in addition to epidemiological evidence. Four associations were supported by epidemiological evidence found exclusively in *children*, while 20 and 13 associations were supported by evidence generated from *'only adults',* and *'both adults and children'* respectively.

Table 4: Example of the evaluation of positive 'drug-adverse event' associations for 'quinine-therombocytopenia' and 'clarithromycin-QT prolongation'

ATC Code	Drug Name	Event Type	Labelled as AE in SPC[Yes/No]	Type/No. of Supporting LiteratureCitations
P01BC01	Quinine	thrombocytopenia	Yes *eMC (Special warnings and precautions for use; Undesirable effects) #Micromedex (Summary): Blackbox warning;(Contraindications/Warnings→Contraindications; precautions); (Adverse effects→serious)	Total number of supporting citations = 20 Biological studies = 8 Review of biological studies = 4 Systematic review = 1 Case series = 1 Case reports = 4 Review of Spontaneous reports = 2
J01FA09	Clarithromycin	bullous eruption	Yes *eMC (Special warnings and precautions for use; Undesirable effects) #Micromedex (Summary): (Contraindications/Warnings→Contraindications; precautions); (Adverse effects→serious)	Total number of supporting citations = 8 Cohort study = 2 Cross-sectional study = 1 Case reports = 5

Table 5: Comparison of GRiP, EU-ADR and OMOP reference sets

AKI – acute kidney injury; ALI – acute liver injury; SIDS – sudden infant death syndrome

	PROJECT	bullous eruption	aplastic anaemia	agranulocytosis	thrombocytopaenia	psychosis	suicide	ventricular arrhythmia	sudden death	QT prolongation	thrombo embolism	anaphylaxis	seizure	AKI	ALI	sepsis	SIDS
isoniazid	GRiP																
	EU-ADR																
	OMOP																
m'dazole	GRiP																
	EU-ADR																
	OMOP																
fluticasone	GRiP																
	EU-ADR																
	OMOP																
ibuprofen	GRiP																
	EU-ADR																
	OMOP																

8 Reference set for performance testing of paediatric vaccine safety signal detection methods and systems

Yolanda Brauchli Pernus[1*], Cassandra Nan[2*], Thomas Verstraeten[2], Mariia Pedenko[3], Osemeke U. Osokogu[3], Daniel Weibel[3], Miriam Sturkenboom[3], Jan Bonhoeffer[1,4], on behalf of the GRiP consortium.

[1] Brighton Collaboration Foundation, Switzerland

[2] P95 Pharmacovigilance and Epidemiology Services, Leuven, Belgium

[3] Erasmus University Medical Center, The Netherlands

[4] University Children's Hospital Basel, University Basel

[*]shared first authorship

Corresponding author

Yolanda Brauchli Pernus

Brighton Collaboration Foundation

Spitalstrasse 33

4056 Basel, Switzerland

contact@brightoncollaboration.org

T+41 61 704 12 12

F+41 61 704 12 13

8.1 Abstract

Background: Safety signal detection in spontaneous reporting system databases and electronic healthcare records is important for detection of previously unknown adverse events following immunization. Various statistical methods have been developed, however none are geared to the pediatric population. Further development and evaluation of performance requires the availability of a reference set listing vaccine-adverse event associations with a high likelihood for causal relationships (positive controls [PC]) and an absence of any relationship (negative controls [NC]).

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. Criteria for the selection of vaccines considered in the reference set were routine and global use in the pediatric population. Adverse events needed to be clearly defined and if possible serious entities. The approach for classifying selected vaccine-adverse event associations into PC or NC was based on evidence in expert committee reports such as the 2011 report by the Institute of Medicine (IOM), primarily outcome-based literature searches, information in Micromedex and summaries of product characteristics. Classification was performed by two experts in parallel according to a pre-defined algorithm and discussed for consensus in case of uncertainties.

Results: We selected 13 vaccines and 14 adverse events to be included in the reference set. From a total of 182 vaccine-adverse event associations, 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 associations, an underlying pathomechanism was considered unlikely classifying the association as NC.

Conclusion: A reference set of vaccine-adverse event associations was developed. The usability of this reference set to guide methods development for pediatric signal detection methods will be tested against spontaneous reporting databases and electronic health care databases.

Mesh terms: vaccine, pediatrics, pharmacovigilance, data mining

8.1 Introduction

Vaccination programs usually target a large, often healthy pediatric population . Thus, newly observed adverse events (signals) following immunization (AEFI) need to be rapidly assessed for a targeted individual and public health response. Emerging unjustified safety concerns need to be rapidly and reliably refuted due to their potential derailing of effective immunization programs protecting this vulnerable population. On the other hand, true product or programmatic safety issues need to be recognized and lead to rapid regulatory decision making to modify the indication, withdraw the product from the market or provide subject compensation. Such decision-making requires the best possible evidence at the time of concern and effective signal detection and verification systems. This typically tends to occur during the introduction of new or new to market vaccines, when numbers are small and international collaboration may support the country where such concerns arise.

Various definitions of what constitutes a signal, exist today including the one from the World Health Organisation (WHO) and the following more recent definition by the Council for International Organizations of Medical Sciences (CIOMS): '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 sufficient likelihood to justify verificatory action'.[1,2] Various methods for signal detection in spontaneous reporting system (SRS) databases and electronic healthcare records (EHR) have been developed based on disproportionality analysis or on multivariate modeling techniques.[3] As gold standards of confirmed causal drug/vaccine-adverse event associations do not exist for performance testing and comparison of these methods, reference sets listing drug/vaccine-adverse event associations with a high likelihood for causal relationships (positive controls [PC]) and an absence of any relationship (negative controls [NC]) are required. Several such standards have been developed for drugs - although none for pediatric drugs.[4] Approaches to develop such standards for drugs varied from consulting reference books such as the physicians drug reference or martindale,[5] considering label changes[6] to a combined approach of information from the summary of product characteristics (SPC) and the literature as in two recent initiatives, the 'Observational Medical Outcomes Partnership (OMOP)' and the 'EU-ADR project'.[7, 8]

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.

8.2 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. 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 statistical methods for signal detection of pediatric vaccines, we only considered vaccines which are used in children for the construction of the reference set. Vaccines also had to be routinely used for several years to ascertain adequate exposure and to allow detection 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: Bacillus 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

Adverse events were first selected on their likelihood of being PCs for at least one vaccine, given the expectation that few such PCs might be found, or of having been evaluated by an official report for at least one vaccine. The list was then narrowed down based on the specificity and seriousness of the event.[9] 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 “serious” 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), intussusception, thrombocytopenia, vaccine-associated paralytic poliomyelitis (VAPP), and wheezing (reactive airway disease). This resulted in a total of 182 vaccine-adverse event associations which needed to be classified into PC or NC, or unclassifiable [UC].

Literature search and included studies

We performed 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 PubMed. All others are available in the online supplemental information. 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 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')[9, 10], or included in WHO information sheets[11] or in the Vaccine Injury Table (VIT)[12] (91 in total). For each vaccine-event pair of interest, 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.

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. A first extraction of relevant articles was performed individually by CN, MP and YB. Subsequent classification of vaccine-adverse event associations based on the extracted literature (described below) was done by two reviewers (from the list of authors) in parallel and then discussed for consensus with a third arbitrator (JB or TV) in case of uncertainties. The quality of the extraction process of relevant articles was randomly double-checked.

Classification of vaccine-adverse event pairs

If a vaccine-adverse event association had been evaluated by the IOM, WHO or VIT sources, we accepted this classification. Vaccine-adverse event associations, which were pathophysiologically not possible (e.g. disseminated Oka VZV following HBV vaccine) were classified as NC. For all other associations, a literature review was performed and the algorithm as shown in Table 2 was applied. "*Evidence"* was defined as at least one 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). 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. Figure 1 displays our classification method graphically.

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 associations 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 Characteristics (SPC) of European centrally authorized products based on a table created in the frame of the IMI project PROTECT.[13] If not available, then the UK SPC was used as it is in English or the WHO information leaflets. We did not change the classification according to US labels as the inclusion of adverse events in the US label is not dependent on evidence or suspicion of a causal association, as is the case in Europe.[14]

8.3 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 publications, 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 useful for classification. Table 3 exemplifies the classification table for the event thrombocytopenia. A table referencing all studies considered for classification of each vaccine-adverse event association 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.

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 associations 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 associations, 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 associations not already classified by expert committee reports was limited. Furthermore, we did not find any published clinical trials specifically investigating any of the included vaccine- adverse event associations and only three meta-analyses.[15-17]

8.4 Discussion

In this study, we presented our approach to create a reference set or gold standard 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 and unpublished 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. From 182 vaccine-adverse event associations, we classified 18 as PC, 113 as NC and 51 as unclassifiable.

In a study on performance testing of signal detection algorithms, van Holle L et al. have used information in the product label as a proxy for true safety signals.[18] 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.[7] The official sources (mainly the IOM report[9]) classified the majority of the associations as UC (‘*Evidence is inadequate to accept or reject a causal relationship’)* and only very few associations as NC. In contrast, in our review, we classified more than two thirds of the associations as NC and less than one third as UC. This difference is due to the fact that the IOM committee did not consider the absence of evidence as evidence of absence, but only rejected a causal relationship in presence of strong and convincing evidence against a causal relationship. According to our classification system, absence of evidence implies absence of a causal relationship based on current knowledge. As most of the vaccines in our reference set have been on the market for quite some time, we assumed that at least some case reports could have been expected if there was a causal relationship.

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.

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,[19] 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 calendar time of evidence when classifying the vaccine-adverse event associations 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 in case the evaluation of the performance of statistical methods for signal detection in databases deems it 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 may 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. This time-dependency is shown in Figure 2 and needs to be considered and evaluated in the performance testing of the signal detection methods and highlights the need for cyclical revision.

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. Thus, we trust that our work contributes to the improvement of vaccine pharmacovigilance in children.

8.5 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.

8.6 References

1. The importance of Pharmacovigilance - Safety Monitoring of medicinal products: World Health Organization; 2002.
2. Practical aspects of signal detection in pharmacovigilance. Report of CIOMS Working Group VIII. Geneva, CIOMS. 2010.
3. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. *Clinical pharmacology and therapeutics* 2013; **93**(6): 539-46.
4. Osokogu O, Fregonese F, Ferrajolo C, et al. Signal detection in children: A new reference set of 'drug-adverse event' associations for performance testing of databases and data-mining methods. . *in submission*.
5. Lindquist M, Stahl M, Bate A, Edwards IR, Meyboom RH. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. *Drug safety : an international journal of medical toxicology and drug experience* 2000; **23**(6): 533-42.
6. Hauben M, Reich L. Safety related drug-labelling changes: findings from two data mining algorithms. *Drug safety : an international journal of medical toxicology and drug experience* 2004; **27**(10): 735-44.
7. Ryan PB, Madigan D, Stang PE, Overhage JM, Racoosin JA, Hartzema AG. Empirical assessment of methods for risk identification in healthcare data: results from the experiments of the Observational Medical Outcomes Partnership. *Statistics in medicine* 2012; **31**(30): 4401-15.
8. Coloma PM, Avillach P, Salvo F, et al. A reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases. *Drug safety : an international journal of medical toxicology and drug experience* 2013; **36**(1): 13-23.
9. Institute of Medicine (IOM). Adverse effects of vaccines: evidence and causality; 2011.
10. Institute of Medicine (IOM). Influenza Vaccines and neurological complications 2004.

11. WHO. WHO vaccine reaction rates information sheets. http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/ (accessed July 9, 2014.
12. HRSA. Vaccine Injury Table. http://www.hrsa.gov/vaccinecompensation/vaccinetable.html (accessed April 14, 2014.
13. PROTECT. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) - ADR database. http://www.imi-protect.eu/adverseDrugReactions.shtml (accessed July 9, 2014.
14. EMA. A guideline on summary of product characteristics (SmPC), revision 2. 2009. http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf (accessed July 9, 2014.
15. Cheuvart B, Friedland LR, Abu-Elyazeed R, Han HH, Guerra Y, Verstraeten T. The human rotavirus vaccine RIX4414 in infants: a review of safety and tolerability. *The Pediatric infectious disease journal* 2009; **28**(3): 225-32.
16. Arnoldussen DL, Linehan M, Sheikh A. BCG vaccination and allergy: a systematic review and meta-analysis. *The Journal of allergy and clinical immunology* 2011; **127**(1): 246-53, 53 e1-21.
17. El-Zein M, Parent ME, Benedetti A, Rousseau MC. Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. *International journal of epidemiology* 2010; **39**(2): 469-86.
18. van Holle L, Zeinoun Z, Bachau V, Verstraeten T. Using time-to-onset for detecting safety signals in spontaneous reports of adverse events following immunization: a proof of concept study. *Pharmacoepidemiol Drug Saf* 2012; **21**(6): 603-10.
19. Maglione MA, Das L, Raaen L, et al. Safety of vaccines used for routine immunization of US children: a systematic review. *Pediatrics* 2014; **134**(2).
20. Gold MS. Hypotonic-hyporesponsive episodes following pertussis vaccination: a cause for concern? *Drug safety : an international journal of medical toxicology and drug experience* 2002; **25**(2): 85-90.

Tables

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

Pubmed	#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)

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	

[*)] *Evidence*: at least on 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

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

Type of publication	Case report/Case series		Meta-analysis		Clinical trial		Controlled epidemiological study		Events in clinical trials or from surveillance studies*	In MDX?	In SPC?	Classification
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

Table 4: Reference table of positive and negative controls for vaccine-adverse event associations

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.[20]

2) Official report:
IOM (1) = Reports of the Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality (2011)[9]
IOM (2) = Reports of the Institute of Medicine, Influenza Vaccines and neurological complications (2004)[10]
VIT = Vaccine Injury Table (July 2011)[12]
WHO = WHO, World Health Organisation, vaccine reaction rates information sheets[11]

* = for febrile seizure
** = unclassifiable for children <5 years

	Positive control
	Negative control
	Unclassifiable

Figures

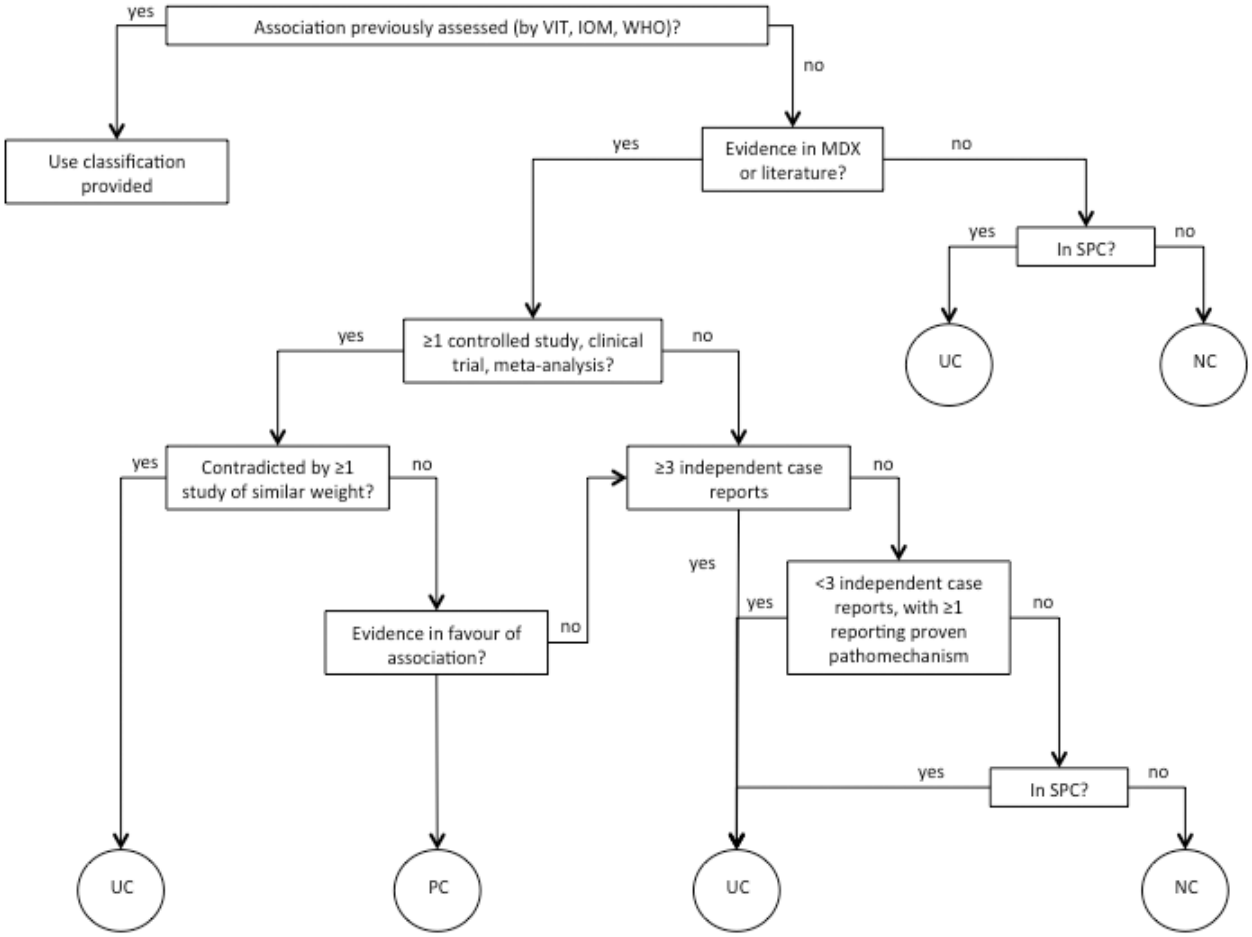


Figure 1: Classification algorithm for development of the reference set for performance testing of signal detection methods and systems
(considers pathophysiologically possible vaccine-adverse event associations only)
VIT, vaccine injury table; IOM, reports of the Institute of Medicine; MDX, micromedex;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

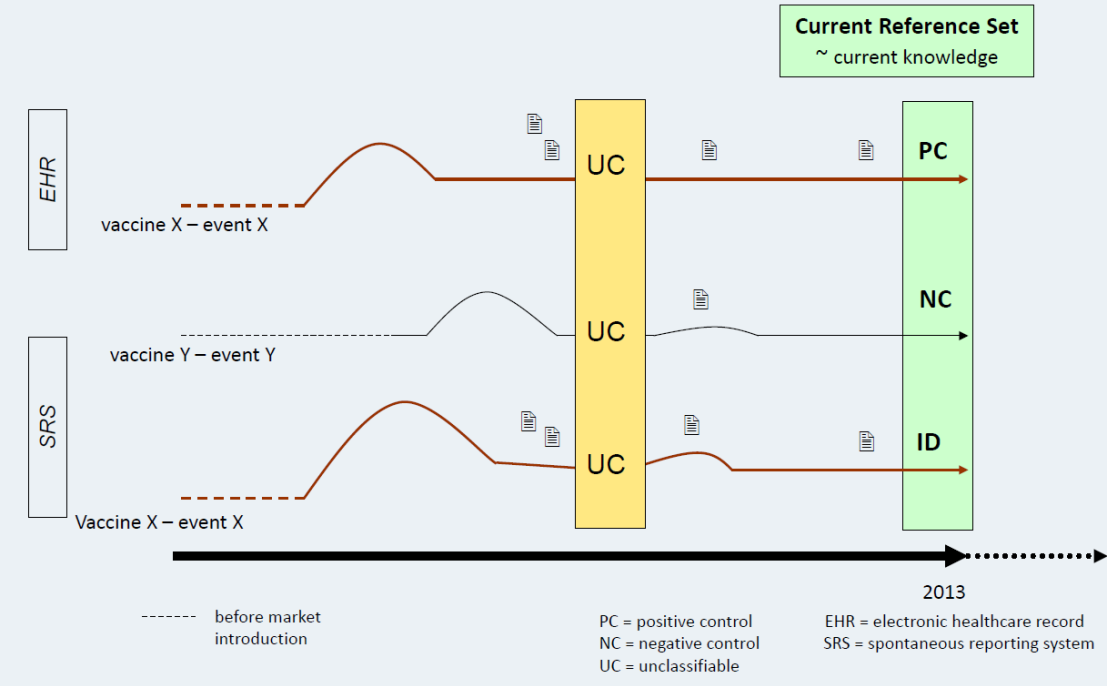


Figure 2: Time-dependency of reference set validity

9 Spontaneous reporting data, type, cleaning and common data model

In the GRiP project we will test methods on the public version of the FDA FAERS database, the EUDRAVIGILANCE database from EMA, and the VAERS database from CDC.

9.1 VAERS

Below a description as obtained from (http://wonder.cdc.gov/wonder/help/vaers/VAERS%20Technical%20Notes.htm#Description)

The U.S. Department of Health and Human Services (DHHS) established the Vaccine Adverse Event Reporting System (VAERS), which is co-administered by the Food and Drug Administration (FDA) and the Centers for Disease Control (CDC), to accept all reports of suspected adverse events, in all age groups, after the administration of any U.S. licensed vaccine. On November 1, 1990 VAERS replaced CDC's Monitoring System for Adverse Events Following Immunization (MSAEFI) for public sector reporting and FDA's Spontaneous Reporting System for private sector and manufacturer reporting. The primary purpose for maintaining the database is to serve as an early warning or signalling system for adverse events not detected during pre-market testing. In addition, the National Childhood Vaccine Injury Act of 1986 (NCVIA) requires health care providers and vaccine manufacturers to report to the DHHS specific adverse events following the administration of those vaccines outlined in the Act. All reports are coded and entered into the VAERS database. The adverse events described in each report are coded utilizing the FDA's Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) which are key words representing the medical condition(s) described in the case report. An individual report in these files may include up to a total of 8 vaccines administered and 20 COSTART terms describing the event.

VAERS data are from a passive surveillance system and represent unverified reports of health events that occur after vaccination. Such data are subject to limitations of under-reporting, simultaneous administration of multiple vaccine antigens, reporting bias, and lack of incidence rates in unvaccinated comparison groups.

When reporting and evaluating data from VAERS, it is important to note that for any reported event, no cause and effect relationship has been established. The event may have been related to an underlying disease or condition, to drugs being taken concurrently, or may have occurred by chance shortly after a vaccine was administered.

A report often involves more than one vaccine and may involve more than one reported adverse event. A given report may meet more than one criterion for classification as "serious."

Accumulations of events reported to a passive surveillance system do not allow incidence rate calculations due to the generally unknown extent of under-reporting as well as lack of information on the number, age, and gender of people being vaccinated. VAERS researchers apply procedures and methods of analysis to help us closely monitor the safety of vaccines. When a concern arises, action is taken. We hope that this brief explanation of the factors

associated with vaccines and adverse events will assist you in understanding the data you are viewing.

9.2 FAERS

The US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) is a database that contains information on adverse event and medication error reports submitted to the FDA. AERS is a passive surveillance system that relies on voluntary reporting of adverse events to FDA by healthcare professionals and consumers, as well as required reporting by pharmaceutical manufacturers. AERS includes spontaneous reports from US sources; serious and unlabelled spontaneous reports from non-US sources; and serious, unlabelled, and attributable post-marketing clinical trial reports from all sources.

FAERS data is publicly available and data files containing the raw data of individual case safety reports (ICSRs) as contained within the database can be downloaded.

The information in the AERS datasets included seven files comprising the following information: 1. patient demographic and administrative information (1 record per ICSR); 2. drug/biologic information for as many medications as were reported for the event (1 or more per event); 3. preferred terms of MedDRA (Medical Dictionary for Regulatory Activities) of the adverse events (1 or more); 4. patient outcomes for the event (0 or more); 5. report sources for the event (0 or more); 6. therapy start dates and end dates for the reported drugs (0 or more per drug per event); and 7. indications of use (diagnosis) for the reported drugs (0 or more per drug per event).

9.3 EUDRAVIGILANCE

The EudraVigilance Data Analysis System has been developed by the EMA to support the EU pharmacovigilance activities and the implementation of the EU risk management strategy. The EudraVigilance Data Analysis System allows stakeholders to analyse adverse event data or subsets of data based on statistical methods to identify potential safety issues related to medicinal products. In this guidance, ‘statistical signals’ originating from statistical methods measuring disproportionality of reporting of drug-event pairs are referred to as Signals of Disproportionate Reporting (SDR). For GRiP a subset of data was requested using an academic license application. All ICSR related to children were obtained.

9.4 Data management

9.4.1 Common data model

Data was extracted from 2 publicly available spontaneous reporting databases: FAERS and VAERS. Data from Eudravigilance was provided by EMA and is a subset of the database. A common data model capturing the necessary data was constructed and each database structure was mapped to this model (see appendix 2).

9.4.2. Data cleaning

Data was extracted from each of the 3 databases and organized into the tables composing the common data model. Adverse events were mapped to MedDRA

preferred terms and SOCs using the PROTECT database that was obtained from EMA, and exposures in FAERS were mapped to ATC codes using the following methods (Erik van Mulligen, EMC).

The task of mapping unstructured drug names as occurring in a database to ATC codes requires a number of text mining and code mapping steps. These drug names literally present themselves in all possible forms, with and without dosage information, with and without comments, and with and without spelling errors. The original data file contains 357568 unique drug names collected from the FAERS database from January 2004 till the third quarter of 2012 (so through the end of August 2012). Examples of drug names are:

- 'MET^ THIAZOLIDINEDIONE
- (BOPIVACAINE)
- (ACETYLSALICYLIC ACID) - FORM : UNKNOWN - UNIT DOSE : UNKNOWN
- 0.9% NORMAL SALINE BAG 100MG BBRAUN
- 5-FLUOROURACIL

The text mining and mapping task is to extract the informative part from the name and map that to the ATC codes that are associated with the drug. We used a two step process where we first mapped the drug name to an RxNorm identifier and subsequently mapped the RxNorm identifier to a set of ATC codes.

Issues occurring

1. Several active substances map to more than one ATC code and the route of administration, when available, cannot be used in RxNorm to map the ATC codes more precisely. Therefore, it was decided to map all active substances to RxCUI numbers that are unique for each substance. However, there is no hierarchical coding in RxNorm to point to a drug class for each active substance. For this reason, analysis will be performed using RxCUI numbers and the ATC codes will be retrieved only (probably manually) for those substances that have significant safety signals. A separate table with ATCs associated with each RxCUI will be created and linked via the CUI to facilitate automated ATC look-up.
2. European brand names of drugs are not mapped with RxNorm. Therefore, for brand names not mapped by RxNorm, the active substance name will be retrieved from the DrugBank and then it will be mapped to a RxCUI number by RxNorm.

The mapping process consisted of the following steps:

1. The first step is to feed the original drug name to the RxNorm[1] system. The RxNorm system provides its functionality as a web service. The RxNorm system

[1] http://www.nlm.nih.gov/research/umls/rxnorm/

tries to normalize the provided search drug name using their string normalization algorithm[2].

2. If step 1 delivers a (set of) RxNorm identifier(s) the mapping process has been completed. If not, we try to match the drug name to one of the terms contained in another database, DrugBank.[3]. We installed this DrugBank database at our server and use a Levenhstein algorithm[4] to compute the distance between the drug name and the DrugBank drug names. The Levenhstein algorithm indicates how many inserts and deletes are necessary to transform the input term into one of the terms available in a dictionary. Misspellings are resolved by a case invariant Levenhstein string matching algorithm. This process matches the drug names to different terms among which we choose the the preferred DrugBank drug name. The latter is then used to search in RxNorm using the same procedure as a in initial step 1 process. We provide the distance as an additional output parameter in our mapping.

3. If the previous step delivers a (set of) RxNorm identifier(s) we are done. If not, we try whether we can match the drug name to one of the brand names contained in DrugBank. DrugBank also contains many European brand names which are currently lacking in RxNorm. The preferred drug name from DrugBank is again used to search in RxNorm for the closests RxNorm as in step 1.

4. Finally, output for the mapping process is generated into a primary file that contains the original drug name with some identification information and the identified RxNorm identifiers (rxcuis) with some information about the mapping method and some additional output parameters. During this output step the ingredients from the mapped initial drug name are also retrieved and outputttted with their associated RxNorm identifiers.

5. For each of the RxNorm identifiers the associated ATC codes are retrieved for each unique rxcui from RxNorm as well. This information is saved in a secondary output file.

From the 357568 unique drug names we were not able to map 15509 drug names. These drug names led to 480 unique RxNorm unique identifiers.

Demographics data were cleaned using the following steps:

a. Variables were checked for implausible values (future dates, non-existent genders, etc). If found these were set equal to missing.

[2] http://rxnav.nlm.nih.gov/RxNormNorm.html

[3] http://www.drugbank.ca

[4] http://en.wikipedia.org/wiki/Levenshtein_distance

b. A follow-up number was generated based on the combination of case and FDA date (as specified in the common data model)
c. Age in years was calculated based upon reported age and reported age unit. If age or unit contained implausible values (negative or non-numeric age, numeric age code, etc) these were set to missing.
d. Subjects with age equal to zero were checked for PT codes including prenatal exposures by searching for preferred terms including the words maternal, intrauterine, transplacental, foetal, antenatal, prenatal, etc. Those subjects with prenatal exposures and age zero were removed.
e. The most recent report for each case was retained based upon the calculated follow up variable.

9.5 Statistical analysis

A statistical analysis plan for the analysis of the data was drafted.

This analysis has two overarching goals:

1. To evaluate the effect of pediatric specific adaptations on signal detection (e.g. stratification vs. crude analyses) in each SRS database using a set of standard measures of disproportionate reporting.
2. To measure the performance of each method in each database to detect signals .

9.5.1 Goal 1: Signal Detection in SRS databases adaptation to pediatrics

Data sets:

FAERS database, VAERS database, Eudravigilance database. Data preparation: Refer to GRiP data management plan

Descriptive analyses:

In order to better understand the data from the different databases the following graphs will be created:

a. Events of interest in the reference set over calendar time (histogram and cumulative) for positive and negative controls in the reference set by SRS database
b. Events of interest in the reference set by month (seasonality) for positive and negative controls in the reference set by SRS database
c. Events of interest in the reference set by age over calendar time for positive and negative controls in the reference set by SRS database
d. Reports (all AEs) by drug/vaccine from the reference set (both cumulative and seasonal)
e. Reports (AEs of interest in reference set) by drug/vaccine from the reference set (both cumulative and seasonal)

f. For each drug in the reference set we will assess the year of first AE report (any) per database.

Disproportionality analyses:
Standard measures of disproportionate reporting for deliverable:

1. Bayesian Information Component (IC)
2. Proportional Reporting Ratio (PRR)
3. Reporting Odds Ratio (ROR)
4. Gamma Poisson Shrinker (GPS)
5. Potential novel measures of disproportionate reporting for explorative analysis. The following analyses may be applied, depending upon sufficient development of the methods and necessary code during the course of analysis:
    g. Linear combination of existing methods
    h. Aberration Detection/Pattern Recognition
    i. Drug*Drug interaction signal detection
    j. SCCS for spontaneous reporting databases
    k. Application of Kulldorff Scan to SRS databases

Exclusions:

Route of administration: Exclude topically applied drugs.

Comparator: 2 comparators will be used for each drug/event pair in the reference set

a) All other reports (not AE of interest related to all other drugs)
b) All other reports (not AE of interest, related to drugs in same ATC group)

Stratifications: Measures of disproportionate reporting will be created by stratum and for the non-stratified population

1. Age
    a. Age based on ICH categories (Neonate, Infant, Child, Adolescent)
    b. Age categories based on organ maturation and for vaccines immunologically based
2. Vaccine/non-vaccine (In databases containing both)
3. Type of reporter (Healthcare professional vs. non-healthcare professional). Where there are healthcare professional and non-healthcare professional report sources for the same event, the healthcare professional report will be used.
4. Drug characterization (Primary/Secondary suspect, interacting) – only in those databases for which this data is available.
5. Sex (Male, Female)
6. Calendar year of report (receive date)
7. Time periods following first report (0-2 years, 2-5 years, > 5 years)
8. Non-antigen components (vaccines only)

Effect of the outcome definition

9. Narrow /broad definitions of the outcome of interest
10. Seriousness (Serious, non-serious based upon outcome) – only in those databases for which this data is available.

9.5.2 Goal 2: Performance Measurement in SRS databases

Standard Measures:

1. Descriptive Measures
    a. Graphical Displays of detected disproportionalities in each combination of different measures at standard cutoffs (i.e. PRR vs. IC)
    b. Distribution of disproportionality measures for PC and NC – in order to see where they overlap
    c. Distribution of disproportionality measures with confidence intervals over time – this should demonstrate how they stabilize as additional cases are accrued
2. Area Under the ROC Curve: AUCs will be calculated on the basis of the reference set for
    a. For crude and stratified analysis within each SRS database and for each disproportionate analysis measure
    b. At cut-points as determined by minimum distance to (0,1) and Youden's Index
3. Positive Predictive Value (PPV) and Negative Predictive Value (NPV)
    a. At standard cut-points
    b. At cut-points as determined by minimum distance to (0,1) and Youden's Index
4. Comparison of databases using each database's best performing method.

Exploratory measures of performance:

1. Time to detection of positive controls (shorter time indicative of better performance) using Cox PH regression by method and time to detection of negative controls (eventually vs. never "detected"). Compare number of unique reports accrued in each database at time of detection of positive controls.
2. Leave-pair-out cross-validation
3. Partial AUC between limits of interest for sensitivity and specificity
4. Incorporate 'cost' of false positives and false negatives.

9.5.3 Analysis for this deliverable

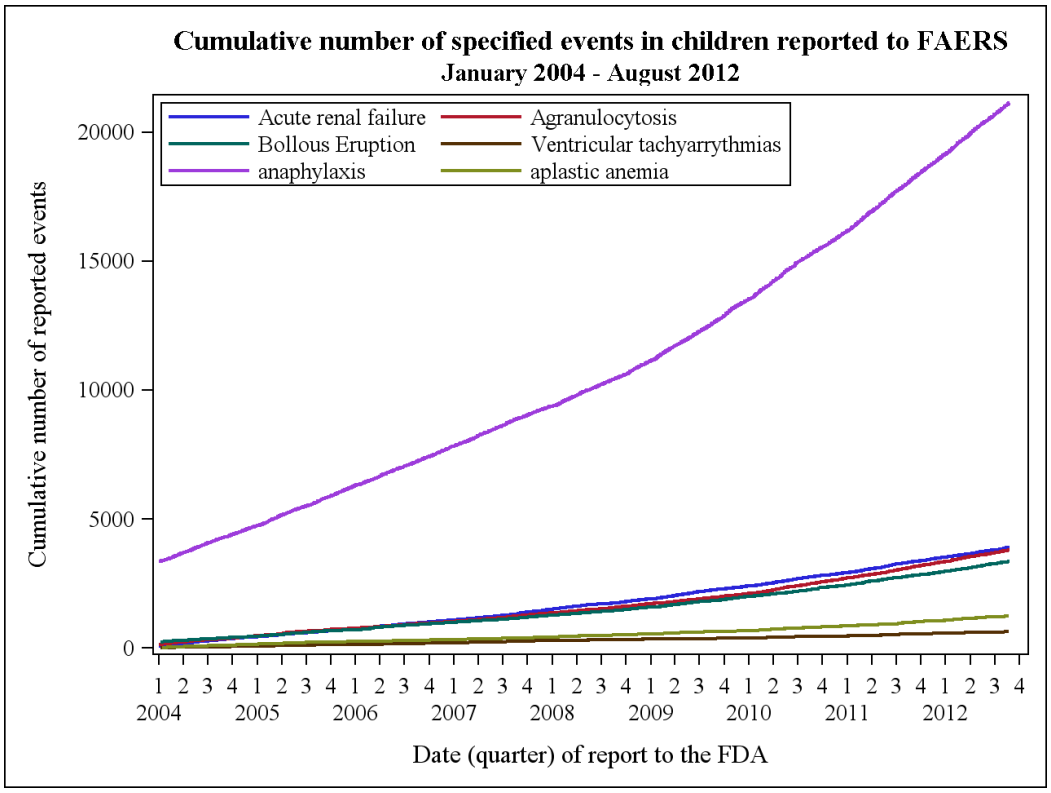
As preliminary results for this deliverable we looked at some descriptives in the FAERS database.

10 Results

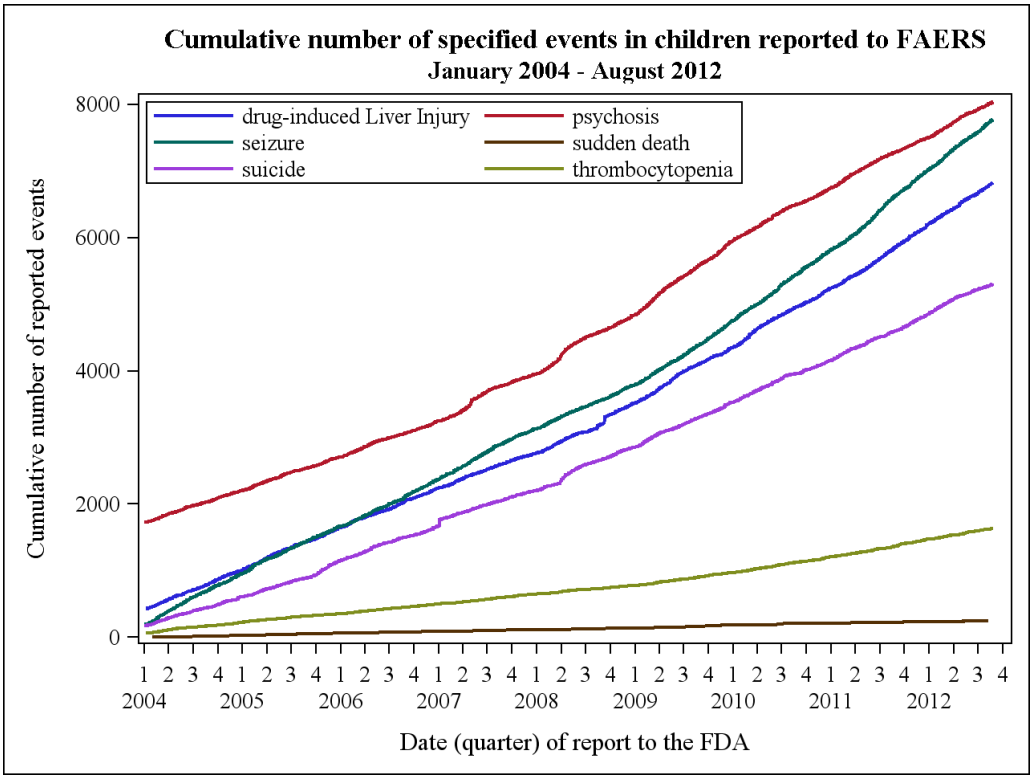
The preliminary results were done on the FAERS data.

A total of 490,950 ICSR for children were included for this analysis during the years 2004-2012. Mean age of the children for the ICSR was 8.6 years with a median of 9 (range 0-17.99 years). Events belonging to the drug reference set were extracted. The rate of reports including those events (independent of exposure is described in the graphs

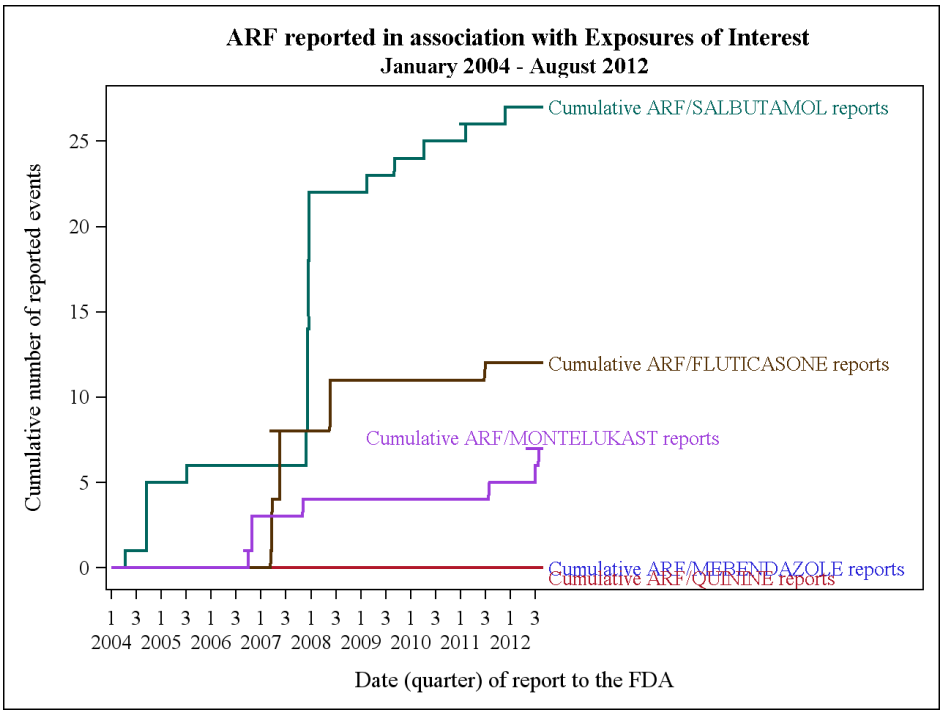
10.1 Events from reference set



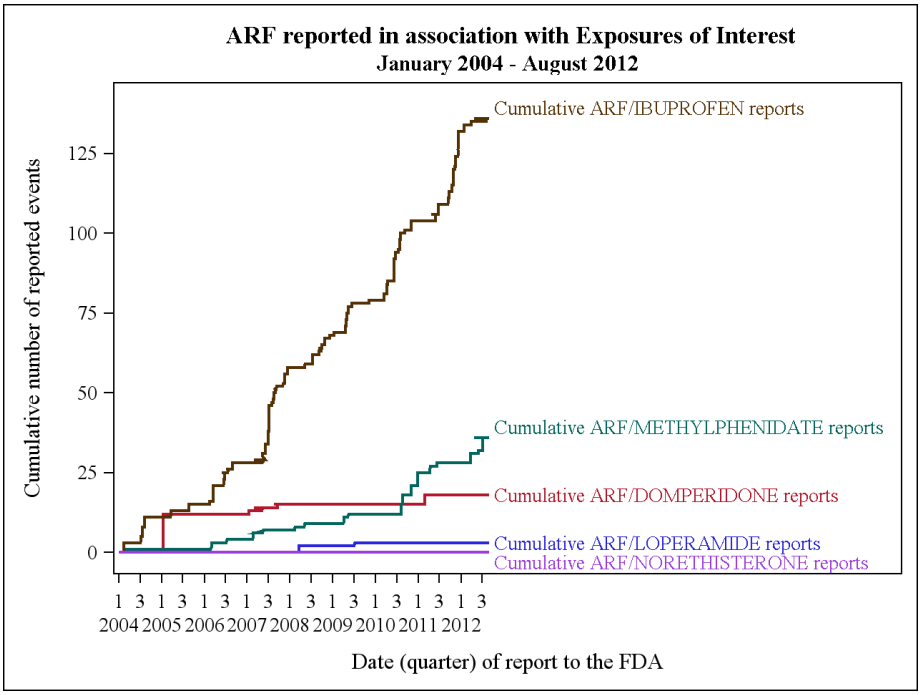
Graphs are displayed with different y-axes and grouped according. Especially the cumulative number of anaphylaxis reports is rising quickly. For sudden death and thrombcytopenia there are very few events.

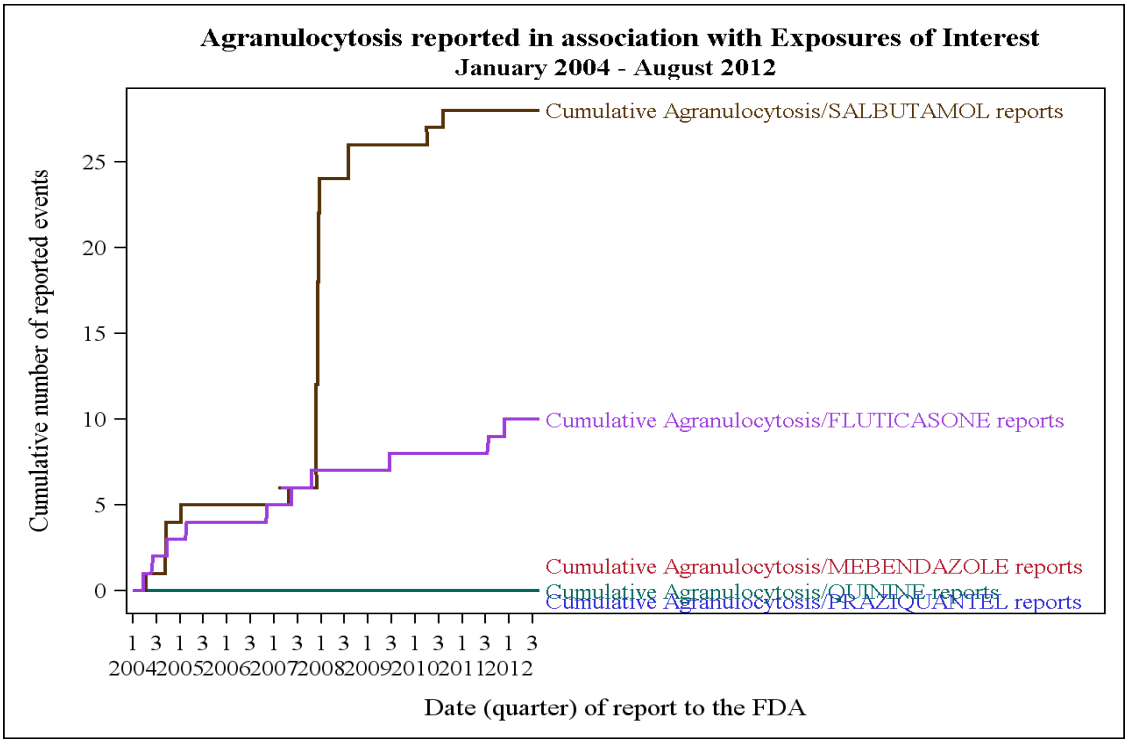

Cumulative number of specified events in children reported to FAERS
January 2004 - August 2012
drug-induced Liver Injury
psychosis
seizure
sudden death
suicide
thrombocytopenia
Cumulative number of reported events
8000
6000
4000
2000
0
1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
2004
2005
2006
2007
2008
2009
2010
2011
2012
Date (quarter) of report to the FDA

10.2 Positive controls: event drug combinations

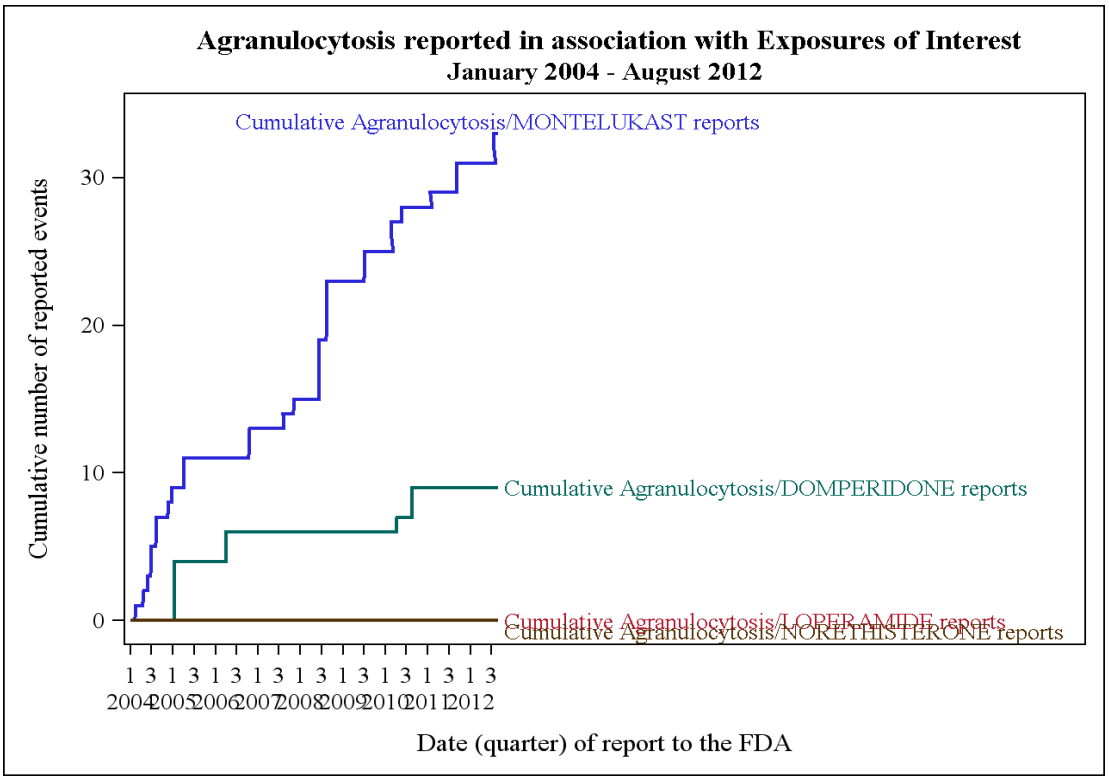


This graph shows the cumulative number of associations with acute kidney injury for the drugs that were listed as positive controls. Most reports are related to salbutamol and fluticasone. However this may be biased since these drugs are used more frequently.

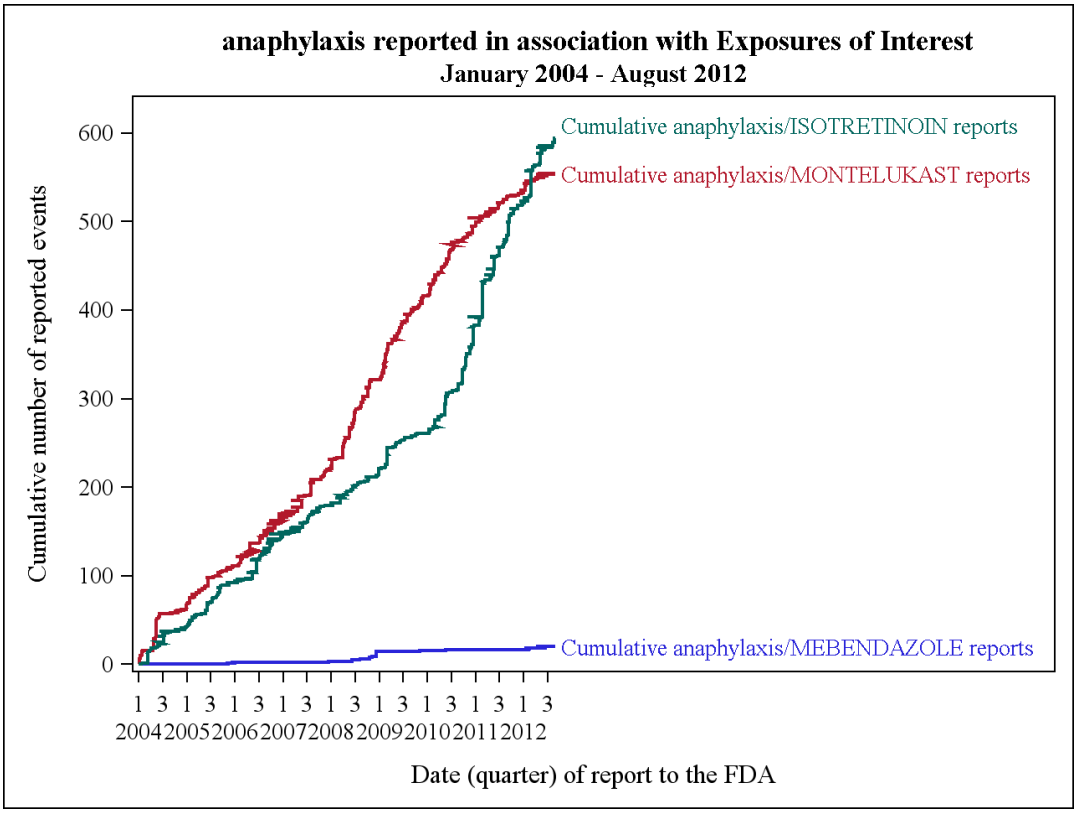




The above graph shows the reports related to drug-agranulocytosis pairs. Again, most reports relate to salbutamol and fluticasone.



For anaphylaxis most reports were related to isotrenoin and montelukast



11 Conclusions/Subsequent steps

This deliverable shows that we have created reference sets, analysis plans and a common data model for spontaneous reporting databases. Also we started some initial analyses on FAERS. In the coming months we will complete the analyses on all databases according to the statistical analysis plan.

Appendix 1: Evaluation of all positive drug-adverse 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 se report = 3
P02CA01	mebendazole	agranulocytosis	Yes *eMC (Special warnings and precautions for use; Undesirable effects) #Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 1 Cohort study = 1

ATC Code	Drug Name	Adverse Event (AE) Type	Labelled as AE in SPC[Yes/No]	*Type/No. of Supporting Literature Citations
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

ATC Code	Drug Name	Adverse Event (AE) Type	Labelled as AE in SPC[Yes/No]	*Type/No. of Supporting Literature Citations
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) #Micromedex (Drugdex): Cautions → Adverse Reactions	Total number of supporting citations = 4 Cohort study = 2 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	s *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 se series = 1

ATC Code	Drug Name	Adverse Event (AE) Type	Labelled as AE in SPC[Yes/No]	*Type/No. of Supporting Literature Citations
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	s *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

ATC Code	Drug Name	Adverse Event (AE) Type	Labelled as AE in SPC[Yes/No]	*Type/No. of Supporting Literature Citations
A03FA03	domperidone	sudden death	s MC (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): (Contraindications/Warnings→ precautions); (Adverse effects→serious)	Total number of supporting citations = 5 Review of pharmacology = 1 Review of spontaneous reports = 1 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

ATC Code	Drug Name	Adverse Event (AE) Type	Labelled as AE in SPC[Yes/No]	*Type/No. of Supporting Literature Citations
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

ATC Code	Drug Name	Adverse Event (AE) Type	Labelled as AE in SPC[Yes/No]	*Type/No. of Supporting Literature Citations
J04AC01	Isoniazid	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 = 7 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

Appendix 2: GRiP COMMON DATA MODEL

Authors: Alexandra Pacurariu, Caitlin Dodd, Florentia Kaguelidou, Marius Gheorghe

***In red characters: data transformation that will follow the data extraction**

Table definitions

Report table

ID_REPORT (character) – Primary Key

FOLLOW_UP (numeric) – the version of the report (1 = initial, 2, 3…)

REPORTER (character) – qualification of the reporter – extracted as reported in each database. (Data will be further classified as: MD= physician; PH+ pharmacist; OT= other health professional; LW= lawyer; CN=consumer)

DATE (date) – the date of registration of the report in the database (DDMMYYYY)

COUNTRY (character) – the country, region or state of origin of the report, this is not the country where the event occurred.

TYPE_SERIOUSNESS(character) – the type of seriousness of the report based on the WHO categories(Hospitalization or prolongation of existing hospitalization; Life-threatening; Death; Significant or persistent disability/incapacity; Congenital anomalies; other relevant conditions).More than one criterionmay be present per report(to be put in same variable: later choose the most relevant)

Drug table

ID_DRUG (numeric) – Primary Key

ID_REPORT (character) – Foreign Key (FK) from **Report table**

NAME (character)- international nonproprietary name (when possible) = active substance name

MANUFACTURER (character) – this information will be extracted only for vaccines

ATC (character) - code assigned to an active substance

DOSE_AMOUNT (character) – the quantity of active substance per intake = drug dose per intake

DOSE_UNIT (character) – the unit of the drug dose per intake

DOSE_FREQ (character) – the frequency of drug administration

CUMULATIVE_DOSE (numeric) – the quantity of active substance until first event

CUMULATIVE_DOSE_UNIT (character) – the unit of the drug cumulative dose

RECHALLENGE (character) – this variable is defined as follows: positive= event reoccurred when drug therapy was restarted; negative= event did not reoccur when drug therapy was restarted; unknown; does not apply

DECHALLENGE (character) – this variable is defined as follows: positive= event abated when drug therapy stopped; negative= event did not abate when drug therapy stopped; unknown; does not apply

ROUTE (character) – the route of administration (to be classified as: topical, enteral and parenteral)

DOSE_NB (numeric) –current number of administrations at the occurrence of event. This information will be extracted only for vaccines.

LOT_NUMBER (numeric) – this information will be extracted only for vaccines.

ROLE (character) – drug's reported role in the event (will be classified as suspect, concomitant, interacting)

Indication table

ID_REPORT (character) – FK from the **Drug table**

ID_DRUG (numeric) – FK from the **Drug table**

IND_DESC (character) – MedDRA preferred term (PT) describing the indication for the use of the drug

IND_CODE (numeric) – MedDRA code corresponding to the PT for drug indication

Event table

ID_REPORT (character) – Foreign Key (FK) from the **Report table**

FOLLOW_UP (numeric) – FK from the **Report table**

DATE (date) – the date of occurrence of the eventOUTCOME (character) - reported outcome of the (Fully recovered/resolved; Recovering/resolving; Not recovered/not resolved; Recovered/resolved with sequelae; Caused death; Unknown)

PT_DESC (character) – preferred term (PT) of the MedDRA terminology describing the reported adverse event

PT_CODE (numeric) –MedDRA code corresponding to the PT term

SOC_DESC (character) – system organ class (SOC) of the MedDRA terminology of the reported adverse event

SOC_CODE (numeric) –MedDRA code corresponding to the SOC

Therapy table

ID_REPORT (character) – Foreign Key (FK) from the **Report table**

ID_DRUG (numeric) – Foreign Key from **Drug table**

START (date) – the date the therapy begins

END (date) – the date the therapy ends

DURATION (numeric) – the length of the therapy in days

START_UNTIL_EVENT (numeric) – difference between START (T**herapy)** and DATE (**Event)**(where missing, to be calculated)

END_UNTIL_EVENT (numeric) – difference between END (T**herapy)** and DATE (**Event)**(where missing, to be calculated)(allowed to be negative)

Demographics table (a.k.a Patient table)

ID_REPORT (character) - FK from the **Report table**

FOLLOW_UP (numeric) – the version of the report (if not present: to be calculated)

CALCULATED_AGE – age at occurrence of the eventalready calculated by the database

UNIT_CALCULATED_AGE – unit of calculated age

REPORTED_AGE – age at occurrence of the event provided in the report

UNIT_REPORTED_AGE – unit of reported age

AGE_GROUP (character) – as provided by the database (variable to be created as: newborn <= 27; infant/toddler = 28d – 2y; child = 2y+1d – 11y; adolescent = 12y - <18y; unknown)

AGE (numeric) – in months, either from 'calculated_age' or 'reported_age'; if both provided, 'calculated age' is to be kept

SEX(character) – choice between FEMALE, MALE, UNKNOWN

MAPPING Eudravigilance

Report table

ID_REPORT – EV_LOCAL_NUMBER (grip_cases)

FOLLOW_UP – create from EV_LOCAL_NUMBER (grip_cases) and MESSAGEGATEWAYDATE (grip_cases) (sorted dates and based on those figure out initial = first date and so on)

REPORTER – QUALIFICATION_TXT (grip_cases)

DATE – MESSAGEGATEWAYDATE (grip_cases)

COUNTRY –to be calculated from REPORTERSUBREGION(grip_cases)

TYPE_SERIOUSNESS – N/A – can be assumed that all is to be considered serious

Drug table

ID_DRUG -FK_DRUG_SUBSTANCE or FK_DRUG_PRODUCT (grip_drugs)- to be chosen

ID_REPORT – EV_LOCAL_NUMBER (grip_drugs)

NAME - ACTIVESUBSTANCENAME_REC (grip_drugs).

MANUFACTURER –only for vaccines N/A

ATC – ATCCODE (grip_drugs) – mostly empty – Eric mapping subsequently

DOSE_AMOUNT – DRUGSTRUCTUREDDOSAGENUMB (grip_drugs)

DOSE_FREQ– DRUGSEPARATEDOSAGENUMB+ DRUGINTERVALDOSAGEUNITNUMB + DRUGINTERVALDOSAGEDEFINITION_TXT (grip_drugs)

DOSE_UNIT – DRUGSTRUCTUREDOSAGEUNIT_TXT (grip_drugs)

CUMULATIVE_DOSE – DRUGCUMULATIVEDOSAGENUMB (grip_drugs)

CUMULATIVE_DOSE_UNIT – DRUGCUMULATIVEDOSAGEUNIT_TXT (grip_drugs)

RECHALLENGE – DRUGRECURREADMINISTRATION_TXT (grip_drugs)

DECHALLENGE – N/A -combination between ACTIONDRUG_TXT (grip_drugs) and REACTIONOUTCOME_TXT (grip_reactions)

ROUTE – DRUGADMINISTRATIONROUTE_TXT(grip_drugs) and if DRUGPARADMINISTRATION_TXT has value then fill “Transplacental”

DOSE_NB – N/A

LOT_NUMBER – N/A

ROLE – DRUGCHARACTERIZATION_TXT(grip_drugs)

Indication table

ID_REPORT – FK from the **Drug table**

ID_DRUG – FK from the**Drug table**

IND_CODE – N/A

IND_DESC – N/A

Event table

ID_REPORT – EV_LOCAL_NUMBER (grip_reactions)

FOLLOW_UP – N/A - to be calculated from MESSAGEGATEWAYDATE and ID_REPORT – sorted dates

DATE–N/A

OUTCOME – reactionoutcome_txt (GRiP_REACTIONS)

PT_CODE – pt_code (GRiP_REACTION)

PT_DESC– N/A - will be taken from MedDRA based on the code

SOC_CODE– N/A - will be completed by biosemantics based on the code

SOC_DESC – N/A - will be taken from MedDRA based on the code

Therapy table

ID_DRUG – FK **Drugtable**

START – N/A

END – N/A

DURATION – DRUGTREATMENTDURATION_CALC(grip_drugs)

START_UNTIL_EVENT – DRUGSTARTPERIOD(grip_drugs)

END_UNTIL_EVENT – DRUGLASTPERIOD(grip_drugs)

Demographics table (a.k.a Patient table)

ID_REPORT - EV_LOCAL_NUMBER (grip_cases)

FOLLOW_UP – N/A

AGE – AGEREACTION_CALC_MIN + PATIENTONSETAGE+PATIENTONSETAGEUNIT_TXT(grip_patients) – to be converted into months

AGE_GROUP – PATIENTAGEGROUP_TXT(grip_patients)

SEX – PATIENTSEX_Txt(grip_patients)

MAPPING FAERS

Report table

ID_REPORT- ISR (demographic file)

FOLLOW_UP – Create using ISR and FDA_DT (demographic file)

DATE – FDA_DT (demographic file)

REPORTER – OCCP_COD (demographic file)

COUNTRY –REPORTER_COUNTRY (demographic file)

REPORTER_COUNTRY is only available starting from 2005Q3

SERIOUSNESS – OUTC_COD (outcome file)

Drug table

ID_DRUG – own generated identifier

ID_REPORT –ISR (drug file)

ISR is used up till (and including) 2012Q3

NAME – DRUGNAME (drug file)

MANUFACTURER – N/A

ATC – N/A, to be added by Erik

DOSE_AMOUNT – DOSE_AMT (drug file)

DOSE_UNIT – DOSE_UNIT (drug file)

DOSE_FREQ – DOSE_FREQ (drug file)

RECHALLENGE - RECHAL (drug file)

DECHALLENGE - DECHAL (drug file)

ROUTE – ROUTE (drugs file)

DOSE_NB – N/A

LOT_NUMBER – LOT_NUM(drug file)

ROLE – ROLE_COD (drug file)

Indication table

ID_REPORT – FK from the **Drug table**

ID_DRUG – FKfrom the**Drug table**

IND_CODE – N/A (to be mapped)

IND_DESC – INDI_PT (indication file)

Event table

ID_REPORT –ISR (reaction file)

FOLLOW_UP N/A

DATE –EVENT_DT (demographicfile)

OUTCOME –N/A

PT_CODE – N/A

PT_DESC –PT (reaction file)

SOC_CODE –N/A

SOC_DESC – N/A

Therapy table

ID_DRUG – FK **Drugtable**

START –START_DT (therapy file) – sometimes only year and month

END –END_DT (therapy file) – most of the times missing

DURATION – DUR + DUR_COD (therapy table)

START_UNTIL_EVENT – N/A

END_UNTIL_EVENT – N/

Demographics table (a.k.a Patient table)

ID_REPORT –ISR (demographicfile)

FOLLOW_UP –CREATE FROM ISR AND FDA_DT (demographic file)

CALCULATED_AGE – N/A

UNIT_CALCULATED_AGE – N/A

REPORTED_AGE – AGE (demographic file)age at occurrence of the event provided in the report

UNIT_REPORTED_AGE – GE_COD (demographic file)

AGE_GROUP – N/A

AGE – N/A

SEX – GNDR_COD (demographic file)

MAPPING VAERS

Report table

ID_REPORT - VAERS_ID (vaersdata, vaerssymptoms, vaersvax)

FOLLOW_UP – Create from VAERS_ID + RECVDATE (vaersdata)

DATE – RECVDATE (vaersdata)

REPORTER – N/A

COUNTRY – STATE (vaersdata)

TYPE_SERIOUSNESS – DIED (vaersdata) + L_THREAT (vaersdata) + ER_VISIT (vaersdata) + HOSPITAL (vaersdata) + X_STAY (vaersdata) + DISABLE (vaersdata) + congenital anomalies that have to be extracted from the vaerssymptoms via PT

Drug table

ID_DRUG – own generated identifier

ID_REPORT – VAERS_ID (vaersdata)

NAME – VAX_NAM (vaersvax)

MANUFACTURER – VAX_MANU (vaersvax)

ATC – N/A

DOSE_AMOUNT – N/A

DOSE_FREQ – N/A

DOSE_UNIT – N/A

CUMULATIVE_DOSE – N/A

CUMULATIVE_DOSE_UNIT – N /A

RECHALLENGE - N/A

DECHALLENGE - N/A

ROUTE – VAX_ROUTE (vaersvax)

DOSE_NB – VAX_DOSE (vaersvax)

LOT_NUMBER – VAX_LOT (vaersvax)

ROLE – N/A

Indication table

ID_REPORT – FK from the **Drug table**

ID_DRUG – FK from the**Drug table**

IND_CODE –N/A

IND_DESC – N/A

Event table

ID_REPORT – VAERS_ID (one of the following vaersdata, vaerssymptoms, vaersvax)

FOLLOW_UP – Create from VAERS_ID + recvdate (vaersdata)

DATE – ONSET_DATE (vaersdata)

OUTCOME –DIED, RECOVD (vaersdata), if no info in DIED or RECOVD the value is 'unknown')

PT_CODE – add PT_CODE from symptom1-symptom5 (vaerssymptoms)

PT_DESC – SYMPTOM1 – SYMPTOM5 (vaerssymptoms)

SOC_CODE –add from Symptom (vaerssymptoms)

SOC_DESC – add from Symptom (vaerssymptoms)

Therapy table

ID_DRUG – FK from the Drug Table

START – N/A

END – N/A

DURATION – N/A

START_UNTIL_EVENT – NUMDAYS (vaersdata) – days from vaccination to onset

END_UNTIL_EVENT – N/A

Demographics table (a.k.a Patient table)

ID_REPORT - VAERS_ID (one of the following vaersdata, vaerssymptoms, vaersvax)

FOLLOW_UP – Create from VAERS_ID + recvdate (vaersdata)

AGE – AGE_YRS (vaersdata) + CAGE_YR (if calculated age is missing (CAGE), AGE_YRS is to be kept)+ CAGE_MO (both CAGE_YRS and CAGE_MO necessary to create Calculated age variables) – to be converted into months

AGE_GROUP –N/A – to be created from AGE

GENDER – SEX (vaersdata)

12 References

1. Scurti, V., M. Romero, and G. Tognoni, *A plea for a more epidemiological and patient-oriented pharmacovigilance.* European Journal of Clinical Pharmacology, 2012. **68**(1): p. 11-19.
2. Meyboom, R.H.B., *Pharmacovigilance in a changing world.* Klinicka Farmakologie a Farmacie, 2011. **25**(3): p. 102-111.
3. Meyboom, R.H.B., et al., *Pharmacovigilance in perspective.* Drug Safety, 1999. **21**(6): p. 429-447.
4. Van Grootheest, K., *The dawn of pharmacovigilance: An historical Perspective.* International Journal of Pharmaceutical Medicine, 2003. **17**(5-6): p. 195-200.
5. Pandolfini, C. and M. Bonati, *A literature review on off-label drug use in children.* Eur J Pediatr, 2005. **164**: p. 552-558.
6. Conroy, S., et al., *Survey of unlicensed and off label drug use in paediatric wards in European countries.* BMJ, 2000: p. 7982.
7. Dunne, J., *The European Regulation on medicines for paediatric use.* Paediatr Respir Rev, 2007. **8**(2): p. 177-83.
8. Breslow, L.H., *The Best Pharmaceuticals for Children Act of 2002: the rise of the voluntary incentive structure and congressional refusal to require pediatric testing.* Harvard J Legis, 2003. **40**(1): p. 133-93.
9. Choonara, I. and S. Conroy, *Unlicensed and off-label drug use in children: implications for safety.* Drug Safety, 2002. **25**: p. 1-5.
10. *World Health Organization. Make medicines child size, 2007 http://www.who.int/childmedicines/en/ accessed May 4 2008.*
11. Star, K., et al., *Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase.* Drug Saf, 2011(34): p. 415-28.
12. de Bie, S., et al., *Vaccine-based subgroup analysis in VigiBase: effect on sensitivity in paediatric signal detection.* Drug Safety, 2012. **35(4)**: p. 335-46.
13. *Practical Aspects of Signal Detection in Pharmacovigilance. Report of CIOMS Working Group VIII.* 2010, CIOMS: Geneva.
14. Stang, P., P. Ryan, and J. Racoosin, et al., *Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership.* Annals of internal medicine., 2010. **153**: p. 600-6.
15. Coloma, P., et al., *Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project.* Pharmacoepidemiol Drug Saf. , 2011. **20**: p. 1-11.
16. Schuemie, M.e.a., *Using electronic healthcare records for drug safety signal detection: a comparative evaluation of statistical methods.* Medical Care, 2012. **in press**.
17. de Bie, S.e.a., *The power of electronic healthcare databases for active drug safety surveillance in children and adolescents.* submitted, 2012.
18. Coloma, P.M., et al., *Electronic healthcare databases for active drug safety surveillance: is there enough leverage?* Pharmacoepidemiol Drug Saf, 2012. **21**(6): p. 611-621.
19. Sturkenboom, M., et al., *Drug use in children: cohort study in three European countries..* BMJ, 2008. **337**(a2245. doi: 10.1136/bmj.a2245.).