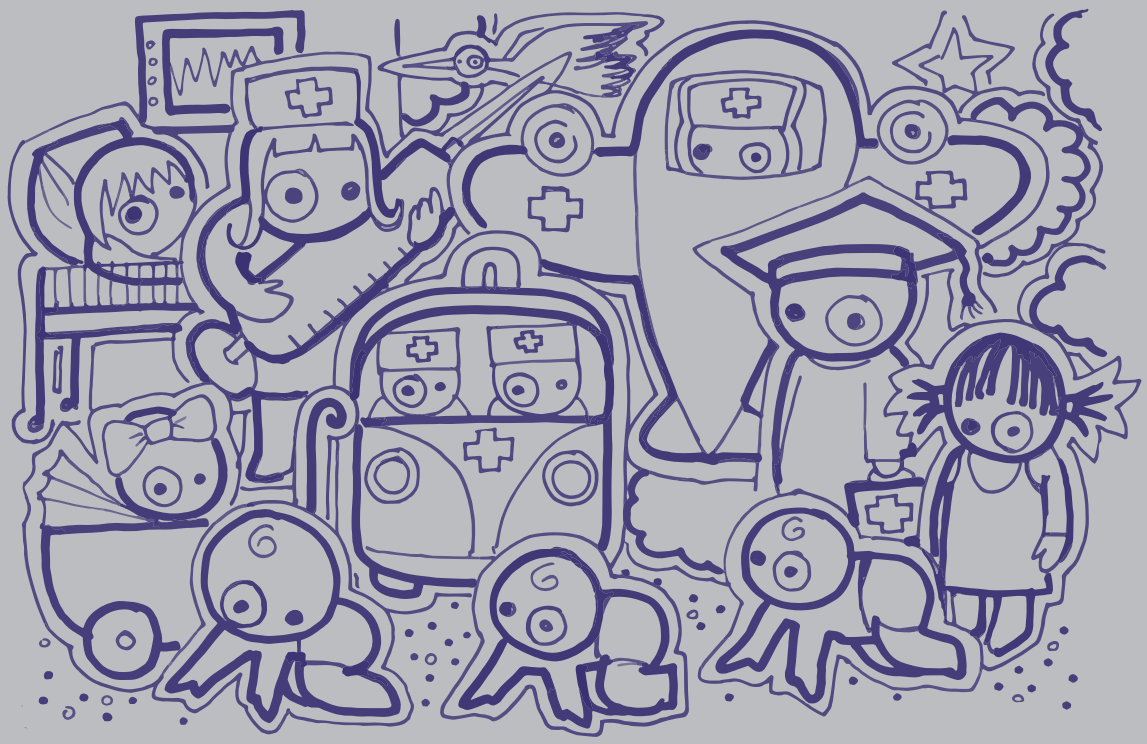
Studying use and risks of medicines in children

a European approach



Sandra de Bie

Studying use and risks of medicines in children: a European approach

Sandra de Bie

The work described in this thesis was conducted at the department of Medical Informatics of the Erasmus University Medical Center, Rotterdam, the Netherlands in collaboration with the department of Pharmacovigilance of the Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, the Netherlands.

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Studying Use and Risks of Medicines in Children: a European Approach

Een Europese aanpak voor het bestuderen van het gebruik en risico's van geneesmiddelen bij kinderen

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
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door

Sandra de Bie
geboren te Hellevoetsluis

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	Dr. K.M.C. Verhamme

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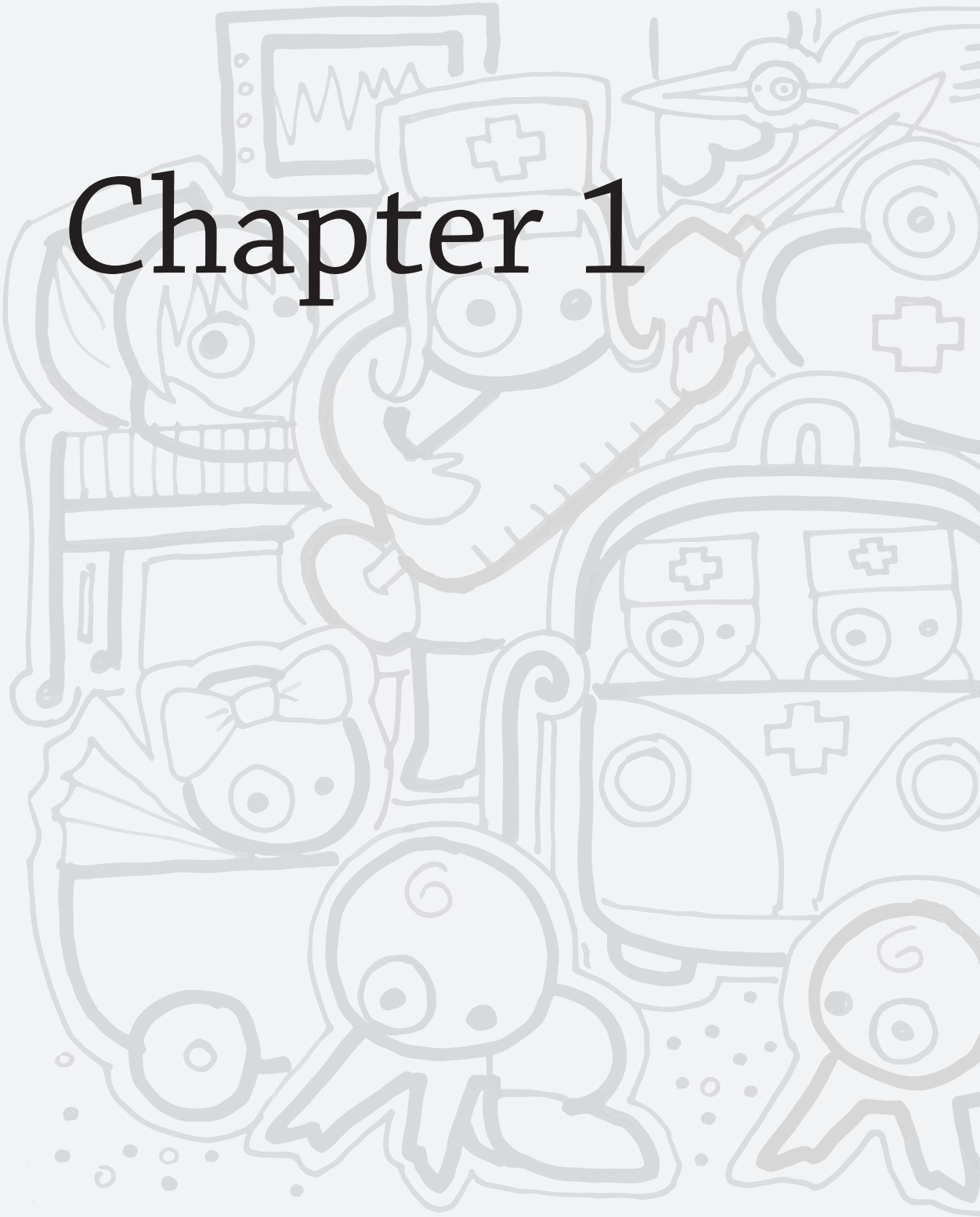
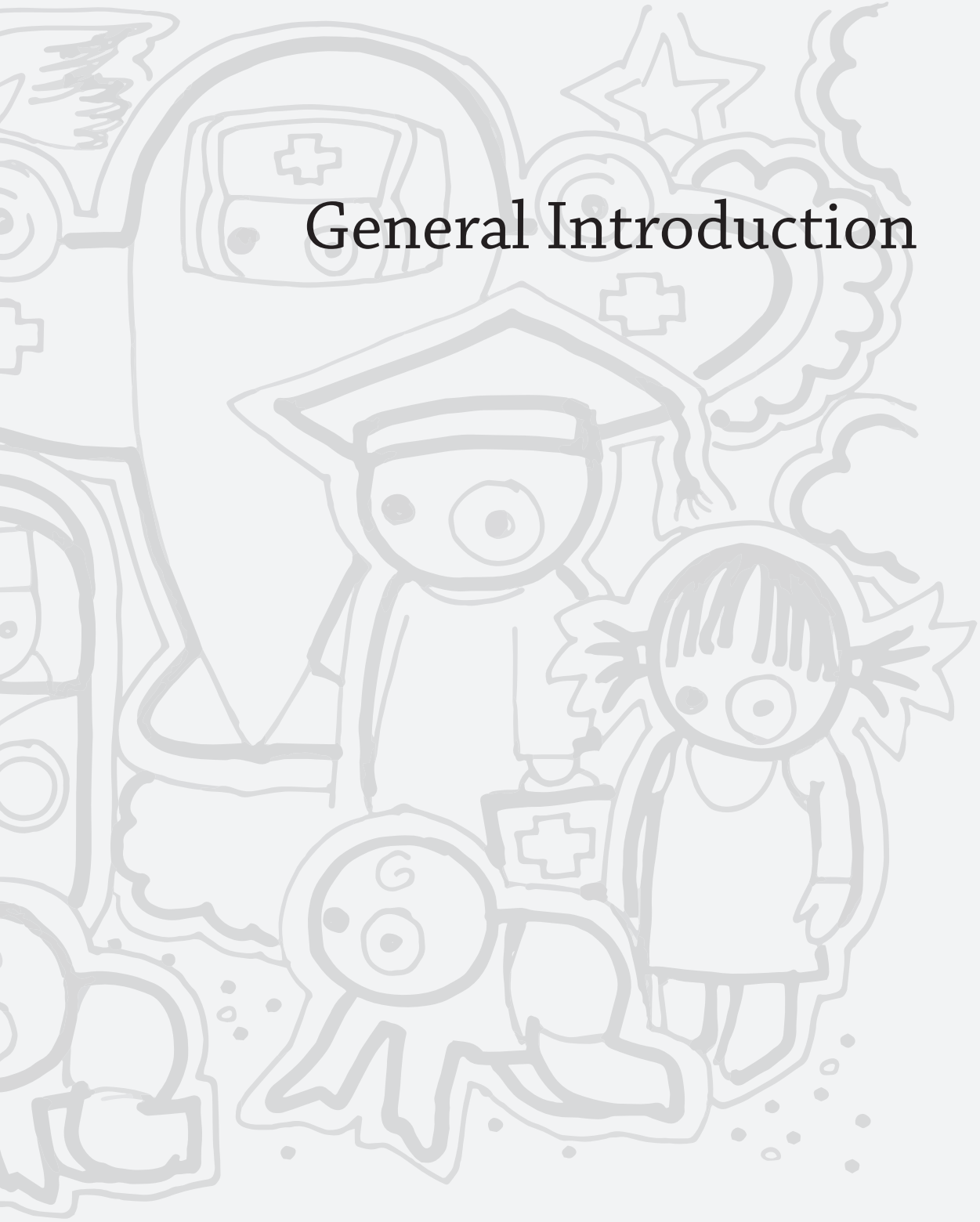


General Introduction



In recent years the awareness of the knowledge gap on the safety and efficacy of medicines used in children increased.[1] While pharmacovigilance systems were established worldwide since the sixties of the 20th century,[2] even more than 50 years after the thalidomide disaster the safe use of medicines in children has received relatively little attention in drug safety regulation.[3] This implies that both paediatric pharmacovigilance and paediatric pharmacoepidemiology are still in their childhood. Pharmacovigilance has been defined by the World Health Organisation (WHO) as *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem*,[2] and pharmacoepidemiology has been defined as *the study of the use of and the effects of drugs in large numbers of people, which uses the methods of epidemiology to study the content area of clinical pharmacology.*[4]

Few randomised clinical trials studied the efficacy and safety of drugs in children, implying that most of the data on the effectiveness and risks of use of medicines in children need to be collected after registration and during the use of these medicines. Around the beginning of the 21th century, the number of post-marketing studies on the use of medicines in children has increased. These studies mainly focused on the off-label and unlicensed use of medicines.[5-11]

There are concerns on the risks of medicines used in children: A review showed that in the period 2001-2007, for 28 medicines or drug classes used in the paediatric population safety warnings have been issued.[12] These warnings included cardiovascular adverse events and neuropsychiatric symptoms for medicines to treat ADHD (attention deficit hyperactivity disorder), the increased risk of suicidal ideation with the use of antidepressants, serious adverse events (including death) for cough and cold medicines and the increased risk of extrapyramidal symptoms with the use of domperidone.

The limited knowledge on the effects of medicines in children has boosted initiatives by the WHO and triggered new legislation in recent years.[13-15] Since the introduction of new paediatric regulations in both the United States (US) and Europe, the number of paediatric pre-registration clinical trials has increased but these clinical trials are designed primarily to assess efficacy.[1] This reinforces the importance to monitor the safety of a (paediatric) drug during the post-marketing phase.

How do we learn about drug safety in children? As said, safety information from clinical trials is limited. First of all, so far relatively few randomised clinical trials have been conducted in the paediatric population and within the studies that have been done, many have a small sample size and lack long term follow-up. Post-marketing safety of a medicine is not only monitored via spontaneous reporting systems such as the Vigibase from the WHO but also through observational and pharmacoepidemiological studies. These studies are crucial to monitor the safety of a medicine because they study the use of medicines under "real life"

circumstances, have a large sample size and long-time follow-up.[16] To monitor the safe use of medicines in children it is important to know to which extent the medicines are used in children (*drug utilisation studies*) and which adverse drug reactions (ADRs) are reported for children. Statistical methods make it possible to draw inferences on ADRs reported in children (*signal detection*). These topics will be further introduced in this chapter.

Topics

Drug utilisation studies

Drug utilisation research is an essential part of pharmacoepidemiology as it *describes the extent, nature and determinants of drug exposure*.[17] Drug utilisation research provides insights into the patterns, quality, determinants, and outcomes of use. Drug utilisation research has been applied at large extents to investigate off-label use in children. When using population-based longitudinal electronic healthcare records it is possible to describe use of medicines on a population level. The extent and type of use of medicines in children and adolescents is essential to identify knowledge gaps and to seek where there is room for improvement of prescribing (e.g. in case of inappropriate prescribing). Knowledge on actual use is also important as it defines the denominator in studying ADRs.

Adverse drug reactions and Spontaneous Reporting Databases

Post-marketing drug safety surveillance using spontaneously reported ADRs is an important source for identifying drug safety signals.[18,19] An ADRs is defined as *a response to a medicinal product which is noxious and unintended*, and an adverse event is defined *as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment*.[20-23] Earlier definitions of ADRs included that there should be a reasonable possibility that the product caused the response.[20] Since this change in definition ADRs and adverse events are used interchangeable.

Nationally reported ADRs are internationally gathered in the form of individual case safety reports (ICSRs) in spontaneous reporting systems. Spontaneous reporting systems are passive public health surveillance systems and have been set up over the world since the 1960s.[24] Large spontaneous reporting systems include VigiBase of the WHO Uppsala Monitoring Center (WHO-UMC), the Adverse Event Reporting System (AERS), maintained by US Food and Drug Administration (FDA), the Vaccine Adverse Effect Reporting System (VAERS), maintained by FDA and CDC (Centers for Disease Control and Prevention), and EudraVigilance of the

European Medicines Agency (EMA).[25-28] These systems include ICSRs reported by healthcare professionals, pharmaceutical companies and consumers.[23] ICSRs reported to VigiBase and AERS were used in this thesis.

VigiBase is a global ICSR database system which was established in 1968 and currently holds more than 5.0 million ICSRs.[29] VigiBase is maintained on behalf of the WHO Programme by the WHO-UMC and currently 97 countries participate in the WHO International Drug Monitoring program. ICSRs are submitted periodically through the national pharmacovigilance centres. The WHO Programme member countries submit ICSRs to the UMC on a regular basis; preferably once per month, but at least every quarter.[26] Data on the ICSRs submitted to VigiBase related to children and adolescents (0-<18 years), submitted in the period 2000-2006 were used in *chapter 8* of this thesis. In **figures 1.1** and **1.2** an overview of the reported medicines (by Anatomical main group of Anatomical Therapeutic Chemical (ATC) classification system[30]) and of the reported ADRs (by the system organ class (SOC) level of MedDRA) is presented for children aged 0-18 years. These figures illustrate that both use of medicines and the type of reported ADRs are age-dependent, implying that within the paediatric population age-related important differences exist.

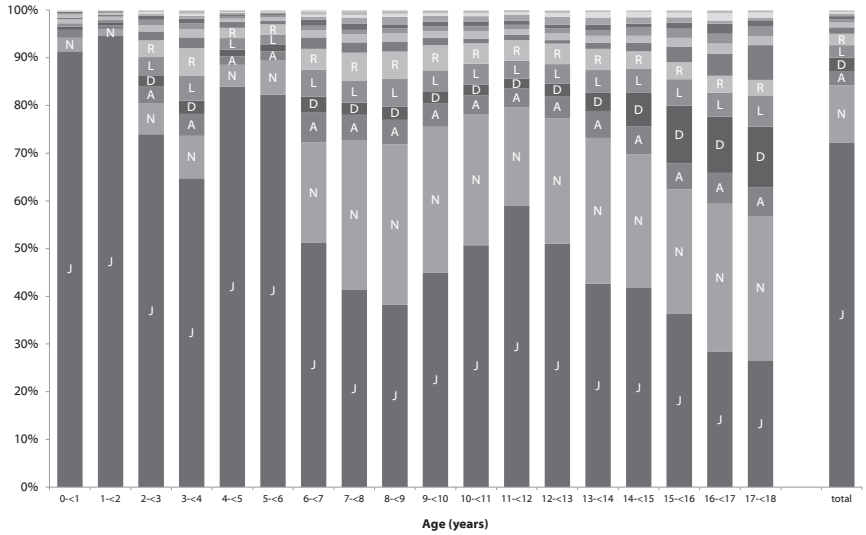
AERS is a database that contains information on adverse events and reports on medication errors submitted to FDA. It is a passive surveillance system that relies on voluntary reporting by healthcare professionals and consumers, as well as required reporting by pharmaceutical manufacturers. AERS includes 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.[31] Paediatric ICSRs reported to AERS in the period 2004-2011 are described in *chapter 7* of this thesis.

Spontaneous reporting systems are a great source for safety information. The advantages include that they i. are large-scaled, inexpensive and easy to operate, ii. cover all medicines during their whole life-cycle, iii. cover the whole population and iv. can be used for hypothesis generating purposes. Limitations encompass i. that reports often lack detailed clinical information, ii. the risk of underreporting, which leads to a decreased sensitivity, iii. a reporting rate which is seldom stable over time, and iv. finally the lack of denominator data.[16] Despite these potential limitations, 36-50% of drug withdrawals is based on spontaneous reports only.[24,32-34]

Signal detection

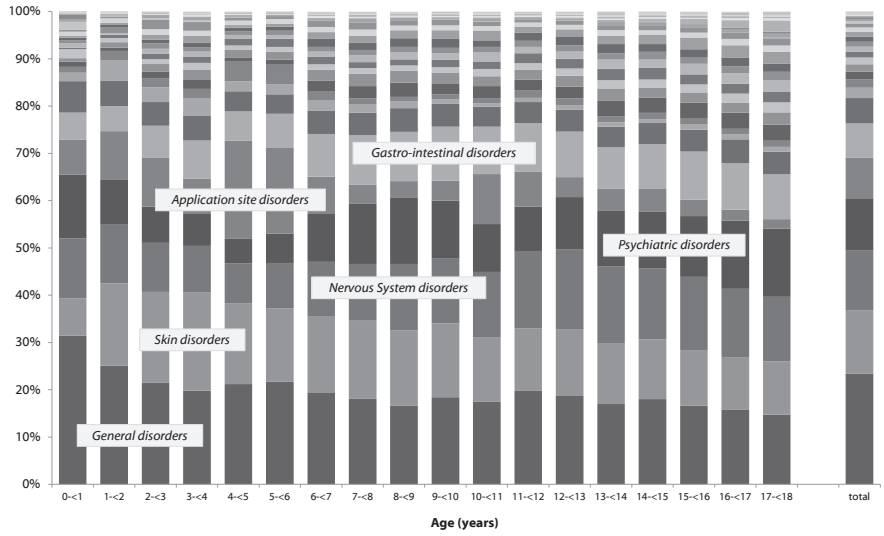
As said, spontaneously reported ADRs are an important source to identify drug safety signals.[18] A safety signals is defined as *information that arises from one or multiple sources (including observations and experiments), which suggests a new*

Figure 1.1 Overview of the reported medicines in VigiBase (0-≤18 years)



Overview of the reported medicines in VigiBase. The anatomical main groups of ATC-classification are given as a proportion of the total number of reports and are stratified by age. J=Anti-infectives; N=Nervous system; A=Alimentary tract and metabolism; D=Dermatologicals; L=Antineoplastic and immunomodulating; R=Respiratory system.

Figure 1.2 Overview of the reported adverse drug reactions in VigiBase (0-≤18 years)



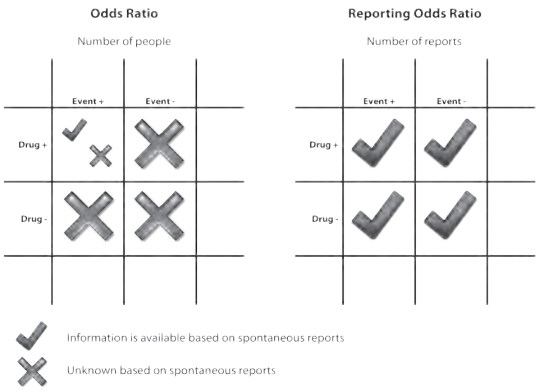
Overview of the reported ADRs in VigiBase. The System Organ Classes of MedDRA are given as a proportion of the total number of reports and are stratified by age.

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, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions.[35]

For efficient signal detection, data mining methods have been developed that are mainly based on measures of disproportionality. Since ADR reports lack proper denominator data on the total number of patients exposed, it is not possible to calculate incidence rates. Using the information on the ADR-reports only, key in signal detection is the question: *do we observe what we expect?* Well known examples are the Reporting Odds Ratio (ROR), the Proportional Reporting Ratio (PRR), the Information Component (IC), and the Empirical Bayes Geometric Mean (EBGM).[36-40] The ROR and PRR are so-called frequentist methods and are comparable to the odds ratio (OR) and rate ratio (RR) as used in case-control and cohort studies. Both the IC and EBGM are methods that use Bayesian statistics to shrink estimates of risk and thereby reduce the influence of small numbers. All methods are based on a two-by-two contingency table (**figure 1.3**).

These data mining methods are used as a first signal identification method. Subsequently, further case evaluation is necessary to determine whether the signal of disproportionality is a real safety signal.[24,41]

Figure 1.3 Reporting odds ratio versus odds ratio



Signal detection in electronic healthcare databases

Spontaneous reporting systems have proven their value for safety surveillance, however they also come with well recognised limitations and biases due to as selective underreporting, stimulated reporting and the lack of exposure data.[24,42,43] To complement spontaneous reporting systems and other traditional monitor-

ing systems, initiatives in the US and in Europe have set up population-based surveillance systems that make use of longitudinal healthcare data.[44-46] Chapters 9 and 10 focus on the use of one of these systems, the EU-ADR network, for signal detection using electronic healthcare records in children and adolescents.

Description of the projects

The work described in this thesis is part of several European projects that focus on studying safety of medicines. Most projects include paediatric data only, while the EU-ADR project includes the whole population. These projects are introduced briefly.

TEDDY (Chapter 4, Chapter 8, Chapter 11)

The *Task-force in Europe for Drug Development for the Young* (TEDDY) was a Network of Excellence funded under the Sixth European Commission (EC) Framework Programme for Research and Technological Development and ran between 2005 and 2010. TEDDY included a total of 19 partners from 11 countries aiming to promote the availability of safe and effective medicines for children in Europe by integrating existing expertise and good practices, as well as stimulating paediatric drug development.

ARPEC (Chapter 2, Chapter 3)

The study *Antibiotic Resistance and Prescribing in European children* (ARPEC) is an initiative by the European Society of Paediatric Infectious Diseases (ESPID).[47] The overall objective of ARPEC is to improve antimicrobial prescribing in hospitals and in the community by obtaining up-to-date, clinically relevant data on variation in clinical management and antimicrobial resistance rates and to feed this back, via a number of educational initiatives, to paediatricians across Europe. ARPEC has received co-funding from the European Union in the framework of the Health Programme.

GRiP (Chapter 7)

The *Global Research in Paediatrics Network of Excellence* (GRiP) is an EC-funded consortium, which aims to implement an infrastructure facilitating the development and safe use of medicines in children. This entails the development of a comprehensive educational programme in paediatric clinical pharmacology and integrated use of existing research capacity, whilst reducing the fragmentation and duplication of efforts.[48,49]

EU-ADR (Chapter 9, Chapter 10)

The *Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge* (EU-ADR) project ran between 2008 and 2012 and was a collaboration of 18 public and private institutions. EU-ADR aimed to exploit information from various electronic healthcare record and other biomedical databases in Europe to produce a computerised integrated system for the early detection of drug safety signals.[44] The EU-ADR platform comprised data from eight databases in four European countries covering all ages in the population which are now transferred into the EU-ADR Alliance.

Outline and aims of this thesis

The work as described in this thesis is based on large observational studies across Europe as introduced above and aims to study the use and risks of medicines in children and adolescents. Many of the chapters deal with methodological issues specific to studying the paediatric population. The chapters are divided into studies on *drug utilisation*, *adverse drug reactions*, *methods in paediatric safety signal detection*, and *safety signal detection and safety warnings*. The thesis is concluded with a *general discussion* and *summary*.

Research questions in this thesis include:

- To which extent are children and adolescents exposed to medicines?
- What is the frequency of adverse events?
- Which specific methodological issues arise to identify new safety issues in children and adolescents?
- What is the effect of safety warnings on the subsequent prescribing of medicines?

Drug Utilisation

The first part of this thesis focuses on drug utilisation studies. Antibiotics are the most frequently prescribed medicines in children.[50] Over the years much effort has been put in educating both physicians and patients on the rational use of antibiotics to prevent antimicrobial resistance. As part of the ARPEC project, in **Chapter 2** we describe the extent of antibiotic prescribing in children (0-<18 years) in the Netherlands, the United Kingdom and Italy during a ≥10 years study period using similar population-based primary care databases according to a common study protocol and harmonised data elaboration.

The occurrence of the influenza A(H1N1)pdm09 pandemic in 2009 implied that oseltamivir, an antiviral medicine, was for the first time used on a large scale in infants since its registration in 2002. Using the same data sources as in chapter 2, in **Chapter 3** we report on the utilisation of the antiviral medicine oseltamivir during the influenza A(H1N1)pdm09 pandemic.

Gastro-intestinal medicines are frequently prescribed, especially in young children.[50] Studies in adults showed an increase in prescribing of proton pump inhibitors (PPIs) at the expense of histamine-2-receptor antagonists (H_2RAs) in the last years. In young children, PPIs and H_2RAs are prescribed for the treatment of gastro-intestinal reflux, which is very common in this population. In **Chapter 4** we describe the extent of PPI and H_2RA prescribing in children and adolescents in Spain, the Netherlands and Italy. We compare prescribing between the countries and assess the trend of PPI-prescribing over time and the ratio to H_2RA prescribing.

Adverse Drug Reactions

Recognition, quantification, and prevention of adverse drug reactions is the main focus of pharmacovigilance. Collections of these reports form a unique source to study the risks of medicines in children.

In **Chapter 5,** we describe the results of a nationwide study of all hospital admissions in children and adolescents (aged 0 to 20 years) in the Netherlands for the period 2000 to 2005. For this study, information on ADR-related hospital admissions was obtained from a Dutch nationwide registry of hospital discharges. We describe which medicines most frequently lead to hospitalisation and assess the risk for ADR-related admissions in relations to use of medicines and the number of residents in the individual age categories.

The occurrence of the influenza A(H1N1)pdm09 pandemic not only implied large-scale use of oseltamivir, but also several pandemic H1N1 vaccines were licenced using fast track procedures with limited data on the safety in children and adolescents. **Chapter 6** reviews safety experience and adverse events from 25 clinical studies and numerous analyses of spontaneous ADR reports for the different pandemic H1N1 vaccines.

While chapters 5 and 6 focus on specific ADRs namely those in vaccinated children or those ADRs leading to hospitalisation, **Chapter 7** describes all ADR reports for children and adolescents as reported to FDA-AERS.

Methods in Paediatric Safety Signal Detection

Both the use of medicines and the type of reported ADRs are age-dependent and differ between children and adults. As seen in *figure 1.2*, most reports in children are for anti-infective drugs and these are mainly vaccines. The potential influence of this cluster of vaccines on safety signal-detection for medicines in children is studied in **Chapter 8.**

With the increasing number of initiatives exploring the use of electronic healthcare databases for safety signal detection we explored in **Chapter 9** the potential role of such systems is in paediatric drug safety surveillance using data from the EU-ADR network.

Safety Signal Detection and Safety Warnings

In a sequel to the study described in chapter 9, in **Chapter 10** we compare signal detection in VigiBase, a spontaneous reporting system, with EU-ADR, using electronic healthcare records for upper gastro-intestinal bleeding. We test the performance of different data mining algorithms in both VigiBase and EU-ADR and compare the results of these different sources.

Safety studies can result in safety warnings being issued by regulatory agencies. In the last decade, multiple warnings have been issued for serious adverse events associated with the use of several prokinetic medicines; domperidone, metoclopramide and cisapride. In **Chapter 11** we describe the effect of such safety warnings on the use of prokinetic medicines in Italy, Spain and the Netherlands.

General Discussion and Summary

In **Chapter 12**, we discuss the main findings of the studies included in this thesis and we provide suggestions for future research. The results of all studies in this thesis are summarised in **Chapter 13**.

Drug Utilisation

Chapter 2

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On behalf of the ARPEC study

Developing a Standard Method for Comparing Paediatric Antibiotic Prescribing in Primary Care from a Population-Based Cohort Study in the United Kingdom, Italy and the Netherlands - 1995-2010

Abstract

Objective

To study utilisation patterns of antibiotics in children in primary care in the United Kingdom (UK) (1995-2010), Italy (2001-2010) and the Netherlands (1996-2010).

Methods

A population-based retrospective cohort study using electronic primary care medical records databases in the UK (The Health Improvement Network (THIN)), Italy (Pedianet), and the Netherlands (Integrated Primary Care Information (IPCI)) was conducted. 2,196,312 children aged up to 14 (Italy) or 18 years (UK and the Netherlands), contributing 12,079,620 person-years (PY) were included. Yearly prevalence rates of antibiotic drug prescriptions, defined as the number of children with at least one study drug prescription per year, were calculated. Type and proportion of most prescribed antibiotics were measured using the Drug Utilisation 90%-methodology.

Results

The overall annual prevalence of antibiotic prescriptions was 18.0 users/100PY (%) in the Netherlands, 36.2% in the UK and 52.0% in Italy and has slightly decreased over time. Prevalence was highest in the youngest children. Almost half of all prescriptions were for amoxicillin with or without clavulanic acid. Third-generation cephalosporins were frequently prescribed in Italy but rarely in the other countries.

Conclusions

The prevalence of antibiotic prescribing was high and varied with age - in the youngest age category one third to one half of all children were prescribed an antibiotic during one year of follow-up. Prevalence was lowest in the Netherlands and two to three-fold higher in the UK and Italy respectively. The consumption of third-generation cephalosporins is high in young Italian children. There is a need for development of internationally agreed paediatric specific quality indicators for primary care.

Introduction

There is clear evidence that antibiotic-resistance of pathogens is linked to antibiotic prescribing.[51] Antibiotic prescribing in the adult outpatient population in Europe remains high and shows wide variability, with the rate in the Netherlands being 3-5 fold lower than in Italy.[52] Rational and reduced prescribing of antibiotics is important to decrease selection and transmission of antibiotic resistant strains within the community. ESAC-Net (European Surveillance of Antimicrobial Consumption Network) developed quality indicators, using data on outpatient adult antibiotic use in Europe, to assess the quality of national antibiotic prescribing in Europe.[53,54]

Children, and especially young children, are high consumers of antibiotics with the majority of antibiotics given for minor upper respiratory tract infections.[50,55] High rates of antibiotic prescribing in primary care for children, often for mild viral infections,[56] warrant monitoring of antibiotic prescribing habits, but there have been few initiatives so far aimed at specifically improving the quality of antibiotic prescribing for children.[57] The adult quality indicators developed by ESAC-Net cannot be extrapolated directly to paediatric antibiotic use in Europe since no age-specific DDDs (defined daily doses) exist and there are differences in the prevalence of clinical infection syndromes by age. A key barrier to compare existing data on community paediatric antibiotic is the lack of a standard methodology.

The study Antibiotic Resistance and Prescribing in European children (ARPEC) is an initiative by the European Society of Paediatric Infectious Diseases (ESPID).[47] The overall objective of ARPEC is to improve antimicrobial prescribing in hospitals and in the community by obtaining up-to-date, clinically relevant data on variation in clinical management and antimicrobial resistance rates and then to feed this back via a number of educational initiatives to paediatricians in-training and in clinical practice, across Europe.

With this study we want to describe and compare the prescription pattern of antibiotic drugs to children in primary care in the United Kingdom (UK), Italy and the Netherlands during a ≥10 years study period using similar population-based primary care databases, a common study protocol and harmonised data elaboration. This antibiotic prescription data from various European countries is important to develop quality indicators of paediatric specific outpatient antibiotic use internationally.

Patients and Methods

Study design

A population-based retrospective cohort study was conducted to describe antibiotic prescribing in children and adolescents in the Netherlands, the UK and Italy.

Setting and data collection

This study is part of the ARPEC project.[47] For the current study, data were used from three population-based primary care databases in the Netherlands, the UK, and Italy according to a common study protocol. In the Netherlands and the UK, the general practitioner (GP) is responsible for the primary care of children whereas in Italy family paediatricians (FPs) are the gatekeepers of primary care for children. The databases contain the complete automated patient files, with detailed information on the population, diagnoses and prescriptions, and use of these databases has been proven valid for pharmacoepidemiological research.[58,59]

Details of the databases have been described elsewhere.[60-63] In brief, the *Integrated Primary Care Information (IPCI) database* from the Netherlands comprises paediatric and adult electronic medical records from more than 400 Dutch GPs since 1996.[60,61] *The Health Improvement Network (THIN)* is a database of primary care medical records from the UK, prospectively collecting data since September 2002 which contains retrospective data since the late 1980's.[59] The *Pedianet* database contains paediatric electronic medical records from 150 FPs in Italy since 2000.[62] Primary care of children in Italy is provided by FPs until the age of 14 years. From 14 years on, health care is taken on by GPs.

Data from the different databases were pooled using a distributed network approach, in which data holders maintain control over their original data and only aggregated data are shared. This was done through generation of the data into a common format followed by local aggregation using custom-built software, Jerboa©.[44]

Study population

As the start date for data collection differed for the three databases, the start of the study period was defined on January 1st 1995 for the UK, on January 1st 1996 for the Netherlands and on January 1st 2001 for Italy. The study period ended on

December 31st 2010 for all countries.

Children were followed from the start of entry into the study (start of study period, date physician was up to date, date of registration plus 6 months or just born) until their 18th (Netherlands and UK) or 14th (Italy) birthday, the end of the study period, leaving the practice, death, or latest data drawn down, whichever came first.

Definition of exposure

Antibiotics are grouped under the therapeutic subgroup J01 'Antibacterials for systemic use' of the Anatomical Therapeutic Chemical (ATC) classification system.[30] All drugs listed under J01 were included in the study. For these drugs, the prescription patterns were studied and expressed in i. annual prevalence rates; ii. monthly prevalence rates; iii. drug utilisation 90% (DU90%), and iv. the ratio of broad spectrum penicillins, cephalosporins and macrolides versus narrow spectrum antibiotics prescribing. The prevalence rates were determined on multiple levels of the ATC classification system.

Statistical analysis

Prevalence rate

Annual prevalence rates were estimated and expressed as the number of users per 100 person years (PY). Monthly prevalence rates were estimated and expressed per 100 person months (PM). Because of the dynamic nature of the population we used person time rather than number of individuals as denominator for the prevalence rate. Both the annual prevalence and monthly prevalence rate will be notated as a percentage for ease of interpretation (%).

For the prevalence rates, the number of children *being prescribed* the study drug within a calendar year (annual rate) or in a specific calendar month was counted (monthly rate); these children received at least one prescription for an antibiotic in this calendar year or in this calendar month. Prevalence rates should thereby be interpreted as the number of children per 100 in the study population in a specific month or year, who used the study drug in that specific month or year.

Drug utilisation 90%

The number of individual drugs accounting for 90% of drug use in terms of defined daily doses (DDDs), the DU90%, is considered an indicator of the quality of drug prescribing.[64,65] The proportion of children being prescribed antibiotics, combined with the use of DU90% profiles has been proposed as the simplest

method to compare differences in use and the quality of prescribing.[66] Since no DDDs for children are available, we determined how many and which antibiotics covered 90% of all prescriptions (DU90%) for antibiotics within the studied countries for different age categories, using the number of prescriptions as denominator.

Broad and narrow spectrum antibiotics

The ratio between the number of users of broad spectrum penicillins, cephalosporins and macrolides (J01CR, J01DC, J01DD and J01F (without J01FA01)) and the number of users of narrow spectrum antibiotics (J01CE (beta lactamase sensitive penicillins), J01DB (first generation cephalosporins) and J01FA01 (macrolides)) was determined and stratified by country, age and calendar-year. This ratio is one of the quality indicators as determined by ESAC-Net and gives an estimate of the balance between prescribing of broad spectrum versus narrow spectrum antibiotics and allows comparison of patterns of antibiotic use.[54]

Stratification by age

Age was stratified in one-year periods (0-<1 years etc.) and in broader age categories; 0-<1 years, 1-<5 years, 5-<12 years, and 12-<18 years.

Results

In this population-based retrospective cohort study a total of 2,195,312 children, contributing 12,079,620 PY of follow up were included; 239,293 children from the Netherlands (10.9%), 1,725,798 from the UK (78.6%), and 230,275 from Italy (10.5%).

Figure 2.1 Annual prevalence rate of antibiotic prescriptions stratified by year

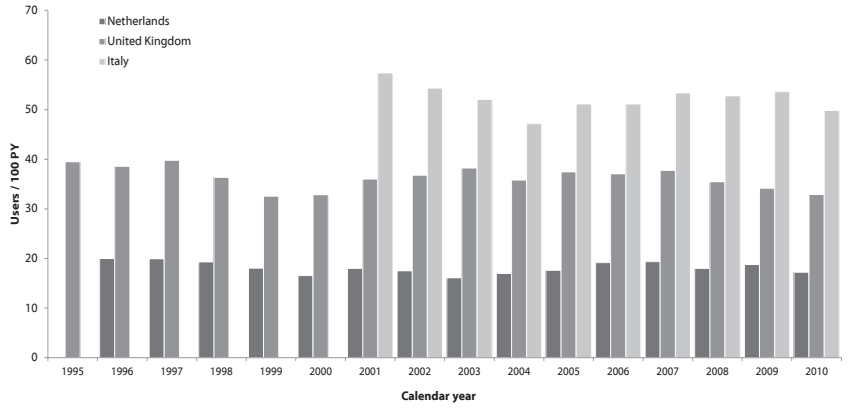
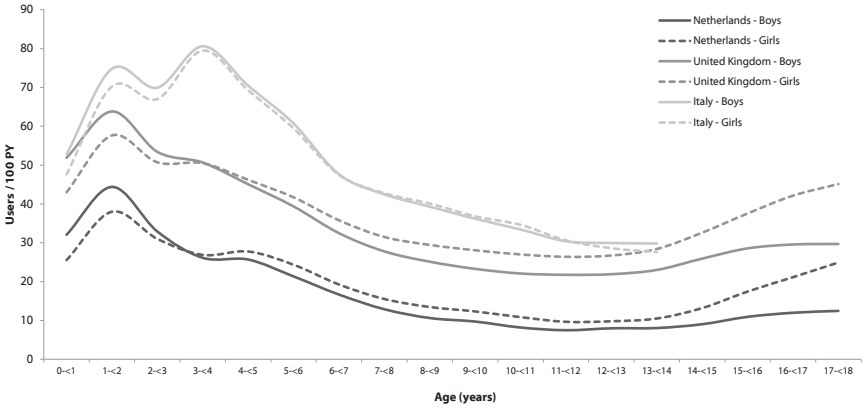


Figure 2.2 Annual prevalence rate of antibiotic prescriptions stratified by age and sex



The overall annual prevalence of antibiotic prescriptions was 18.0 users/100PY (%) in the Netherlands, 36.2% in the UK and 52.0% in Italy. At the start of the study (1996), the prevalence in the Netherlands was 20.0%. In the following years it fluctuated between 16.1 and 19.9%, and was 17.2% in 2010. In the UK the prevalence at start of the study period (1995) was 39.5%, after which it fluctuated between 32.5 and 39.9%, arriving at 32.9% in 2010. In Italy, the prevalence at start of the study (2001), was 57.4%, after which it gradually decreased to 49.8% in 2010 (**figure 2.1**).

Both in the Netherlands and the UK, the prevalence peaked at the age of 1-<2 years, after which it decreased and increased again from adolescence on. A similar pattern was observed in Italy, however a biphasic peak was present, with a second (and highest) peak at age 3-<4 years. In all countries the prevalence in boys was higher than in girls in the first years of life. In both the Netherlands and the UK this was up to the age of 3 years after which the prevalence in girls was higher. This difference became more substantial with increasing age and was highest after puberty. In Italy the differences between boys and girls was highest in first years of life after which the prevalence was similar (**figure 2.2**).

Stratified by calendar month, the prevalence was highest in February in Italy (7.9 users/100 PM (%)) and in December in both the Netherlands (2.6 %) and the UK (6.0%). Prevalence was lowest in August in all three countries; 1.2% in the Netherlands, 2.6% in the UK and 2.8% in Italy.

Ninety percent of all antibiotic prescriptions (DU90%) (0-18 years) were covered by 9 drugs in the Netherlands, by 8 drugs in the UK and by 8 drugs in Italy. In both the Netherlands and the UK the number of drugs accounting for the DU90% increased with age, while this number was stable in Italy **(table 2.1a-c).**

Table 2.1a Antibiotics that cover 90% of the prescriptions in the Netherlands

Age 0-1 years	Age 1-5 years	Age 5-12 years	Age 12-18 years	Overall
Amoxicillin (73.3%)	Amoxicillin (57.8%)	Amoxicillin (43.8%)	Amoxicillin (17.2%)	Amoxicillin (45.1%)
Amoxicillin and enzyme inhibitor (10.4%)	Amoxicillin and enzyme inhibitor (14.0%)	Amoxicillin and enzyme inhibitor (16.5%)	Doxycycline (12.3%)	Amoxicillin and enzyme inhibitor (13.5%)
Clarithromycin (5.7%)	Azithromycin (7.6%)	Azithromycin (8.0%)	Nitrofurantoin (12.1%)	Azithromycin (7.5%)
Azithromycin (3.2%)	Clarithromycin (7.1%)	Clarithromycin (8.0%)	Amoxicillin and enzyme inhibitor (10.2%)	Clarithromycin (7.0%)
	Pheneticillin (4.2%)	Pheneticillin (6.1%)	Pheneticillin (9.0%)	Pheneticillin (5.7%)
		Nitrofurantoin (4.1%)	Azithromycin (8.5%)	Nitrofurantoin (4.4%)
		Flucloxacillin (3.9%)	Minocycline (6.6%)	Doxycycline (3.1%)
			Clarithromycin (6.3%)	Flucloxacillin (3.0%)
			Flucloxacillin (5.2%)	Sulfamethoxazole and trimethoprim (2.8%)
			Trimethoprim (3.5%)	

Table 2.1b Antibiotics that cover 90% of the prescriptions in the United Kingdom

Age 0-1 years	Age 1-5 years	Age 5-12 years	Age 12-18 years	Overall
Amoxicillin (64.6%)	Amoxicillin (54.9%)	Amoxicillin (41.9%)	Amoxicillin (22.3%)	Amoxicillin (44.0%)
Erythromycin (9.5%)	Erythromycin (10.1%)	Phenoxymethyl-penicillin (16.6%)	Phenoxymethyl-penicillin (17.4%)	Phenoxymethyl-penicillin (12.9%)
Flucloxacillin (6.3%)	Phenoxymethyl-penicillin (8.8%)	Flucloxacillin (11.3%)	Flucloxacillin (11.8%)	Erythromycin (10.3%)
Trimethoprim (5.2%)	Flucloxacillin (6.7%)	Erythromycin (9.8%)	Erythromycin (11.5%)	Flucloxacillin (9.3%)
Phenoxymethyl-penicillin (4.2%)	Trimethoprim (5.6%)	Trimethoprim (5.8%)	Oxytetracycline (7.8%)	Trimethoprim (5.5%)
Cefalexin (2.8%)	Amoxicillin and enzyme inhibitor (4.3%)	Amoxicillin and enzyme inhibitor (4.6%)	Trimethoprim (5.0%)	Amoxicillin and enzyme inhibitor (4.0%)
		Cefalexin (3.8%)	Lymecycline (4.8%)	Cefalexin (3.4%)
			Minocycline (4.3%)	Oxytetracycline (1.8%)
			Amoxicillin and enzyme inhibitor (3.0%)	
			Cefalexin (2.8%)	

Table 2.1c Antibiotics that cover 90% of the prescriptions in Italy

Age 0-1 years	Age 1-5 years	Age 5-12 years	Age 12-18 years	Overall
Amoxicillin (33.5%)	Amoxicillin (25.7%)	Amoxicillin and enzyme inhibitor (24.5%)	Amoxicillin and enzyme inhibitor (25.6%)	Amoxicillin (25.2%)
Amoxicillin and enzyme inhibitor (21.4%)	Amoxicillin and enzyme inhibitor (22.8%)	Amoxicillin (22.9%)	Amoxicillin (21.2%)	Amoxicillin and enzyme inhibitor (23.4%)
Clarithromycin (8.6%)	Cefaclor (10.6%)	Azithromycin (11.6%)	Azithromycin (15.2%)	Azithromycin (10.2%)
Cefaclor (8.4%)	Azithromycin (9.5%)	Clarithromycin (10.2%)	Clarithromycin (12.8%)	Clarithromycin (9.2%)
Azithromycin (6.0%)	Clarithromycin (8.3%)	Cefixime (7.6%)	Cefixime (6.7%)	Cefaclor (8.8%)
Cefixime (5.0%)	Cefixime (7.0%)	Cefaclor (7.2%)	Cefpodoxime (3.5%)	Cefixime (7.1%)
Ceftibuten (3.9%)	Ceftibuten (3.8%)	Cefpodoxime (4.1%)	Cefuroxime (2.3%)	Cefpodoxime (3.6%)
Clofoctol (3.5%)	Cefpodoxime (3.5%)	Ceftibuten (2.9%)	Cefaclor (2.0%)	Ceftibuten (3.4%)
			Ceftibuten (1.4%)	

Penicillins with extended spectrum (ATC code J01CA) were the most frequently prescribed antibiotics and were predominantly prescribed in the first years of life (**figure 2.3**). The most common antibiotic prescribed was amoxicillin with a prevalence of 9.2% in the Netherlands, 19.7% in the UK and 18.0% in Italy.

Amoxicillin prescriptions peaked at the age of 1-<2 years with a maximum annual prevalence of 30.5% in the Netherlands, 46.0% in the UK and 31.3% in Italy. Prescriptions for the class *combinations of penicillins, including beta-lactamase inhibitors* (J01CR) were frequent in the Netherlands and Italy, while in the UK prescriptions for *beta-lactamase sensitive penicillins* were very frequent (J01CE).

Macrolides (J01FA) were also an important group of antibiotics prescribed; 3.5% in the Netherlands (maximal 7.5% at 1-<2 years), 5.3% in the UK (maximal 10.2% at 1-<2 years), and 14.9% in Italy (maximal 23.9% at 3-<4 years). Among the macrolides, erythromycin was the main prescribed antibiotic in the UK, with a prevalence rate of 4.5% and peaking at 1-<2 years of age (8.7%). The prescribed macrolides in the Netherlands and Italy were mainly clarithromycin (1.1% - maximal 3.3% at 1-<2 years) and azithromycin (1.6% (maximal 3.4% at 1-<2 years)). In Italy, the prevalence rate of clarithromycin was 7.1% (maximal 11.1% at 3-<4 years) and 7.6% (maximal 12.8% at 3-<4 years) for azithromycin.

Tetracyclines (J01AA) were prescribed from the age of 11 up in the Netherlands and the UK (no data for this age category available for Italy) (**figure 2.3**). The prevalence of tetracyclines in the UK was higher in boys than in girls with maximal 9.4% for boys and 6.5% for girls at 16-<17 years of age. In the Netherlands the

Figure 2.3 Prevalence of prescribed classes of antibiotics stratified by age

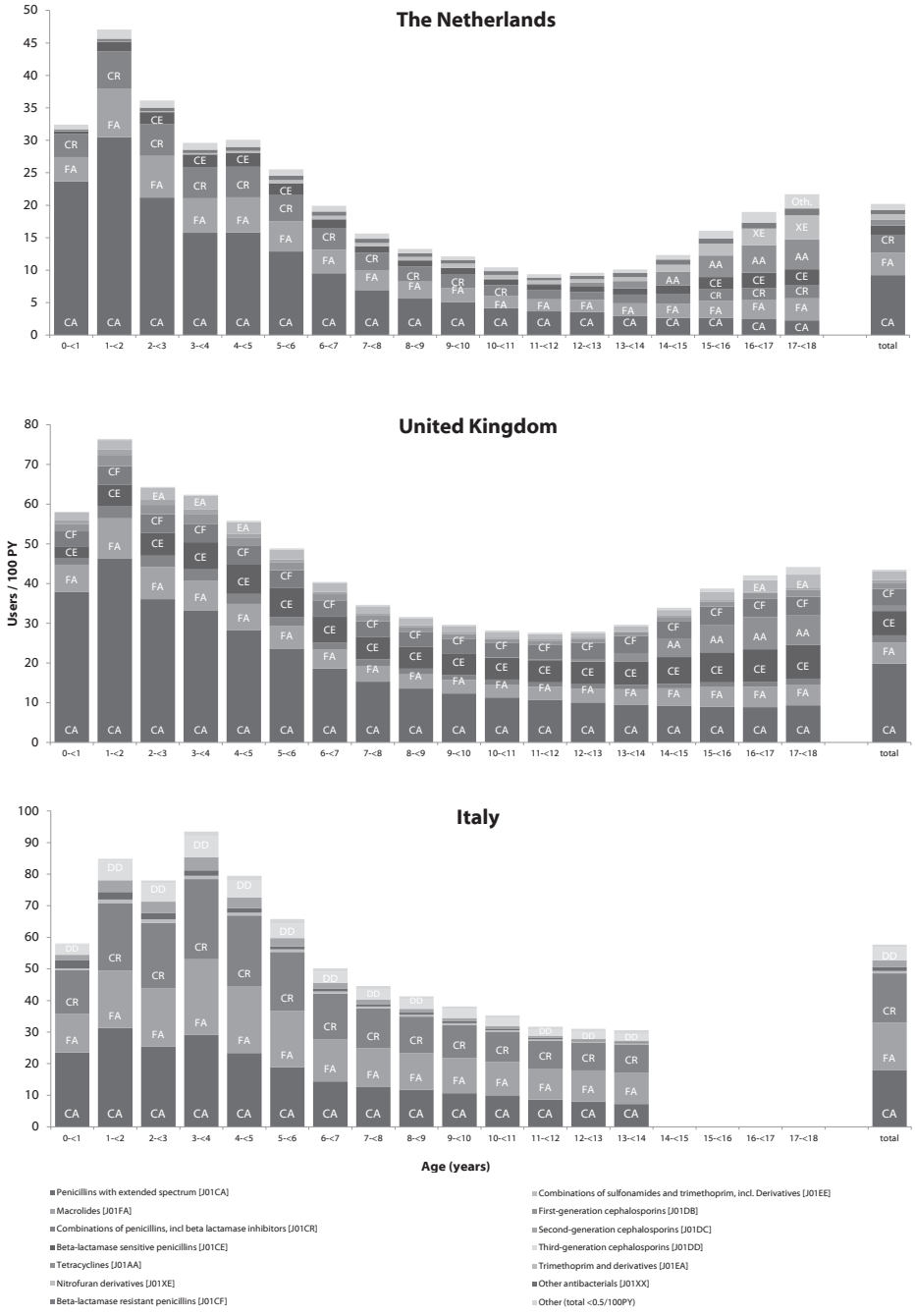


Table 2.2 Ratio of broad versus narrow spectrum antibiotic prescribing

Age	2001			2006			2010			Overall		
in years	NL	UK	Italy	NL	UK	Italy	NL	UK	Italy	NL	UK	Italy
0-<1	5.9	0.31	27.1	6.5	0.33	66.8	6.6	0.41	149.5	5.7	0.35	60.8
1-<2	3.1	0.36	54.6	4.2	0.36	90.3	5.9	0.40	689.5	4.8	0.39	145.9
2-<3	2.7	0.35	67.2	4.6	0.34	65.7	5.4	0.39	538.2	4.0	0.37	113.2
3-<4	3.4	0.31	37.5	3.8	0.32	73.4	4.5	0.36	357.1	3.6	0.34	89.0
4-<5	2.1	0.28	25.0	3.8	0.29	65.8	4.4	0.32	202.0	3.3	0.31	80.2
5-<6	2.7	0.27	21.4	2.1	0.27	58.5	4.0	0.30	171.5	3.6	0.28	73.7
6-<7	3.7	0.25	14.0	2.8	0.26	65.0	4.9	0.31	166.5	3.7	0.27	66.9
7-<8	3.3	0.24	12.9	4.8	0.24	52.5	4.4	0.31	247.9	3.7	0.26	58.8
8-<9	1.9	0.22	11.2	3.3	0.25	44.7	5.2	0.31	195.9	3.5	0.24	52.9
9-<10	3.7	0.23	9.5	3.0	0.23	55.8	3.7	0.29	132.9	3.2	0.23	49.9
10-<11	2.8	0.20	10.4	5.2	0.24	61.5	2.8	0.27	125.5	3.0	0.22	54.2
11-<12	1.7	0.19	11.7	1.8	0.21	54.7	3.2	0.26	237.3	3.0	0.21	67.0
12-<13	1.5	0.17	8.1	2.0	0.20	40.9	4.1	0.28	103.9	2.4	0.20	54.8
13-<14	4.5	0.16	12.2	2.3	0.20	40.5	2.9	0.26	129.6	2.8	0.19	69.2
14-<15	1.9	0.15	-	2.1	0.18	-	3.0	0.23	-	2.3	0.17	-
15-<16	1.6	0.13	-	2.7	0.17	-	2.4	0.25	-	2.0	0.17	-
16-<17	1.0	0.14	-	2.0	0.18	-	2.1	0.26	-	1.7	0.18	-
17-<18	1.6	0.16	-	1.8	0.19	-	2.4	0.29	-	2.0	0.20	-
All ages	2.6	0.24	19.2	3.1	0.25	62.7	3.8	0.31	217.9	3.2	0.27	74.7

The ratio between the number of users of broad spectrum penicillins, cephalosporins and macrolides (J01CR, J01DC, J01DD and J01F (without J01FA01)) and the number of users of narrow spectrum antibiotics (J01CE, J01DB and J01FA01) stratified by country, age and calendar-year. NL=the Netherlands; UK=the United Kingdom.

prevalence rate was similar between the sexes with maximum prevalence rates at the age of 17-<18 years of age (4.5-4.6%). The prevalence of *second and third generation cephalosporins* (J01DC-DD) was considerably high in Italy; up to 4.1% and 6.8% at 3-<4 years of age (**figure 2.3**), while the prevalence of cephalosporin overall (J01D) was low in the UK (2.3%) and rare in the Netherlands (0.02%). The most prescribed antibiotics among the third generation cephalosporins in Italy were the oral cephalosporins; cefixime (2.8% at 3-<4 years), cefpodoxime (2.0% at 3-<4 years) and ceftibuten (1.1% at 1-<2 years) and the parental cephalosporin ceftriaxone (0.8% at 3-<4 years). The ratio between broad and narrow antibiotic prescribing was highest in Italy for all ages and all calendar-years. In all countries, the ratio was highest in the youngest children; 0.39 in children aged 1-<2 years in the UK, 5.7 in children aged 0-<1 years in the Netherlands and 145.9 in children aged 1-<2 years in Italy. When comparing the periods 2001, 2006 and 2010, the ratio increased (**table 2.2**).

Discussion

In this cohort study we described and compared primary care prescription patterns of antibiotic agents in children in three European countries. The current study is unique in its size, period of follow-up and by using of a standard methodology. Almost 3 million children aged 0-<18 years were included, contributing over 12 million PY of follow up over a period of 10 to 16 years. This allowed us to study prescribing patterns over time and to study a wide range of drugs.

The antibiotic prevalence rates amongst the studied countries varied with the Netherlands having the lowest prevalence and a two to three-fold higher prevalence rate for the UK and Italy respectively, which is in line with previous publications.[50,55,67] There was a clear seasonal trend present in the prevalence rates for antibiotics, with the highest rates present in winter and low rates in summer, in line with the seasonal trend of the incidence of upper respiratory tract infections.[68] In agreement with studies reporting a higher incidence of childhood infectious diseases in young boys,[69] the prevalence in boys was higher than in girls in the first years of life. The higher rate of antibiotic prescribing in boys remained up to the age of 3 years after which the prevalence became higher in girls. This sex-specific difference in prevalence rate became more important with increasing age and was highest after puberty. In Italy the differences between boys and girls were highest in first years of life after which the prevalence was comparable. Broad spectrum antibiotic prescribing increased in all countries during the studied period and was highest in Italy. Ratios of broad versus narrow spectrum outpatient antibiotic prescribing were highest in the youngest children. The overall ratios (0-<18 years) were somewhat lower than the ESAC-Net findings for adults over 2004 for the UK (0.27 vs. 0.56) and the Netherlands (3.2 vs. 5.12) and higher in Italy (74.7 vs. 50.9).[54] Since the use of broad spectrum antibiotics may be related to either an actual or perceived increase in rates of antibiotic resistance, this increasing ratio is worrying.

The study period encompassed up to 16 years. In these years considerable effort has been put in reducing the prescriptions of antibiotics.[57,70,71] Despite these efforts, the change in prevalence rates over time was relatively small. In the Netherlands the prevalence in 1996 was already low with 20.0 users/100PY (%) and decreased to 17.2% at the end of the study period. In the UK the prevalence decreased from 39.5% in 1995 to 32.9% in 2010. And finally in Italy, the prevalence decreased from 57.4% in 2001 to 49.8% in 2010. That interventions can effectively reduce inappropriate antibiotic prescribing is illustrated in France.[72] National campaigns especially focussing on inappropriate antibiotic prescribing for respiratory tract infections of viral origin or in children aged 0 to 6 years reported a 50.4% reduction in antibiotic prescriptions in children.

As expected, amoxicillin with or without an enzyme inhibitor was the most com-

monly prescribed antibiotic. The other classes of antibiotics were comparable between the Netherlands and UK. Strikingly, in Italy, cephalosporins, especially third-generation cephalosporins were commonly used – a phenomenon which was not observed in the other countries. This high consumption of cephalosporins in children in primary care in Italy has been described before.[67]

The differences in prescribed antibiotics among the countries can partly be explained by availability of antibiotics and differences in guidelines. For example, penicillin V is not available in Italy whereas it is widely used in the UK. For the treatment of acute pharyngitis, amoxicillin is the first choice of treatment in Italy, but also treatment with second generation cephalosporins is considered in this guideline, while in other countries treatment with narrow-spectrum penicillins is recommended.[73,74] Also the type of prescriber can explain differences in prescription patterns. In Italy, prescriptions by FPs were studied, while in the Netherlands and the UK prescriptions by GPs only were considered. An Italian study showed that more penicillins were prescribed by FPs, while GPs more often prescribed macrolides and cephalosporins to children.[75] Another Italian study found differences in prescription patterns between the northern and the southern part of Italy. While the overall prescription rate in that study was 50.5%, the prevalence in the northern regions was 46.5% and in the southern regions 61.1%.[76] The average prevalence rate in Italy in our study of 52.0% illustrates that the Pedianet database is a representative sample of the total Italian paediatric population.

A limitation of the current study is that we could not stratify the results by indication as these were not collected. In future studies, stratification by indication may give more insight on differences into prescribing practice between the countries. Based on the indication it is possible to draw inferences on i. differences in types of antibiotics prescribed for a certain indication but also on ii. the proportion of children treated for a specific indication. This information is vital to assess whether appropriate antibiotic prescribing policies can be further optimised.

In this study we included one of the quality indicators as developed by ESAC-Net, broad versus narrow spectrum antibiotic prescribing.[53,54] Analysis of this indicator supports the development of age-specific indicators since both antibiotic prescribing and the prevalence of infectious diseases are age-dependent. Since children are an important target group to improve antibiotic prescribing,[77] we would like to make plea for paediatric specific surveillance and data-collection. The Transatlantic Task Force on Antimicrobial Resistance (TAFTAR) aims identification of urgent antimicrobial resistance issues that could be better addressed by intensified cooperation between the United States and the EU, which includes appropriate therapeutic use of antimicrobial drugs.[78] TAFTAR would be a useful form to develop internationally agreed quality indicators of paediatric primary care antibiotic prescribing. Both overall prescription rates of antibiotics and specifically of broad spectrum antibiotic prescribing in children may be appropriate quality indicators of good prescribing practice. Since broad spectrum antibiotic

prescribing also depends on existing resistance patterns and available medicines, probably more paediatric specific quality indicators are needed. DU90% turned out not to be helpful in assessing paediatric antibiotic prescribing since the results were comparable between the countries. Indication specific data collection will be necessary to identify targets to specifically optimise paediatric antibiotic prescribing in the community.

Conclusions

The prevalence of antibiotic prescribing was high and varied with age - in the youngest age category a third to a half of all children were prescribed an antibiotic during one year of follow-up. Prevalence was lowest in the Netherlands and two to three-fold higher in the UK and Italy respectively. The consumption of third-generation cephalosporins is high in young Italian children. The Transatlantic Task Force on Antimicrobial Resistance would be a useful form to develop internationally agreed quality indicators of primary care antibiotic prescribing.

Chapter 3

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Marked Variation in Paediatric Oseltamivir Prescriptions in Primary Care During the 2009 Influenza A(H1N1) pdm09 Pandemic: a Population-Based Cohort Study in the United Kingdom, Italy and the Netherlands

Abstract

Objective

To describe the prescription pattern of oseltamivir, an antiviral drug, to children in primary care in the United Kingdom (UK), Italy and the Netherlands during the 2009 influenza A(H1N1)pdm09 pandemic.

Methods

Design and setting: Population-based retrospective cohort-study within Electronic primary care medical records databases in the UK (The Health Improvement Network (THIN)), Italy (Pedianet), and the Netherlands (Integrated Primary Care Information (IPCI)).

Participants: 1,182,104 children aged up to 14 (Italy) or 18 years (UK and Netherlands), contributing a total of 12,667,752 person-months (PM) of follow-up in 2009.

Main outcome measure: Monthly prevalence of oseltamivir prescriptions in 2009; defined as the number of children with at least one prescription per month. In a secondary analysis, using an ecological study design, the prevalence of oseltamivir prescriptions were compared to the national reported influenza-like-illness (ILI) rates.

Results

In 2009, the monthly prevalence of oseltamivir prescriptions showed a large summer-peak followed by an autumn/winter-peak. In line with the number of ILI-cases reported, the summer-peak was most prominent in the UK (6.6 users/1,000PM) while the autumn/winter-peak was most prominent in the Netherlands (1.5 users/1,000PM). The prevalence of use in Italy was limited (max. 0.2 users/1,000PM) while the ILI rates in Italy were highest. Monthly prevalence was highest for children aged 1 to 5 years (Netherlands: 2.6/1,000PM in November; UK: 10.7/1,000PM in July).

Conclusions

There was a marked variation in paediatric oseltamivir use during the 2009 influenza A(H1N1)pdm09 pandemic. This variation seems to be driven by public health policy and no clear relationship with disease severity was noted. A European approach to policy recommendations on the use of antiviral drugs in future pandemics is needed.

Introduction

In the end of April 2009, the first cases of influenza A(H1N1)pdm09 occurred in Europe.[79] Especially children and young adults seemed to be susceptible to the disease. Based on laboratory testing, this strain of influenza was susceptible to treatment with neuraminidase inhibitors; oseltamivir and zanamivir.[80] With an increasing number of cases, including many paediatric cases, in the period following and the emerging pandemic in the beginning of May 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) gave guidance on the use of oseltamivir in case of a declared pandemic.[81,82] Since 2002, oseltamivir was licenced for the treatment of influenza in people aged 1 year and older and for the prevention of influenza in people aged 13 years and older. In 2006, the indication was extended to i. the treatment of influenza in patients 6 months of age and older who present with symptoms typical of influenza, when influenza virus is circulating in the community and ii. for post-exposure prevention in individuals one year of age or older.[80,83] In their May 2009 guideline, the CHMP stated that in case of an officially declared influenza pandemic the benefits of the use of oseltamivir in the treatment of children under the age of one year outweigh its risks and announced recommended dosages for the treatment or for prophylaxis of influenza.[82]

The occurrence of the 2009 pandemic and the change in indication of treatment implied that oseltamivir was used for the first time on a large scale in infants since its registration in 2002.[84] In this study we aimed to describe the prescription pattern of oseltamivir to children in primary care in the United Kingdom (UK), Italy and the Netherlands during the influenza A(H1N1)pdm09 pandemic.

Patients and Methods

Study design

A population-based retrospective cohort study was conducted to describe the use of oseltamivir in children and adolescents in the Netherlands, the UK and Italy during the 2009 influenza A(H1N1)pdm09 pandemic. In a secondary analysis, using an ecological study design, the prevalence of oseltamivir prescriptions were compared to the national reported influenza-like-illness (ILI) rates.

Setting and data collection

This study is part of the *Antibiotic Resistance and Prescribing in European Children* (ARPEC) project, a project co-funded by the European Commission DG Sanco

through the Executive Agency for Health and Consumers (EAHC) which aims to improve the evidence base for anti-infective drug prescribing in European Children.[47]

For the current study, data were used from three population-based primary care databases in the Netherlands, the UK and Italy according to a common study protocol and harmonised data elaboration. In the Netherlands and the UK, the general practitioner (GP) is responsible for the primary care of children whereas in Italy family paediatricians (FPs) are the gatekeepers of primary care for children. All databases contain the complete automated patient files, with detailed information on the population, diagnoses and prescriptions, and use of these databases has been proven valid for pharmacoepidemiological research.[58,59]

Details of the databases have been described elsewhere.[60-63] In brief, the *Integrated Primary Care Information (IPCI) database* from the Netherlands comprises paediatric and adult electronic medical records from more than 400 Dutch GPs since 1996.[60,61] *The Health Improvement Network (THIN)* is a database of primary care medical records from the UK, prospectively collecting data since September 2002 which contains retrospective data since the late 1980's.[59] The *Pedianet* database contains paediatric electronic medical records from 150 FPs in Italy since 2000.[62] Primary care of children in Italy is entrusted to FPs until the age of 14 years old. From 14 years on, health care is transferred to the responsibility of GPs.

Study population

The study period ran from the 1st of January 2009 to the 31st of December 2009. Children were followed from the start of entry (start of study period (1st of January 2009), date physician was up to date, date of registration plus 6 months or just born) into the study until their 18th (Netherlands and UK) or 14th (Italy) birthday, the end of the study period (31st of December 2009), leaving the practice, death, or latest data drawn down, whichever came first.

Definition of exposure

Utilisation patterns of oseltamivir were studied by retrieving all prescriptions of oseltamivir (ATC code J05AH02)[30] from the databases. A child was defined as a prevalent user of oseltamivir if, during follow-up, the child received a prescription for oseltamivir.

Disease rates / surveillance

For the secondary analysis, the national reported rates of ILI were estimated us-

ing data from the European Centre for Disease Prevention and Control (ECDC) and the Italian Surveillance Influenza Network (InfluNet).

Within Europe, the *European Influenza Surveillance Network (EISN)* of ECDC collects epidemiological and virological surveillance data on influenza through the European Surveillance System (TESSy).[85] Aggregated data is published and publicly available on the website of TESSy. For the Netherlands and the UK (England), the ILI rate per 100,000 was available for the entire study period. For the UK, also the ARI (acute respiratory infections) rate per 100,000 was available. The ILI rate for Italy was not available for the entire period within TESSy, therefore the InfluNet data was used instead.

InfluNet is in charge of the epidemiological and virological surveillance of influenza in Italy. InfluNet is organised by the Superior Institute of Health (ISS) and the Inter-University Centre of Research on Influenza (CIRI), and has weekly updates on the number of influenza related visits to FPs and GPs, including age category specific (0-≤4 years; 5-≤14 years; 15-≤64 years; 65 years and older) incidence of disease.[86,87]

Statistical analysis

Prevalence rate

Annual prevalence rates of oseltamivir use were estimated and expressed as the number of users per 1,000 person years (PY). Monthly prevalence rates were estimated and expressed per 1,000 person months (PMs). Because of the dynamic nature of the population we used person time rather than number of individuals for the prevalence rate.

For the prevalence rates, the number of children *being prescribed* oseltamivir within 2009 (annual rate) or in a specific calendar month was counted (monthly rate). These children received at least one prescription for oseltamivir in either 2009 or in a specific calendar month. Monthly prevalence rates should thereby be interpreted as the number of children per 1,000 who used oseltamivir in one month and the annual prevalence rate should be interpreted as the number of children per 1,000 who used oseltamivir in 2009. The rates, including the 95% confidence interval (95% CI), were calculated and stratified by age, sex, database and calendar time to account for differences in distributions between populations and to allow for direct comparisons within groups.

Stratification by age

Age was stratified in one-year periods (0-<1 years etc.) and in broader age categories; 0-<1 years, 1-<5 years, 5-<12 years, and 12-<18 years.

Results

In this population-based retrospective cohort study a total of 1,182,104 children and adolescents, contributing 12,667,752 PMs (1,055,646 PY) of follow up during 2009 were included; 153,722 from the Netherlands (13.0%), 863,845 from the UK (73.1%), and 164,537 from Italy (13.9%).

Annual prevalence rate

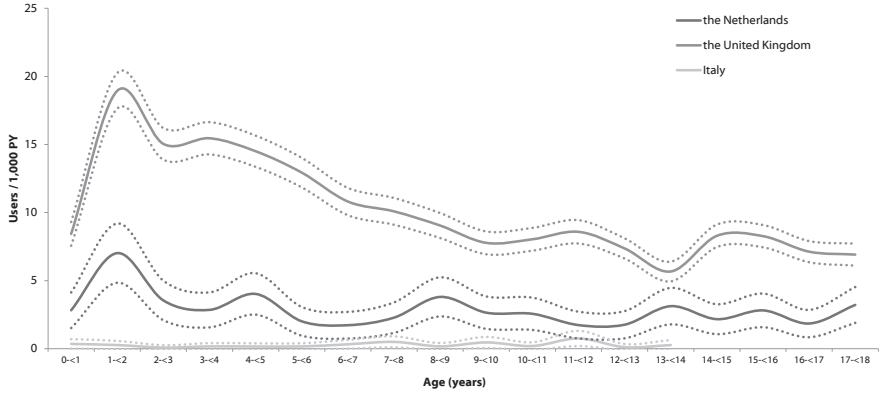
The prevalence rate of oseltamivir prescriptions over 2009 for the total population was 7.9/1,000 PY (95% CI 7.7-8.0/1,000 PY); the rates were 2.8/1,000 PY (95% CI 2.5-3.1) in the Netherlands, 10.1/1,000 PY (95% CI 9.9-10.3) in the UK and 0.3/1,000 PY (95% CI 0.2-0.4) in Italy.

The annual prevalence rate within the one-year age categories was low for all ages in Italy. The pattern of prescriptions by age was similar in the UK and the Netherlands, with the highest rates at 1 to 2 years of age: 18.9/1,000 PY (95% CI 17.6-20.3) in the UK and 7.0/1,000 PY (95% CI 4.8-9.2) in the Netherlands (**figure 3.1**).

Monthly prevalence rate

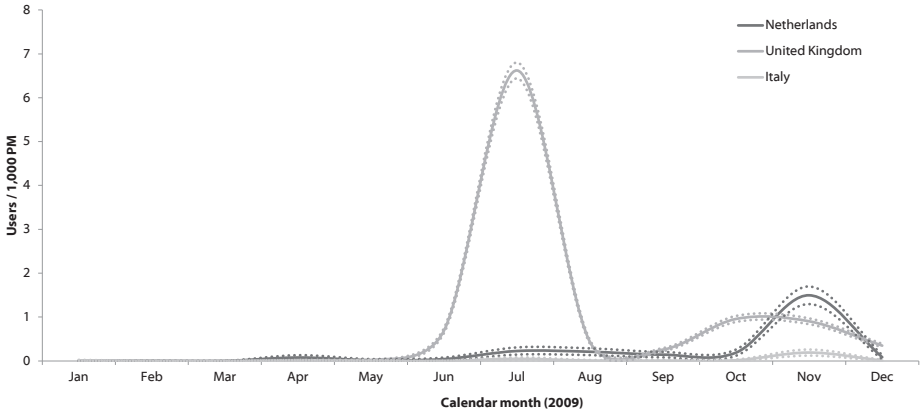
The prevalence stratified by calendar month (number of users per 1,000 PMs) showed a biphasic pattern in all countries: A first peak was present in July 2009 and a second peak in October/November 2009 (**figure 3.2**).

Figure 3.1 Prevalence rate of oseltamivir prescriptions in 2009 stratified by age



The dashed lines show the 95% confidence interval of the estimates. PY=person years.

Figure 3.2 Prevalence rate of oseltamvir prescriptions during the 2009 pandemic

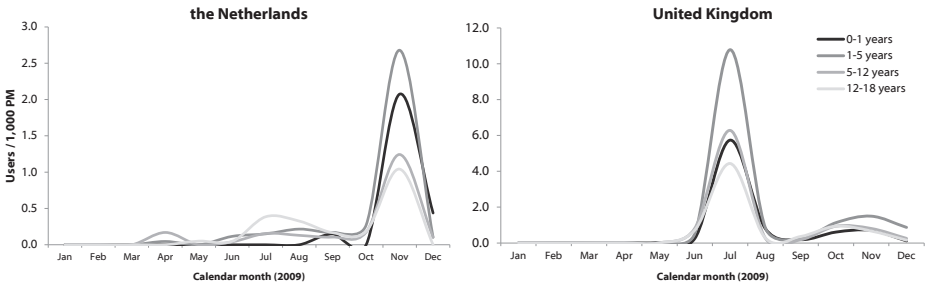


The dashed lines show the 95% confidence interval of the estimates. PM=person months.

In the UK the peak in July was the highest, with a maximum of 6.6 users/1,000 PM (95% CI 6.4-6.8), followed by a smaller peak in October (1.0 users/1,000 PM (95% CI 0.9-1.0)). In the Netherlands the pattern was inverse with a smaller peak in July (0.23 users/1,000 PM; 95% CI 0.14-0.31), followed by a larger peak in November (1.5 users/1,000 PM; 95% CI 1.3-1.7). The pattern in Italy was similar to the Netherlands.

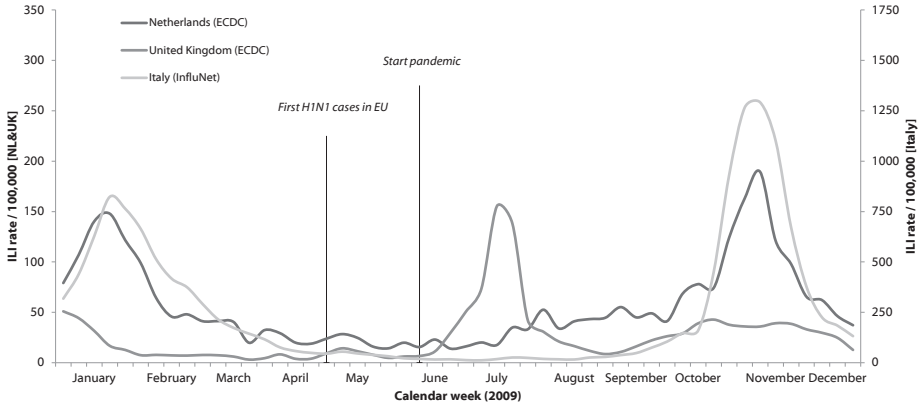
For the Netherlands and the UK, the monthly prevalence was further stratified by age categories. In the Netherlands, prescriptions during first (summer) peak were mainly for older children, while during the second (winter) peak, the prescriptions were mainly for children up to 5 years old. In the UK, in both the summer and winter peak the highest rates were present for children aged 1 to 5 years (**figure 3.3**).

Figure 3.3 Prevalence rate of oseltamvir prescriptions stratified by age categories



The monthly prevalence of oseltamivir, stratified by age categories is presented for the Netherlands and the UK. Abbreviations: PM=person months.

Figure 3.4 Weekly influenza like illness (ILI) rates



The rate of the reported cases of influenza like illness (ILI) for the total population stratifed by country. Please note that the Italian rates are presented on the right X-axis (x50). Data for the Netherlands and the UK are derived from ECDC, the Italian data was derived from Influnet.

Comparison with ILI rates

The ILI rates are presented in **figure 3.4**. In the UK the ILI-rates were highest mid-July (155.3/100,000), whereas the influenza A(H1N1)pdm09 epidemic reached its peak in both the Netherlands (189.4/100,000) and Italy (1,253.4/100,000) in the second week of November 2009. Stratified by age, ILI rates were highest in the youngest children in all countries: In the UK ≈150/100,000 for 0 to 4 years of age and ≈80/100,000 for children aged 5 to 14 years; In the Netherlands ≈650/100,000 for 0 to 4 years of age and ≈500/100,000 for children aged 5 to 14 years; and in Italy ≈4,100/100,000 for 0 to 4 years of age and ≈2,800/100,000 for children aged 5 to 14 years. The Italian ILI rates in the total population were much higher in comparison with the other countries; this is in line with the rates as seen in the beginning of 2009 for the seasonal influenza rates for the season 2008/2009 (**figure 3.4**).

The pattern of the ILI rates and prevalence rates for oseltamivir prescriptions resemble each other, with a peak of prescribing in July 2009 for the UK and highest oseltamivir prevalence rates in November 2009 in the Netherlands and Italy (**figure 3.5**).

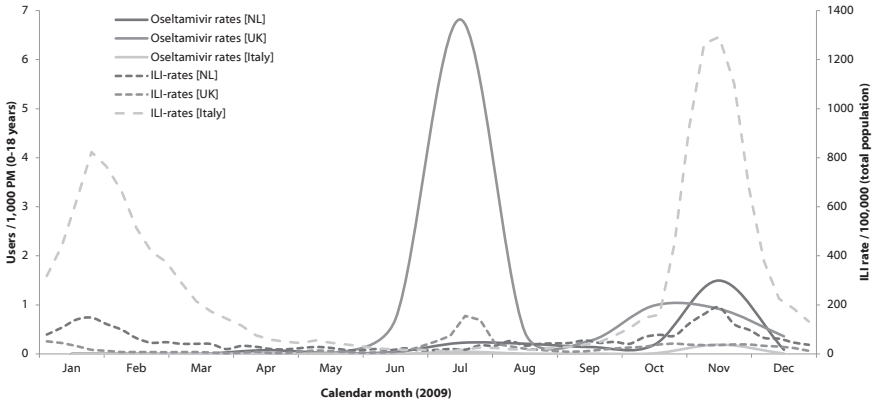
Discussion

In this study we described paediatric oseltamivir utilisation during the 2009 influenza A(H1N1)pdm09 pandemic and showed large differences within three Euro-

pean countries. While the oseltamivir prevalence peaked in November for both the Netherlands and Italy, it had already reached its maximum in July in the UK. The rate of oseltamivir prescriptions was highest for children aged 1 to 5 years during the entire pandemic period in the UK, while in the Netherlands prescriptions in the summer were for older children than the prescriptions in November. The observed patterns of oseltamivir prescriptions are in agreement with the reported ILI rates in both countries. Contrary to other European countries, the summer peak was most prominent in the UK, even though the hospital admission rate and the number of paediatric deaths were higher in the second wave of the pandemic.[79,88-90] Although Italy reported the highest rates of ILI, 4,360 cases per 100,000 for 5 to 14 years of age in the first week of November, the lowest prevalence rate of oseltamivir prescriptions was present, with a maximum of 0.19 users per 1,000 PM in November.

The strength of this study is the large size of the studied population; ≈1.2 million children and adolescents in three European countries. Studying multiple countries allowed us to compare the prescriptions rates and relate the prescription rates to the disease rates. Since we used population-based primary care databases we were able to study the use in the primary care paediatric population while other studies often focus on in-hospital prescriptions or the use in children with underlying medical conditions. A limitation of the study is that some prescriptions are probably missed, since oseltamivir was also available through national public health authorities.[91,92] In England an internet based self-diagnosis service was available for oseltamivir without a doctor's prescription. For the Netherlands it was estimated that the proportion of treatments dispensed by the national health authorities to be about a tenth of the prescriptions by GPs.[93] Finally, as we

Figure 3.5 ILI rates and prevalence rates of oseltamivir prescriptions



The rate of the reported cases of influenza like illness (ILI) for the total population stratifed by country (right X-axis) is presented as well as the prevalence rates of oseltamivir prescriptions (left X-axis).

did not have person level data for the occurrence of ILI or the indication of use, we could not stratify our results for prescriptions for prophylaxis or for treatment of influenza infections.

The differences in prevalence of use reflect differences in national policy during the pandemic period. Apart from guidance on use of oseltamivir by the CHMP in May 2009,[81,82] national guidelines were developed rapidly to control the pandemic.[91,94] In the UK the initial response of the public health authorities to the influenza A(H1N1)pdm09 pandemic was very intensive. From the start of the pandemic till July 2009, all contact persons of H1N1 cases in the UK were advised to receive prophylactic treatment with oseltamivir and schools were closed.[89,95] Also in the Netherlands, oseltamivir treatment was initially recommended (till June 23rd) for all laboratory confirmed cases as for their close contacts, regardless of symptoms.[91,96] In this first summer period of the pandemic, the influenza activity in Italy was limited and no signs of an epidemic were present till the end of October 2009.[97] At that time, oseltamivir prescriptions to children were discouraged and use in children was limited to hospitalised cases because of the risk of developing resistance.[98,99] The huge variation between Italy and the other countries is especially striking since it is known that antimicrobial prescribing in children, including use of other antiviral drugs is much higher in Italy.[50]

We cannot make any statement about over- or under prescribing as the efficacy of oseltamivir in the treatment and prevention of influenza, especially in children, is still under debate.[100,101] As advocated by the BMJ (British Medical Journal) open data campaign it is important to obtain transparency considering the efficacy and safety of oseltamivir use.[102] A European approach on recommendations on the use of antiviral drugs in future pandemics is needed through an expert working group.

Conclusions

There was a marked variation in paediatric oseltamivir use during the 2009 influenza A(H1N1)pdm09 pandemic within studied three European countries. This variation seems to be driven by public health policy. A European approach to policy recommendations on the use of antiviral drugs in future pandemics is needed.

Disclaimer

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Chapter 4

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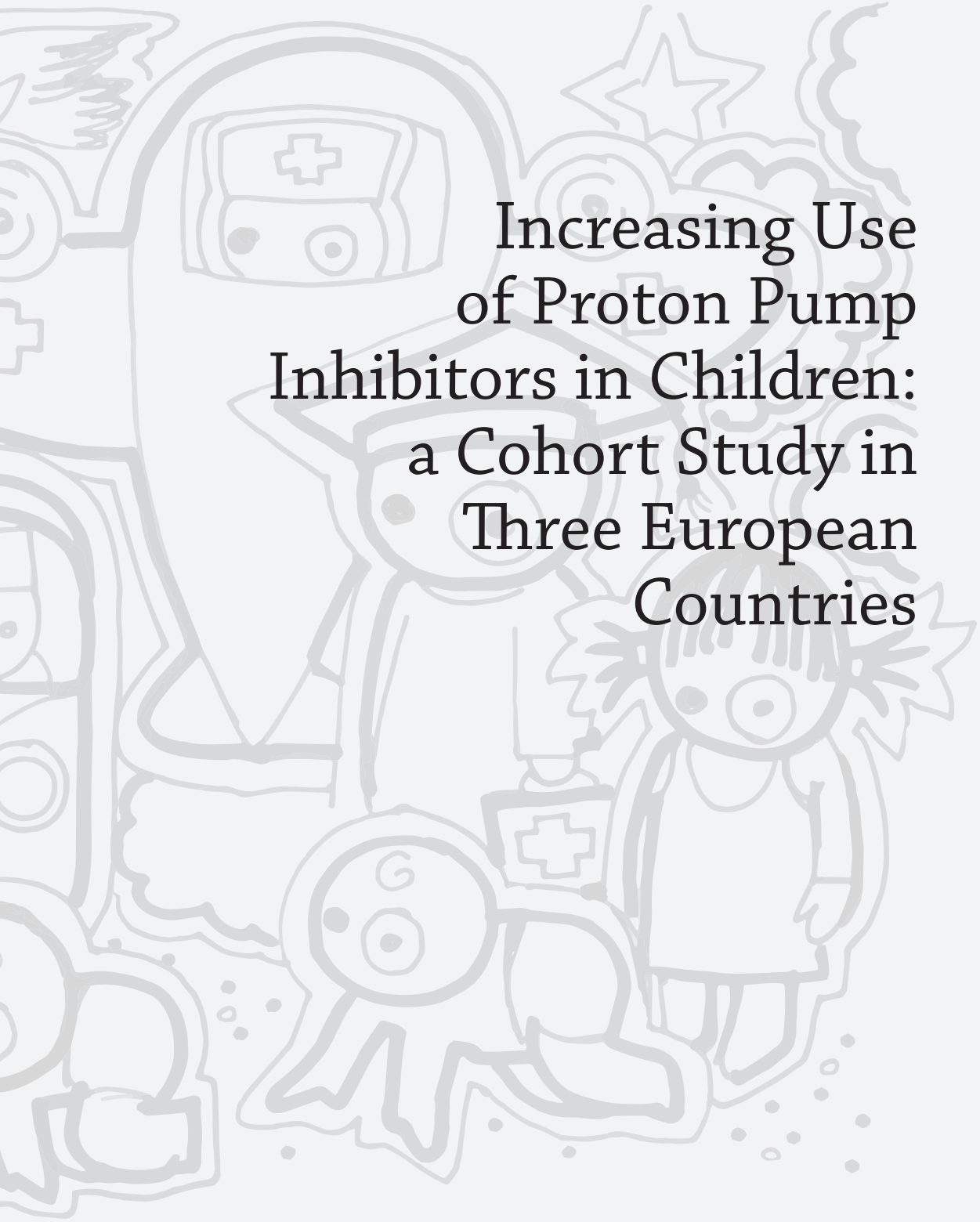


Increasing Use of Proton Pump Inhibitors in Children: a Cohort Study in Three European Countries

Abstract

Background

The use of proton pump inhibitors (PPIs) as gastro-acid suppressing drug increased over recent years and has replaced to a large extent the use of histamine-2-receptor antagonists (H_2RAs) in adults. Little is known on the extent of the use of these drugs in children and adolescents and whether there are geographical differences.

Objectives

To describe the prescription patterns of PPIs and H_2RAs in children and adolescents using prescription data from 3 European countries. To study the proportion of PPI prescriptions over time.

Methods

A retrospective population-based cohort study was conducted using data from 3 primary care electronic healthcare databases in the Netherlands, Italy, and Spain in the period 2001-2008. Annual prevalence of use for PPIs and H_2RAs was calculated (number of users per 1,000 person years (PY)) and stratified by country, calendar-time, age and sex. The proportion of PPI prescriptions versus H_2RA prescriptions was calculated. We applied χ^2 and Poisson regression analyses to compare the prevalence rates and proportions over time.

Results

The overall prevalence of H_2RAs was lowest in Italy with 2.1 users/1,000 PY (95% CI 2.0-2.1), followed by 3.3 users/1,000 PY (95% CI 3.1-3.5) in the Netherlands, and 3.9 users/1,000 PY (95% CI 3.8-4.0) in Spain. Also the prevalence of PPIs was lowest in Italy with 1.2 users/1,000 PY (95% CI 1.1-1.3), followed by the Netherlands (4.1 (95% CI 3.8-4.5)) and Spain (8.5 (95% CI 8.3-8.7)). During the study period the proportion of PPI prescriptions compared to H_2RA prescriptions increased in all three countries; from 41.1% to 56.6% in the Netherlands (χ^2=36.0; p=0.000), from 24.6% to 48.6% in Italy (χ^2=85.5; p=0.000) and from 48.8% to 75.6% in Spain (χ^2=538.4; p=0.000).

Conclusions

Between 2001 and 2008 PPI use in children and adolescents increased and replaced H_2RA prescriptions, especially in the older children. As few data are available on the safety of these drugs in children, we recommend long term follow up studies in children to assess long term safety of PPI use.

Introduction

The use of proton pump inhibitors (PPIs) as gastro-acid suppressing agent has increased over recent years and has replaced the use of histamine-2-receptor antagonists (H_2RAs) in a large amount in adults.[103] Although PPIs are considered to be safe, there are increasing concerns that use of PPIs might be associated with bone fractures, community-acquired pneumonia and clostridium infections.[104-106]

The registered indications for PPIs and H_2RAs in children include treatment of reflux esophagitis and gastro-oesophageal reflux disease (GERD).[107] In the guideline on the treatment of GERD in children it is stated that acid-suppressant agents like PPIs and H_2RAs are the mainstay of treatment; H_2RAs are useful for on-demand treatment while PPIs are superior for healing of esophagitis and relief of GERD symptoms.[108,109]

There is limited information on the utilisation of these drugs in children and adolescents and whether this differs in different countries. In addition it is unknown whether also in children the use of gastro-acid suppressing agents shifted from H_2RAs to PPIs. In this study we studied utilisation patterns of PPIs and H_2RAs in children and adolescents in primary care in three European countries. Prevalence rates of use were compared between the countries, but also within age-groups and calendar-time. The ratio between PPI and H_2RA prescribing was studied over time.

Patients and Methods

Study design

A retrospective population-based cohort study was conducted to describe the use of PPIs and H_2RAs in children and adolescents

Setting

Data were used from three primary care databases in Italy, the Netherlands and Spain according to a common study protocol. These three population-based databases comprise primary care data on children. In the Netherlands, the general practitioner (GP) is responsible for the primary care of children whereas in Spain and Italy, primary care and family paediatricians are the gatekeepers of primary care for children. These databases contain the complete automated patient files, with detailed information on the population, diagnoses and prescriptions, and use of these databases has been proven valid for pharmacoepidemiological re-

search.[58] Details of the databases have been described elsewhere.[60-63]

In brief, since 2000, the *Pedianet database* contains paediatric electronic medical records from 150 family paediatricians in Italy.[62] Primary care of children in Italy is entrusted to family paediatricians until the age of 14 years old. From 14 years on, health care is taken on by GPs. The *Integrated Primary Care Information (IPCI) database* comprises paediatric and adult electronic medical records from more than 400 Dutch GPs since 1996.[60,61] The *BIFAP database* is a longitudinal observational population-based database kept by the Spanish Agency for Medicines and Medical Devices that collates, from 2001 onwards, the computerised medical records of more than 2,000 primary care physicians, including more than 350 primary care paediatricians throughout Spain.[63] The primary care of children in Spain is entrusted to primary care paediatricians until the age of 14 years. Afterwards, care is taken over by GPs. The BIFAP database combines both the data from primary care paediatricians and GPs.

Study period

The study period ran from January 1st 2001 to December 31st 2008.

Study cohort

Children were followed from the start of entry (start of study period, date physician was up to date, date of registration plus 6 months or just born) into the study until their 18th (the Netherlands and Spain) or 14th (Italy) birthday, leaving the practice, death, or latest data drawn down, whichever came first.

For each child the person time of follow-up was calculated, and stratified by calendar year, age in years and age categories.

A child was defined as a prevalent user of a study drug if, during follow-up, the child received a prescription for any of the study drugs. If during follow-up a child received a prescription of more than one of the study drugs, this child contributed to both drugs.

Definition of exposure

Utilisation patterns of PPIs and H_2RAs were studied. All individual drugs of these classes available during the study period in either of the countries were included. Prescriptions were selected based on the respective ATC (Anatomical Therapeutic Chemical) classification

code of each individual drug.[110] Not all of the individual drugs were prescribed in all studied countries.

Proton pump inhibitors

The following PPIs were studied; omeprazole (A02BC01), pantoprazole (A02BC02), lansaprozole (A02BC03), rabeprazole (A02BA04), and esomeprazole (A02BA05).

Histamine-2 receptor antagonists

The following H_2RAs were studied; cimetidine (A02BA01), ranitidine (A02BA02), famotidine (A02BA03), nizatidine (A02BA04), niperotidine (A02BA05), roxatidine (A02BA06), ranitidine bismuth citrate (A02BA07), lafutidine (A02BA08), combinations with cimetidine (A02BA51), and combinations with famotidine (A02BA53).

Statistical analysis

Prevalence rates

Prevalence rates for the study drugs were estimated and expressed per 1,000 person years (PY). Because of the dynamic nature of the population we used person time rather than number of individuals.

For the prevalence rates, the number of children *being prescribed* a drug in a specific calendar year was counted, these children received at least one prescription for the drug in this calendar year. Annual prevalence rates should thereby be interpreted as the number of children per 1,000 who used a study drug in one year.

Prevalence rates, including the 95% confidence interval (95% CI), were calculated and stratified by age, sex, database and calendar year to account for differences in distributions between populations and to allow for direct comparisons within groups. Poisson regression was applied to investigate the trend of prevalence rates in the study period.

Proportion of PPI prescriptions

To compare the share of PPI prescriptions to the total number of prescriptions over time we calculated the proportion of PPI versus H_2RA prescriptions for each calendar year. Results were stratified by age categories according to the guidelines of the International Conference on Harmonisation (ICH); 0-<2 years, 2-<12 years and 12-<18 years.[111] χ^2 analyses were applied to compare the proportion of PPI-prescriptions over time.

Statistical significance was assumed for two-sided *p*-values <0.05. Statistical

analyses were performed using SPSS software version 20 (SPSS Inc, Chicago, IL, US).

Results

Prevalence of histamine-2-receptor antagonists (H_2RA) prescriptions

The overall prevalence of H_2RA use was lowest in Italy with 2.1 users/1,000 PY (95% CI 2.0-2.1), followed by 3.3 users/1,000 PY (95% CI 3.1-3.5) in the Netherlands, and 3.9 users/1,000 PY (95% CI 3.8-4.0) in Spain. In Spain the prevalence

Figure 4.1 Prevalence rate of H_2RA prescriptions stratified by age

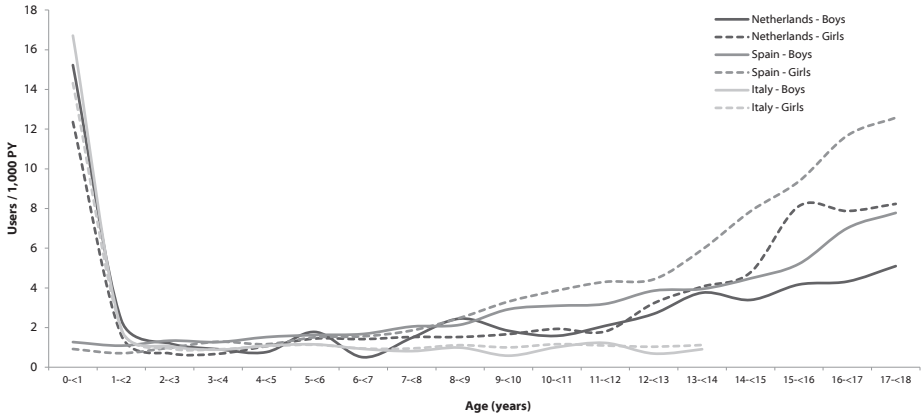
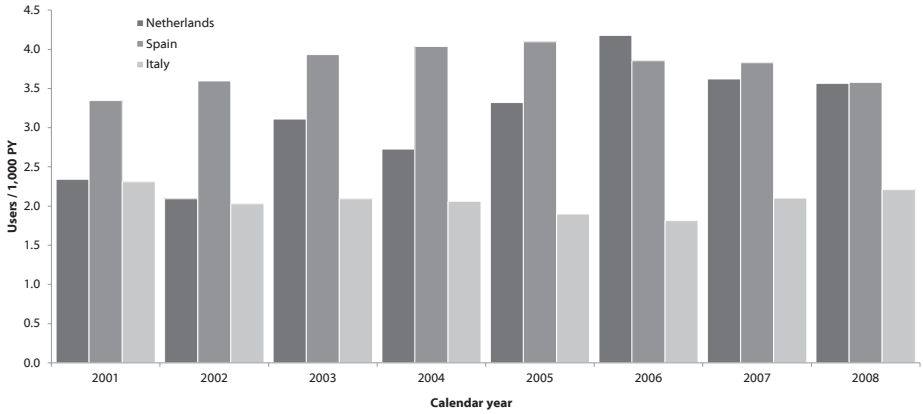


Figure 4.2 Prevalence rate of H_2RA prescriptions stratified by year



was higher in girls than in boys: 4.5 users/1,000 PY (95% CI 4.4-4.7) in girls and 3.2 users/1,000 PY (95% CI 3.1-3.4) in boys. The prevalence was highest in children <1 years of age in the Netherlands and Italy. In both Spain and the Netherlands the prevalence increased from the age of 7 years and older with higher rates in girls (**figure 4.1**). The prevalence of H_2RA prescriptions was relatively stable over time in Italy (β=0.000; *p*=0.98). There were more fluctuations over time in the Netherlands, with a highest peak in 2006 (**figure 4.2**). In Netherlands (β=0.064; *p*=0.000) and Spain (β=0.101; *p*=0.000) the prevalence increased over time.

The most frequently prescribed H_2RA in all countries was ranitidine; 2.0 users/1,000 PY (95% CI 2.0-2.1) in Italy, 3.1 users/1,000 PY (95% CI 2.9-3.3) in the Netherlands, and 3.6 users/1,000 PY (95% CI 3.5-3.7) in Spain. All other H_2RAs had an overall prevalence of <0.2 users/1,000 PY. Famotidine was only prescribed in Spain especially in the beginning of the study period with a prevalence of 0.5 users/1,000 PY in 2001 after which it gradually decreased to 0.07 users/1,000 PY in 2008. Nizatidine had a peak in prescribing in Italy in 2001 (0.2 users/1,000 PY), but was rarely prescribed in the following years.

Prevalence of proton pump inhibitor (PPI) prescriptions

Also the overall prevalence of PPIs was lowest in Italy at 1.2 users/1,000 PY (95% CI 1.1-1.3), followed by the Netherlands (4.1 users/1,000 PY (3.8-4.5)) and Spain (8.5 users/1,000 PY (95% CI 8.3-8.7)). In both the Netherlands and Spain, the prevalence was higher in girls than in boys. In all three countries the prevalence was low until the age of 12 years after which it increased, especially in girls (**figure 4.3**).

During the study period, the prevalence of PPI prescriptions increased in all countries; from 0.8 to 2.1 users/1,000 PY in Italy (β=0.175; *p*=0.000), from 1.6 to 4.7 users/1,000 PY in the Netherlands (β=0.165; *p*=0.000) and from 3.2 to 11.1 users/1,000 PY in Spain (β=0.347; *p*=0.000) (**figure 4.4**). Omeprazole was the main prescribed PPI in all countries. Over the years, lansoprazole was prescribed increasingly in Spain and Italy, while it was rarely prescribed in the Netherlands. Especially in Italy the share of lansoprazole of all PPI prescriptions increased during the study period, this was at the cost of the share of omeprazole prescriptions which decreased. In the Netherlands, the share of rabeprazole prescriptions decreased over time while the share of esomeprazole increased.

In the Netherlands, the proportion of pantoprazole prescriptions increases from the age of 11 years on. In these age categories also the proportion of esomeprazole prescriptions increased (**figure 4.5**). In Italy, where no data was available above the age of 14 years, also the proportion of esomeprazole and pantoprazole increased with age. In Spain, the proportion of lansoprazole prescriptions decreased from the age of 6 years on and was replaced by omeprazole as the

Figure 4.3 Prevalence rate of PPI prescriptions stratified by age

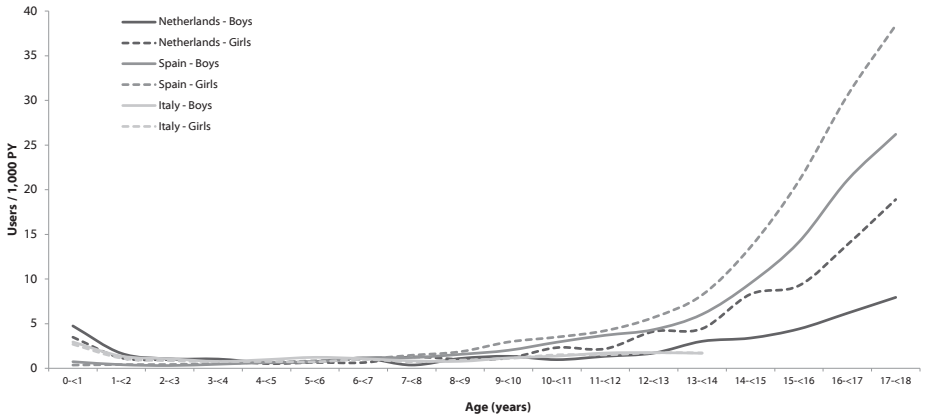
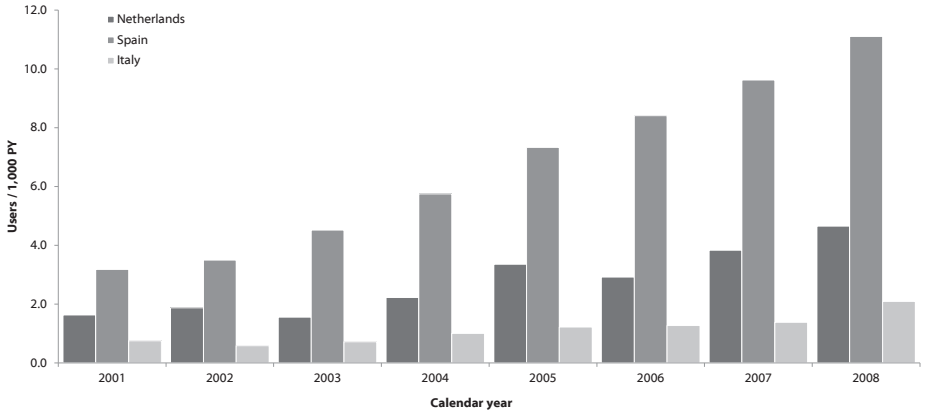


Figure 4.4 Prevalence rate of PPI prescriptions stratified by year



main prescribed PPI.

Proportion of PPI-prescriptions

During the study period the proportion of PPI prescriptions compared to H_2RA prescriptions increased in all three countries; from 41.1% to 56.6% in the Netherlands (χ^2=36.0; p=0.000), from 24.6% to 48.6% in Italy (χ^2=85.5; p=0.000) and from 48.8% to 75.6% in Spain (χ^2=538.4; p=0.000).

After stratification by age categories, the proportion of PPI-prescribing in the Netherlands only increased significantly in the older children; aged 2-<12 (from

Table 4.1 Change in PPI and H_2RA prescribing between 2001 and 2008

	2001			2008				
	H_2RA	PPI	% PPI	H_2RA	PPI	% PPI	Trend %PPI	Ratio PPIs 2001:2008
the Netherlands								
0-<2 years	1.3	0.4	25.0	13.2	4.6	25.9	χ^2=1.3 p=0.99	10.3
2-<12 years	0.9	0.5	38.9	1.5	1.6	51.8	χ^2=16.0 p=0.03	2.9
12-<18 years	5.1	3.8	42.6	4.4	9.9	69.1	χ^2=45.8 p=0.000	2.6
Italy								
0-<2 years	8.5	0.4	4.5	11.4	4.3	27.2	χ^2=42.4 p=0.000	10.7
2-<12 years	1.1	0.8	41.8	1.1	1.7	60.5	χ^2=29.1 p=0.000	2.1
12-<14 years	1.0	1.0	50.0	1.0	2.7	73.6	χ^2=14.5 p=0.04	2.8
Spain								
0-<2 years	0.6	0.0	0.0	0.9	27.2	60.9	χ^2=25.4 p=0.001	*n.a.*
2-<12 years	1.4	0.5	27.6	2.8	60.5	54.2	χ^2=77.2 p=0.000	6.4
12-<18 years	5.7	6.3	52.3	5.8	73.6	82.4	χ^2=655.5 p=0.000	4.3

% PPI= proportion PPI prescriptions of total of PPI and H_2RA prescriptions; Trend % PPI= statistical test for trend of % PPI over time; Ratio PPIs 2001:2008= ratio between PPI prescribing in 2008 and 2001. H_2RA=histamine-2 receptor antagonists. PPI=proton pump inhibitors.

38.9% to 51.8%; χ^2=16.0; p=0.03) and aged 12-<18 years (from 42.6% to 69.1%; χ^2=45.8; p=0.000). In both Italy and Spain the proportion of PPI prescribing increased significantly in all age categories (**table 4.1**).

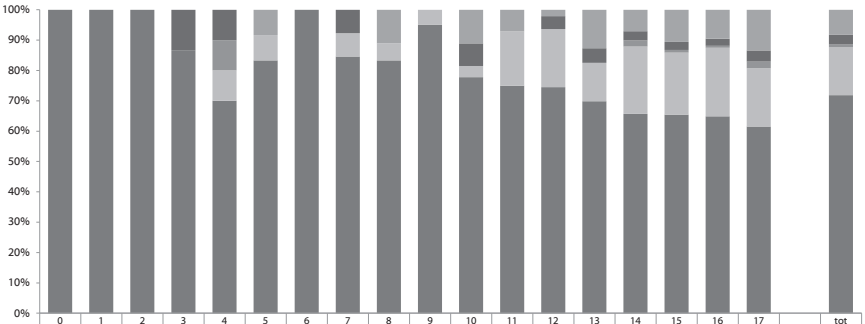
Discussion

In the current study we assessed prevalence rates of prescriptions for PPIs and H_2RAs in children and adolescents in three European countries. The overall prevalence of gastric acid reducing agents was relatively low in children but, in line with previous findings in adults,[112] the proportion of PPI prescriptions with respect to H_2RA prescriptions increased over time, and almost doubled in Italy.

Ranitidine was the main H_2RA prescribed in all three countries. Interesting in Italy and the Netherlands, prescriptions for ranitidine concerned mainly children less than 1 year of age, while this was not seen in Spain. The high peak in the young children is expected since the main indication, GERD, has a high incidence at this age.[113] In addition, ranitidine in Italy and the Netherlands is available as an easy

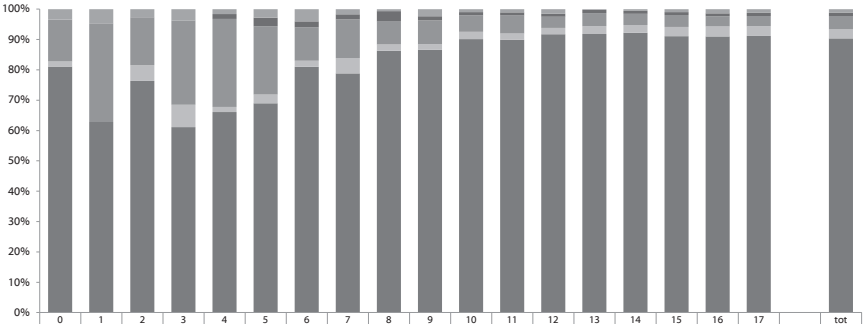
Figure 4.5 Prevalence and proportion of individual PPIs stratified by age

The Netherlands



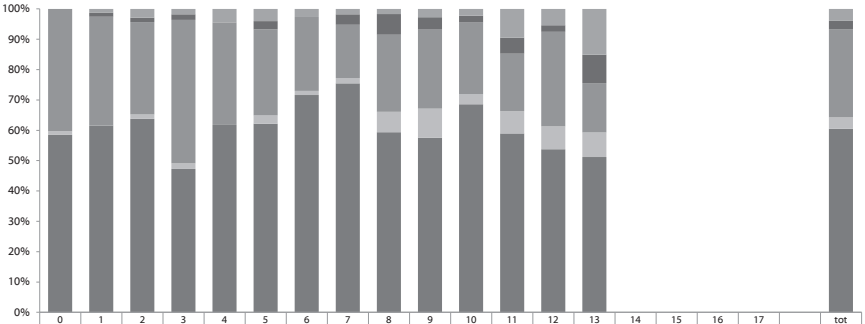
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		tot
Esomeprazole	0.00	0.00	0.00	0.00	0.00	0.06	0.00	0.00	0.12	0.00	0.19	0.13	0.06	0.50	0.43	0.75	1.00	1.89		0.28
Rabeprazole	0.00	0.00	0.00	0.13	0.07	0.00	0.00	0.06	0.00	0.00	0.13	0.00	0.13	0.19	0.19	0.19	0.25	0.53		0.10
Lansoprazole	0.00	0.00	0.00	0.00	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.06	0.06	0.30		0.03
Pantoprazole	0.00	0.00	0.00	0.00	0.07	0.06	0.00	0.06	0.06	0.06	0.06	0.31	0.57	0.50	1.36	1.43	2.38	2.72		0.53
Omeprazole	4.13	1.43	1.03	0.86	0.46	0.65	0.89	0.69	0.94	1.19	1.32	1.32	2.20	2.73	4.01	4.61	6.82	8.69		2.40

Spain



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		tot
Esomeprazole	0.02	0.02	0.01	0.02	0.01	0.02	0.05	0.02	0.01	0.06	0.03	0.04	0.08	0.02	0.07	0.18	0.36	0.41		0.09
Rabeprazole	0.00	0.00	0.00	0.00	0.01	0.02	0.02	0.02	0.06	0.03	0.03	0.04	0.05	0.07	0.11	0.17	0.26	0.34		0.08
Lansoprazole	0.08	0.14	0.06	0.15	0.19	0.18	0.13	0.18	0.13	0.20	0.18	0.24	0.19	0.32	0.43	0.70	0.89	1.10		0.33
Pantoprazole	0.01	0.00	0.02	0.04	0.01	0.02	0.02	0.07	0.04	0.05	0.08	0.08	0.11	0.19	0.30	0.54	0.86	1.05		0.22
Omeprazole	0.47	0.27	0.29	0.34	0.44	0.55	0.93	1.09	1.49	2.17	2.93	3.60	4.69	6.67	10.76	16.24	23.98	29.97		6.67

Italy



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		tot
Esomeprazole	0.00	0.02	0.03	0.01	0.04	0.04	0.03	0.01	0.02	0.03	0.03	0.16	0.10	0.29						0.05
Rabeprazole	0.00	0.02	0.02	0.01	0.00	0.03	0.00	0.03	0.06	0.05	0.03	0.09	0.04	0.18						0.04
Lansoprazole	1.16	0.45	0.32	0.37	0.32	0.29	0.25	0.15	0.23	0.30	0.36	0.33	0.58	0.31						0.38
Pantoprazole	0.03	0.00	0.02	0.01	0.00	0.03	0.01	0.01	0.06	0.11	0.05	0.13	0.14	0.16						0.05
Omeprazole	1.68	0.78	0.67	0.37	0.59	0.64	0.75	0.63	0.53	0.67	1.03	1.02	1.00	0.99						0.79

to administer liquid formulation, while PPIs are only available as tablets, capsules or intravenous solutions. In Spain there is no liquid formulation for either H_2RAs or PPIs available. Paediatricians tend to order ranitidine as a magisterial formulation which is not systematically captured in the BIFAP database. This explains the low rate of use of ranitidine in the young children in Spain. In a previous study we showed that prokinetic drugs are prescribed in the same amount in Spain as in Italy and the Netherlands in these young children, which are available as liquid formulations (*unpublished*). In a previous Spanish study it was shown that there was a high percentage of off-label use of both PPIs and H_2RAs in this age category.[114]

In the Netherlands, the proportion of PPI-prescribing only increased significantly in the oldest children, while in the other countries the increase was present for all ages. This is probably since both H_2RA and PPI prescribing increased during the study period, and the absolute prevalence of PPI prescribing in the Netherlands both increased around 10-times in the young children. The absolute increase in PPI-prescribing in children was seen in all countries, however the H_2RA prescribing increased less in Italy and Spain. The absolute increase in PPI prescribing was also seen in a US study, in which four-fold increase in PPI prescribing from 2000 to 2003 in children younger than 12 months was present.

The off-label use of PPIs in the young children has been subject of debate. According to the international guideline on treatment of GERD, PPIs are the mainstay for the treatment of GERD.[108,115-117] However, none of the current available PPIs have been registered for use in young children.[118] In 2007, the European Medicines Agency (EMA) compiled a list with 'paediatric needs'. This is a list of drugs for which more data is necessary with respect to e.g. pharmacodynamics, pharmacokinetics and safety. Gastric acid reducing drugs are part of this list where a need for alcohol-free formulations of ranitidine and the need of paediatric pharmacokinetics, efficacy, and long term safety data is mentioned for PPIs.[119] Since the implementation of the new paediatric regulation, stimulating research in children,[14] only two paediatric investigations plans for esomeprazole and rabeprazole have been submitted to and evaluated by the EMA.[120,121] Although it has been speculated by some research groups that there is enough data available on the use of PPIs in young children,[118] we agree with EMA that data on long-term safety of PPIs and development of age appropriate formulations remains essential.

In addition, it is important to study whether risks related to the use of PPIs as reported in adults, also hold for children. Indeed, the use PPIs have been associated with a risk of community acquired pneumonia in adults. So far, only one small study investigated this association in children and found an increased risk of acute gastroenteritis and community-acquired pneumonia in children with GERD.[122] Studying this association in children is important as GERD by itself is a risk factor to develop upper airway complications. The risk benefit analysis of use

of PPIs in children is crucial as there is a growing concern that these drugs might be overprescribed in children.[123,124]

Strengths and limitations

A strength of the current study is the large study population of more than 1 million children which were followed in a study period covering 8 years. Using these databases we were able to assess patterns of prescribing PPIs and H_2RAs by country, sex, age category and calendar year.

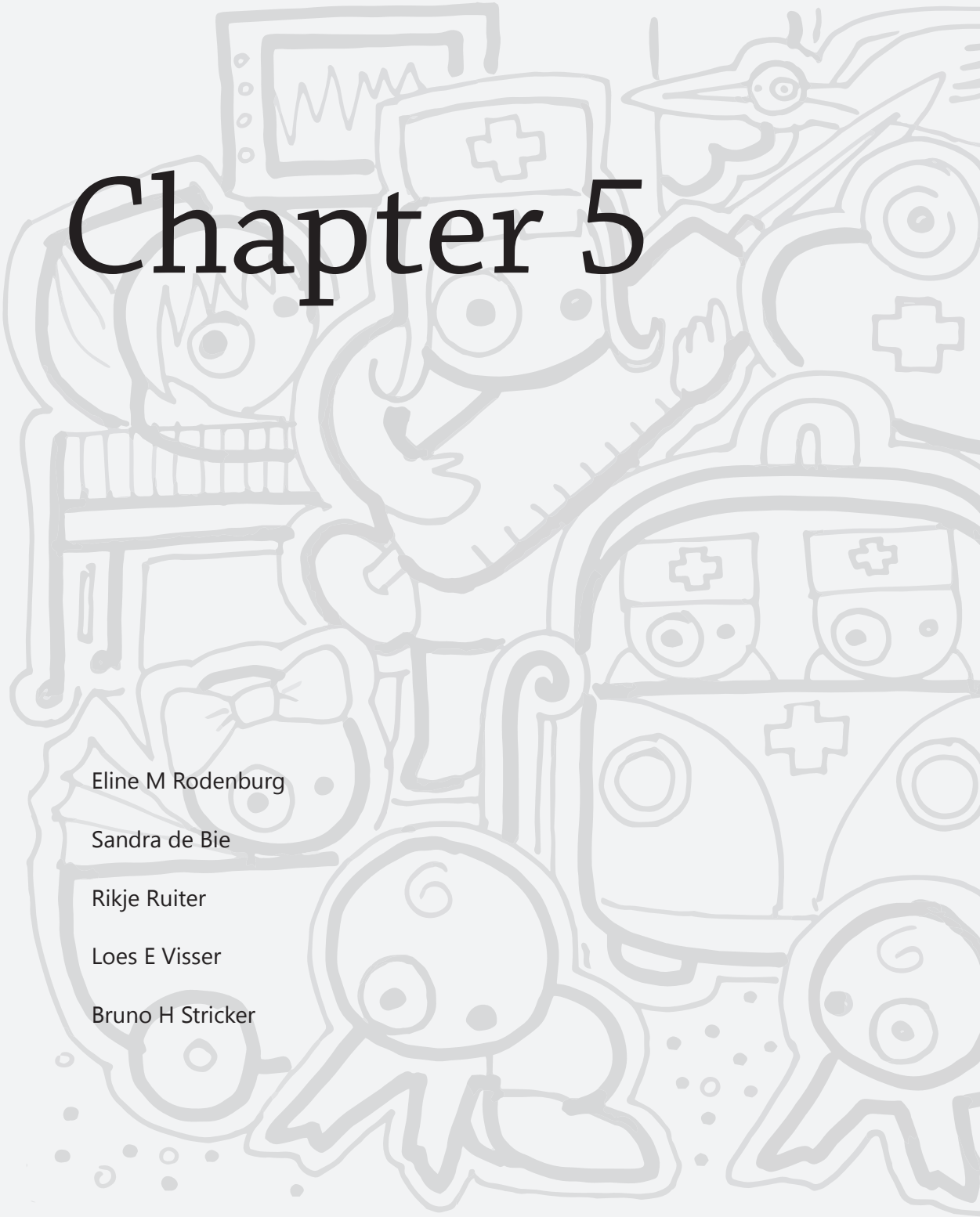
Since we did not link the prescription information to the indication of use we cannot draw conclusions on off-label use or difference of indication by region. In addition, as we only had information on drug prescription and not on actual drug intake, user prevalence data might even be lower.

Conclusions

Between 2001 and 2008 both PPI and H_2RA prescriptions in children and adolescents increased. Especially in the older children the proportion PPI-prescribing of all gastric-suppressant drugs increased. The safety of PPIs and H_2RAs has not been studied in children and there is a need for long term follow up studies in children to assess long term safety.

Adverse Drug Reactions

Chapter 5



Eline M Rodenburg

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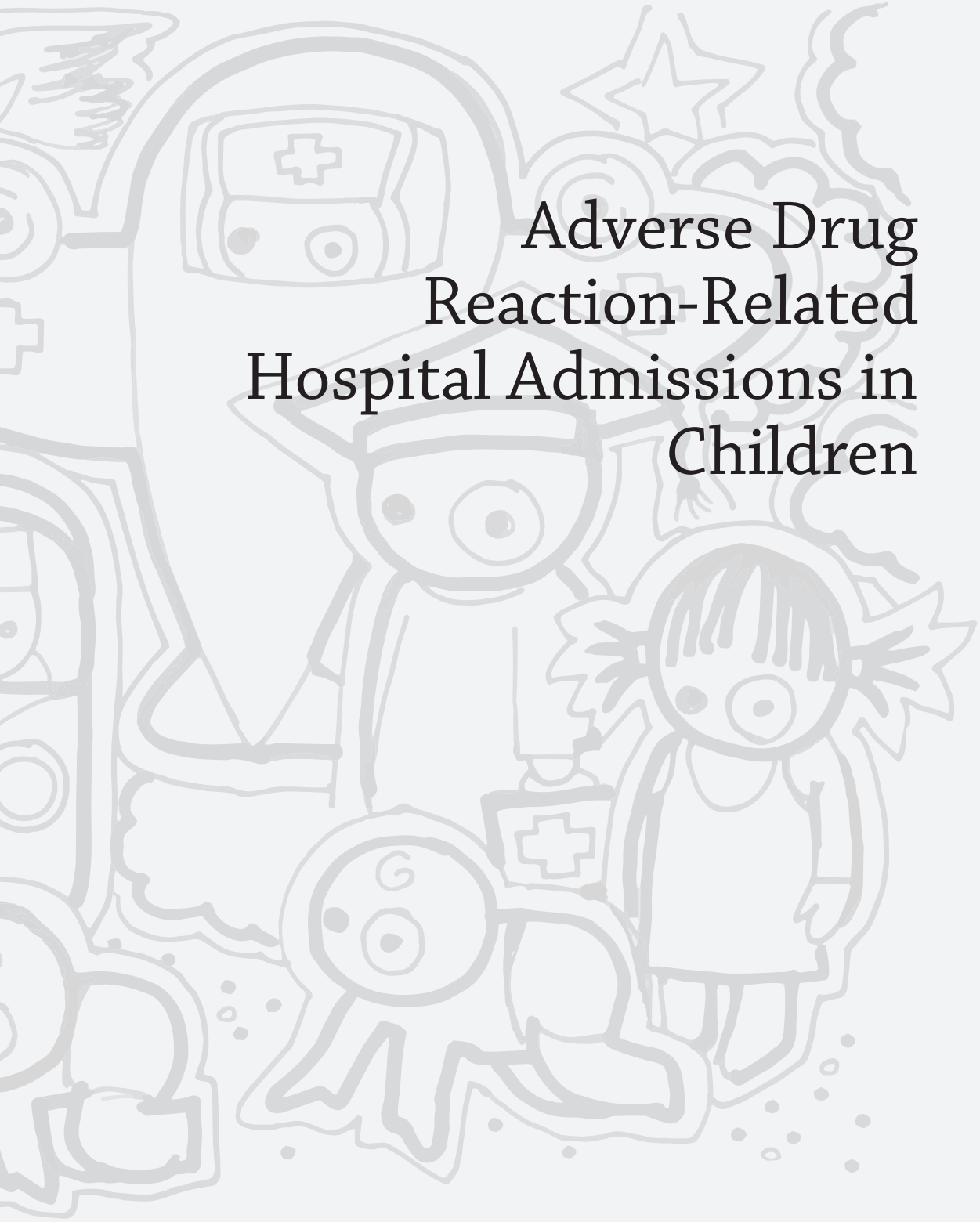

Adverse Drug Reaction-Related Hospital Admissions in Children

Abstract

Background

For many drugs there is a lack of information on efficacy and adverse drug reactions (ADRs) in children. Several authorities have taken measures to increase knowledge on this.

The aim of this study was to determine the extent of ADR-related hospital admissions in children, to reflect the importance of surveillance in this vulnerable patient group.

Methods

We performed a nationwide study of all hospital admissions in children and adolescents in the Netherlands (aged 0 to 20 years) between 2000 and 2005. Hospital admissions were evaluated within predefined age categories, sex and calendar-year. The most prominent drug groups leading to hospitalisation were determined. Risks of hospital admissions were calculated in relation to the total number of Dutch inhabitants and total number of drug prescriptions per age category.

Results

Of all acute admissions in children in the Netherlands, 0.75% (N=5,570) were attributed to an adverse drug reaction. The proportion of hospitalisations was highest in the youngest children, aged 0 to <2 years (169/100,000 children). The majority of the admissions in this age category was related to drug effects through placenta and breast milk and increased over the years. Most frequently involved drugs groups in general were 'antineoplastic and immunosuppressive drugs' (N=344), 'insulins and antidiabetic agents' (N=173), 'pertussis vaccine' (N=109), and 'penicillins' (N=70), with the youngest at highest risk. There were no consistent differences between boys and girls.

Conclusions

These results emphasize the importance of extra precaution regarding drug use in young children, during pregnancy and lactation of the mother.

Introduction

Drugs in children are often prescribed outside their licenced indications (off-label use).[11,125-127] Until recently, clinical trials in children were considered as unethical. For this reason, many drugs are not registered in this young age-group with respect to dosage, age, indication, or route of administration (unlicenced use). Off-label and unlicenced prescription rates in children range from 11-80% in general, with the highest proportion on neonatal wards.[9] The problem with off-label and unlicenced drug use in children is the fact that the drug was not appropriately evaluated before marketing. This may result in deficient information on the risks of the prescribed drugs which may lead to adverse drug reactions (ADRs).[5]

In 2003, the United States (US) changed legislation to improve drug safety in children. Since July 1st, 2007, the Paediatric Regulation has been implemented in the European Union (EU), focusing on registration and research (pre- and post-authorisation) of drugs in children.[14,128] Before registration of a new drug in the EU, the marketing authorisation holder should compose a 'paediatric investigation plan' (PIP) including details on their efforts to study efficacy, safety, dosage adaptations and administration routes of the particular drug in children. Furthermore, they should describe how they will assess post-marketing drug safety. For products not intended for the paediatric population, e.g. due to indication, a waiver or partial waiver can be granted. For medicinal products that are already off-patent a new type of marketing authorisation has been established: Paediatric Use Marketing Authorisation (PUMA). This PUMA is intended for the development of new paediatric formulations for generic drugs used in children. By completing this centralised application, and submitting study results on use in the paediatric population, the pharmaceutical company can benefit from 10 years market protection. The PIPs, waivers and PUMAs are assessed by the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). The Dutch legislation is even more restrictive. The act 'medical research involving human subjects' (WMO) requires negligible risks and minimal objections for medical research in children. [68,129]

The Paediatric Regulation and WMO are implemented to lead to lower the risk for ADRs in this vulnerable patient group. We conducted a nationwide study to investigate ADR-related hospital admissions in children and adolescents. In this study, we also took into account prescription data, age categories and sex.

Methods

Data sources

Data on hospital admissions were obtained from a Dutch nationwide registry of hospital discharges which contains patient characteristics, dates of admission and discharge, main diagnoses at discharge, secondary diagnoses and special codes indicating drug-related hospitalisations (E-codes) based on the ICD-9-CM coding system.[130] Characteristics of hospital admissions are registered by medical doctors on the basis of hospital discharge letters and coded by professional code clerks. The coding is independent of hospital or specialist. All diagnoses are submitted in the same format, mostly electronically. For this study, all patients between 0 to 20 years of age with an acute, non-planned admission to a Dutch hospital in the period between 2000 and 2005 were included. Numbers of residents in the Netherlands per calendar-year, sex and age were obtained from 'Statistics Netherlands'.[71]

Information on prescriptions was obtained from the database of the Dutch Foundation of Pharmaceutical Statistics (SFK), which includes information from 1,805 pharmacies in the Netherlands (92% of total). Data from this database were accessible on pharmacological subgroup level according to the Anatomical Therapeutic Chemical (ATC) classification system.[110] Prescription information was available per calendar-year for the predefined age categories: 0 to <2, 2 to <11 and 11 to 20 years. Per ATC group, the cumulative number of prescriptions was calculated.

Adverse drug reactions

An ADR-related hospital admission was defined as a hospital admission with an E-code between 930-950 as secondary diagnosis or a main diagnosis specifically indicating an ADR. E-codes are auxiliary to the main discharge diagnosis, indicating an ADR as the primary reason for admission. The E-code is indicative for the drug group involved in the ADR. E-codes referring to intended overdoses, errors in administration and therapeutic failure were not included in the analysis. Main diagnoses specifically indicating an ADR consisted of 15 separate codes: iatrogenic hypothyroidism (2443), polyneuropathy due to drugs (3576), toxic myocarditis (42293), shock due to anaesthesia (9954), encephalitis, myelitis, and encephalomyelitis following immunisation procedures (3235), drug-induced or radiation-induced myelopathy (3368), toxic hepatitis (5733), contact dermatitis and other eczema due to drugs and medicines in contact with skin (6923), dermatitis due to substances taken internally due to drugs and medicines (6930), drug reactions and intoxications specific to new-born (7794), noxious influenc-

es affecting fetus or newborn via placenta or breast milk caused by narcotics (76072), hallucinogenic agents (76073), anti-infectives (76074), other (76079), and other and unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered (9952).

Data analysis

ADR-related hospitalisations were identified in total and for separate age categories. Age categories were based on the classification of the available prescription data (0 to <2, 2 to <11, 11 to 20 years). For the initial analysis, the two highest categories were subdivided in two sub-categories to show more details of the effect of age (0 to <2, 2 to <7, 7 to <11, 11 to <16 and 16 to 20 years). The absolute number of ADR-related hospitalisations was determined separately for boys and girls, per age category, and per calendar-year. By age category, the most frequently occurring reactions were studied.

Second, we studied the specific drug groups most frequently causing ADRs, and we selected the ten drug groups related to the highest number of hospital admissions. In this analysis, we used three age categories: 0 to <2, 2 to <11 and 11 to 20 years of age. Proportions of ADR-related admissions were calculated per 100,000 residents and per 1,000 prescriptions. Relative risks (RRs) with 95% confidence intervals (95% CI) were calculated for the two youngest age categories compared to the highest age category, and for girls compared to boys. In the denominator, we used the total number of prescriptions in the study period. The information on prescriptions was combined with the data on hospitalisations based on drugs covered by the E-code.

Results

Within the study period, 740,280 hospital admissions were recorded for children and adolescents in the Netherlands. Of these admissions, 5,570 children (0.75%) were hospitalised due to an adverse drug reaction (ADR). Fifty percent of these children were boys (**table 5.1**). Four children died during hospital admission (aged 0, 14, 14 and 19 years).

The majority of adverse drug reactions occurred in the children aged 0-<2 years (N=4,112; 74%) and 16-20 years (N=511; 9%). In the lowest age category, the proportion of ADR-related admissions was 169/100,000 children. For the oldest children, the proportion was second highest: 11/100,000 children. In the middle age categories, numbers were more or less similar between boys and girls. Within the lowest and highest age categories, girls exceeded boys in number and proportion of ADR related admissions. The proportion of ADR-related admissions almost doubled over the years from 17 to 32 per 100,000 children (relative

Table 5.1 ADR-related hospital admissions stratified by age, sex and calendar-year

Age in years		Number of children N (%)	ADR-related admissions N (%)	ADR-related admissions / 100,000 children	RR (95% CI)
0-<2	Total	2,434,000	4,112	169	15.07 (14.47, 15.68)*
	Boys (%)	1,247,000 (51,2)	2,052 (50)	165	
	Girls (%)	1,187,000 (48,8)	2,060 (50)	174	
2-<7	Total	5,990,000	393	7	0.59 (0.53, 0.65) *
	Boys (%)	3,065,000 (51,2)	245 (62)	8	
	Girls (%)	2,925,000 (48,8)	148 (38)	5	
7-<11	Total	4,777,000	202	4	0.38 (0.33, 0.43) *
	Boys (%)	2,443,000 (51,1)	120 (59)	5	
	Girls (%)	2,334,000 (48,9)	82 (41)	4	
11-<16	Total	5,905,000	352	6	0.53 (0.48, 0.59) *
	Boys (%)	3,020,000 (51,1)	184 (52)	6	
	Girls (%)	2,885,000 (48,9)	168 (48)	6	
16-20	Total	4,557,000	511	11	*Ref*
	Boys (%)	2,334,000 (51,2)	190 (37)	8	
	Girls (%)	2,223,000 (48,8)	321 (63)	14	
All ages	Total	23,663,000	5,570	24	
	Boys (%)	12,109,000 (51,2)	2,791 (50)	23	
	Girls (%)	11,554,000 (48,8)	2,779 (50)	24	
Calendar-year					
2000		3,870,000	673	17	
2001		3,908,000	695	18	
2002		3,941,000	797	20	
2003		3,967,000	994	25	
2004		3,988,000	1,148	29	
2005		3,989,000	1,263	32	

*ADR=adverse drug reaction; RR=relative risk; ref=reference category. * statistical significant*

risk (RR) 1.88, 95% CI 1.05, 3.39).

The admissions for drug effects through the placenta or breast milk accounted for the majority of the ADR-related admissions (N=3,666 (89%)), all within the lowest age category (50% in boys). In 2000, the first year of the analysis 56% of the ADR-related admissions in children were due to drug effects through the placenta or breast milk, increasing to 72% in 2005. Of these, 7% was related to narcotics, 6% to hallucinogenic agents, and 2% was related to anti-infective agents; the majority of these ADRs was related to 'other' drugs. Within the separate age categories, 'antineoplastic and immunosuppressive drugs' and 'insulins and antidiabetic drugs' were the most frequently reported drugs (**table 5.2**).

The five classes with the largest number of admissions due to an ADR were 'primarily systemic agents' (N=402, 7.2%), 'hormones and systemic substitutes' (N=266, 4.8%), 'other and unspecified drugs and medicinal substances' (N=145, 2.6%), 'antibiotics' (N=124, 2.2%), and 'bacterial vaccines' (N=123, 2.2%). Following in this range of admissions, were 'analgesics, antipyretics and antirheumatics', 'psychotropic agents' and 'anticonvulsants and anti-Parkinsonism drugs'.

Within these drug classes, some drug groups caused the majority of reactions. For the five largest classes of admission-causing drugs, these were 'antineoplastic and immunosuppressive drugs' (86% of 402 admissions), 'insulins and antidiabetic agents' (65% of 266 admissions), 'unspecified drug or medicinal substance' (66% of 145 admissions), 'penicillins' (57% of 124 admissions), 'pertussis vaccine, including combinations with a pertussis component' (89% of 123 admissions).

Table 5.2 Most frequently reported drugs causing ADR-related hospital admissions

Age in years	Drug related to admission	N (% within age category)
0-<2 [A]	Pertussis vaccine	108 (26)
	Penicillin	26 (6)
	Thyroid	25 (6)
	Antineoplastic and immunosuppressive drugs	25 (6)
2-<7	Antineoplastic and immunosuppressive drugs	116 (33)
	Insulins and antidiabetic drugs	33 (9)
	Unspecified	25 (7)
	Anticonvulsants	20 (6)
7-<11 [B]	Antineoplastic and immunosuppressive drugs	57 (33)
	Insulins and antidiabetic drugs	37 (22)
	Unspecified	11 (6)
	Anticonvulsants	8 (5)
11-<16 [B]	Antineoplastic and immunosuppressive drugs	64 (23)
	Insulins and antidiabetic drugs	61 (22)
	Adrenal corticosteroids	12 (4)
	Anticonvulsants	12 (4)
16-20 [B]	Antineoplastic and immunosuppressive drugs	82 (19)
	Insulins and antidiabetic drugs	39 (9)
	Antirheumatics	33 (8)
	Penicillin	17 (4)

[A] ADR related admissions attributed to drug effects through placenta or breast milk (N=3,666) are not included in this table. Another large group of ADRs ('drug reaction and intoxication to the newborn'; N=57) is not included because information on related drugs was missing. Percentages are calculated without these admissions. [B] Drug groups causing the ADR 'toxic hepatitis' could not be included because of missing information on drugs related to the admission.

Table 5.3 Numbers and proportions for the ten drug groups most prominent in causing ADR-related hospital admissions.

	Total	0-<2 years			2-<11 years			11-20 years		
Drug group	N	N	N / 100,000 children	N / 1,000 prescrip.	N	N / 100,000 children	N / 1,000 prescrip.	N	N / 100,000 children	N / 1,000 prescrip.
Antineoplastic and immunosuppress drugs (L)										
Total	344	25	1.45	31.37	173	1.03	4.77	146	1.61	1.90
Boys	209	10	1.73	19.46	119	0.80	8.18	80	2.16	2.19
Girls	135	15	1.17	53.00	54	1.26	2.48	66	1.03	1.64
Insulins and antidiabetic drugs (A10)										
Total	173	3	0.73	2.26	70	0.12	1.00	100	0.65	0.44
Boys	88	2	0.73	2.63	37	0.16	1.01	49	0.67	0.42
Girls	85	1	0.74	1.77	33	0.08	0.99	51	0.63	0.46
Pertussis vaccine†										
Total	109	108	0.46	*n.a.*	1	4.44	*n.a.*	0	0.01	*n.a.*
Boys	66	66	0.55	*n.a.*	0	5.29	*n.a.*	0	0.00	*n.a.*
Girls	43	42	0.37	*n.a.*	1	3.54	*n.a.*	0	0.02	*n.a.*
Penicillins (J01C)										
Total	70	26	0.30	0.03	19	1.07	0.01	25	0.18	0.02
Boys	34	15	0.28	0.03	8	1.20	0.01	11	0.15	0.02
Girls	36	11	0.31	0.03	11	0.93	0.01	14	0.21	0.02
Other anticonvulsants (N03A)										
Total	66	14	0.28	0.87	28	0.58	0.12	24	0.26	0.07
Boys	33	6	0.27	0.65	17	0.48	0.13	10	0.31	0.06
Girls	33	8	0.29	1.16	11	0.67	0.11	14	0.21	0.09
Antirheumatics (M01+M02)										
Total	56	8	0.24	0.84	5	0.33	0.20	43	0.05	0.01
Boys	19	3	0.16	0.55	2	0.24	0.17	14	0.04	0.01
Girls	37	5	0.32	1.15	3	0.42	0.23	29	0.06	0.02
Anti-allergic / anti-emetic drugs (A04A+R06A)										
Total	51	9	0.22	0.08	22	0.37	0.02	20	0.20	0.01
Boys	20	4	0.17	5.61	10	0.32	0.29	6	0.18	0.59
Girls	31	5	0.27	15,97	12	0.42	0.51	14	0.23	1.00
Adrenal corticosteroids (H02A/B)										
Total	34	3	0.14	0.54	8	0.12	0.13	23	0.07	0.10
Boys	21	1	0.17	0.45	5	0.08	0.10	15	0.09	0.10
Girls	13	2	0.11	0.71	3	0.17	0.18	8	0.06	0.10
Other antibiotics (J01X)										
Total	34	9	0.14	0.77	12	0.37	0.16	13	0.11	0.10
Boys	17	5	0.14	0.45	6	0.40	0.65	6	0.11	2.05
Girls	17	4	0.15	1.19	6	0.34	0.07	7	0.11	0.03
Thyroid and derivatives (H03A/B)										
Total	27	25	0.11	4.45	2	1.03	0.06	0	0.02	*n.a.*
Boys	14	12	0.12	4.64	2	0.96	0.14	0	0.04	*n.a.*
Girls	13	13	0.11	4.28	0	1.10	*n.a.*	0	0.00	*n.a.*

N.a.=not applicable; absence of cases in the reference category; † Complete prescription data of this vaccine were not available; administration of this vaccine is part of the National Vaccination Program. N=number; Prescrip.=prescriptions.

For the ten most prominent drug groups, most of the proportions of ADR-related admissions were highest in the middle age category, except for 'antineoplastic and immunosuppressive drugs' and 'insulins and antidiabetic drugs' (**table 5.3**). Taking into account the total number of prescriptions within the certain drug groups, the youngest age category was at the highest risk to be admitted to a hospital due to an ADR compared to the oldest children (**table 5.4**). Risks for boys and girls showed large overlap within the different drug groups. However, the risk to be hospitalised due to an ADR related to 'antineoplastic and immunosuppressive drugs' was remarkably high in girls in the youngest age category, compared with both older children and boys (RR 16.53 (95% CI 10.88, 25.11) and RR 2.72 (95% CI 1.24, 5.98), respectively).

Hypoglycaemia, due to 'insulins and antidiabetic drugs', accounted for the majority of admissions (**table 5.5**). For 'antineoplastic and immunosuppressive drugs' the most frequent ADR was neutropenia. Adverse drug reactions due to anticonvulsants were mainly poisoning or unspecified drug reactions. Of the specified reactions, penicillin most frequently caused dermatitis as a reason for hospital admission; most frequent reactions following pertussis vaccine were syncope/collapse and convulsions. Although the number of hospital admissions related to ADRs attributed to pertussis vaccine was relatively high overall, these numbers decreased over the years from 30 admissions in 2000 to 2 admissions in 2005.

Discussion

Our study showed the variety of adverse drug reaction (ADR)-related hospital admissions in children and adolescents in the Netherlands over a six-year period. As far as we are aware, this is the first study in which ADRs are combined with prescription data on a national basis.

In the current study, we showed that ADRs accounted for 0.75% of all paediatric hospital admissions in the period between 2000 and 2005. This is somewhat lower than expected from the literature. A review and meta-analysis from 2001 showed a range from 0.59 to 4.1% of incident ADRs leading to paediatric hospital admissions with a weighted average of the five studies of 2.09% (95% CI 1.02, 3.77).[131] A more recent literature review showed an admission rate between 0.6 and 6% of hospitalisations due to ADRs, with a weighted average of 1.8% (95% CI 0.4, 3.2).[12] These differences can partly be explained by differences in study design of the studies included in the analysis, e.g. lower number of hospitals included, shorter study period and/or broader definition of the outcome. Besides, other factors can contribute to variation in the proportion of ADR related hospital admissions like time and age, the type of drugs and sex, which we will discuss below. The passive coding of ADR relatedness (non-mandatory E-codes) of the admission diagnosis at discharge is most probably responsible for an underestimation of the cumulative incidence of ADR related admissions.

Table 5.4 Relative risks for ADR related hospital admissions relative to the total number of prescriptions.

a. Relative risks by age (11-20 years as reference category)

Drug group (ATC group)	Age 0-<2 years RR (95% CI)	Age 2-<11 years RR (95% CI)	Age 11-20 years
Antineoplastic and immunosuppressants (L)	16.53 (10.88, 25.11) *	2.51 (2.02, 3.13) *	*ref*
Insulins and antidiabetic drugs (A10)	5.17 (1.64, 16.28) *	2.29 (1.68, 3.10) *	*ref*
Pertussis vaccinea	*n.a.*	*n.a.*	*n.a.*
Penicillins (J01C)	1.37 (0.79, 2.37)	0.33 (0.18, 0.59) *	*ref*
Other anticonvulsants (N03A)	12.33 (6.38, 23.83) *	1.67 (0.97, 2.89)	*ref*
Antirheumatics (M01+M02)	58.04 (26.44, 127.44) *	13.87 (7.57, 25.40) *	*ref*
Anti-allergic / anti-emetic drugs (A04A+R06A)	5.96 (2.72, 13.10) *	1.41 (0.77, 2.59)	*ref*
Adrenal corticosteroids (H02A/B)	5.38 (2.30, 12.58) *	1.29 (0.59, 2.84)	*ref*
Other antibiotics (J01X)	7.99 (2.40, 26.60) *	1.62 (0.72, 3.62)	*ref*
Thyroid and derivatives (H03A/B)	*n.a.*	*n.a.*	*n.a.*

b. Relative risks by sex (boys as reference category)

Drug group (ATC group)	Girls versus Boys RR (95% CI)	Girls versus Boys RR (95% CI)	Girls versus Boys RR (95% CI)
Antineoplastic and immunosuppress drugs (L)	2.72 (1.24, 5.98) *	0.30 (0.22, 0.42) *	0.75 (0.54, 1.04)
Insulins and antidiabetic drugs (A10)	0.67 (0.06, 7.39)	0.98 (0.61, 1.57)	1.09 (0.74, 1.61)
Pertussis vaccine[a]	*n.a.*	*n.a.*	*n.a.*
Penicillins (J01C)	0.97 (0.45, 2.11)	1.42 (0.57, 3.54)	0.99 (0.45, 2.18)
Other anticonvulsants (N03A)	1.78 (0.62, 5.12)	0.84 (0.39, 1.79)	1.57 (0.70, 3.53)
Antirheumatics (M01+M02)	2.10 (0.57, 7.83)	1.36 (0.59, 3.16)	1.23 (0.47, 3.21)
Anti-allergic / anti-emetic drugs (A04A+R06A)	2.49 (0.59, 10.40)	1.86 (0.31, 11.15)	1.52 (0.80, 2.87)
Adrenal corticosteroids (H02A/B)	1.59 (0.43, 5.93)	1.77 (0.57, 5.49)	1.03 (0.35, 3.06)
Other antibiotics (J01X)	2.64 (0.24, 29.13)	0.11 (0.03, 0.44) *	0.02 (0.01, 0.04) *
Thyroid and derivatives (H03A/B)	0.92 (0.42, 2.01)	*n.a.*	*n.a.*

*n.a.=not applicable; absence of cases in the reference category; [a]Complete prescription data of this vaccine were not available; administration of this vaccine is part of the National Vaccination Program; *Statistically significant. Ref=reference category*

Time and age

An increase in the proportion of ADR-related admissions was present over time, mainly contributed by an increase in ADRs related to drug effects through the placenta and breast milk in the youngest children. Drug use during pregnancy is of high concern and therefore, pregnancy prevention programs (PPPs) have been implemented for certain teratogenic drugs to prevent pregnancies dur-

ing use. The effect of these programs is however questioned.[132-134] The relatively high proportion of ADRs in children due to drug use of the mother instead of the child, was also seen by a study in the FDA's Adverse Event Reporting System (AERS).[135] Although a notable proportion of these effects were due to narcotics, hallucinogenic agents and anti-infective agents, in the majority of cases the type of drugs was not appointed and marked as 'other drugs' (85%). This could either indicate the involvement of different drugs or the lack of specification in the coding system. Although the administration of drugs during pregnancy cannot always be circumvented, the proportion of ADR-related admissions in children related to maternal causes is high and requires extra attention.

Besides hospital admissions related to these maternal drug effects, admission rates in the youngest children were highest compared to the other age categories. This suggests that either the youngest children are more prone to develop ADRs requiring hospitalisation, or ADRs are more frequently recognised for

Table 5.5 Most frequent ADRs per drug group leading to hospitalisation, accounting for minimal 50% of admissions per drug group (max 4).

Drug Group	Adverse Drug Reaction	N
Antineoplastic and immunosuppressive drugs (N=344)	Neutropenia	100
	Fever	63
	Aplastic anemia	57
Insulins and antidiabetic drugs (N=173)	Hypoglycemia	131
Pertussis vaccine (N=109)	Syncope/collaps	32
	Unspecified	23
	Convulsion	14
Penicillins (N=70)	Unspecified	20
	Dermatitis	17
Anticonvulsants (other) (N=66)	Poisoning	16
	Unspecified	13
	Effects via placenta or breast milk	5
Antirheumatics (N=56)	Poisoning	18
	Other adverse effect	12
Anti-allergic / anti-emetic drugs (N=51)	Poisoning	17
	Other adverse effect	10
	Unspecified pyramidal disease	5
Adrenal corticosteroids (N=34)	Corticoadrenal insufficiency	5
	Diabetes with unspecfied complications	4
	Cushing's syndrome	3
	Fetus affected by drug use	3
Antibiotics (other) (N=34)	Other adverse effect	10
	Dermatitis	8
Thyroid and derivatives (N=27)	Fetus affected by drug use	24

Results are shown for the ten most prominent drug groups in causing ADR-related hospital admissions

these children. Our results are consistent with the literature; an increased risk of ADR-related admissions in children under 12 months of age, relatively to other ages, was shown previously in a study by Kramer *et al*.[136]

The relatively higher frequency and risk of ADR-related hospital admissions, relative to the number of prescriptions, in the youngest children within our study can be explained by several factors. First of all, pharmacokinetics and pharmacodynamics are age-dependent and the largest differences with adults exist in this youngest age category.[137] Due to these differences young children are more prone to develop ADRs. Second, young children are more likely to experience medication and dosing errors since formulations of many drugs are not suitable for young children. It is known that this leads to a higher frequency of ADRs and also more severe ADRs.[138] Third, it is assumed that off-label use is related to a higher frequency of ADRs[7,139] and off-label drug use is highest in the youngest children.[9,11] Our results emphasize that in the youngest children more effort and research is necessary to limit the off-label use and stimulate development of proper paediatric formulations and precautions.

Type of drugs

As also shown by others, the drug groups most frequently accounting for the ADR-related admissions in our study were antineoplastic and immunosuppressive drugs.[140] This is not surprising in view of their toxicity and the indications for which these drugs are used. Antimicrobial drugs and anticonvulsants, the fourth and fifth causing drug groups within this study, were in the top five of causative drugs in other studies as well.[140-142]

We found a large contribution of pertussis vaccine to the ADR-related admissions. Pertussis vaccination has been part of the Dutch National Vaccination Programme since 1952 with a vaccination coverage of approximately 96%.[143] Since 1996, there has been an increase in number of pertussis cases within the Netherlands, especially in children under the age of 3 months.[144] Effectivity of the vaccine had decreased due to adaptation of and increased toxin production by the *B. pertussis* strains.[145] In 1999, a change in the vaccination programme resulted in administration of the first four vaccines a month earlier than usual.[146] This might have led to increased awareness in the beginning of this period, leading to increased reporting of a possible ADR as a cause for hospital admission. The number of pertussis-vaccine-related hospital admissions decreased over the study period. In 2005, a non-cellular vaccine was introduced, which was expected to be more effective and to have a lower risk for ADRs.[146]

Sex differences

Differences in ADR-related hospital admissions between boys and girls have been described in previous studies, though results are conflicting.[136,147,148]

The results from our study suggest that girls are more frequently involved in ADR-related admissions in the lowest and highest age categories, whereas the proportion of ADR-related admissions in the middle age categories is comparable between the sexes. The main difference between boys and girls was seen in the 'antineoplastic and immunosuppressive drugs'. Possibly, pharmacokinetic differences at young age also play a role in this difference.[137,149]

Strengths and limitations

One of the strengths of our study is the availability of nationwide data on discharge diagnoses of all hospitalisations over a six-year period. Data on drug use were also available for the same period, which illustrated the use of the various drugs as a background of ADR occurrence. Our study did not cover the years after implementation of the new European legislation, which made it impossible to study its direct effect on drug safety. Data on drug use were not discernible on an individual basis, so we were unable to match these with the ADR related hospitalisations. Therefore, interaction between the various drugs could not be studied. Although adjustment for age was done in the first analysis, this was not possible in the analysis with total drug prescriptions. Another limitation is the different coding systems used by the two databases in our study. Because of the passive coding of ADR relatedness of the admission diagnosis at discharge, the cumulative incidence of ADR related admissions is probably underestimated. However, this underestimation is probably the same for all age categories and for different sexes and will not influence the relative risks.

Conclusions

Adverse drug reactions accounted for 0.75% of all paediatric hospital admissions in the period between 2000 and 2005. The risk of ADR related hospital admissions was highest in the youngest children in comparison to the older children. Drug effects through placenta and breast milk contributed the largest part to the total number of admissions, affecting the youngest children. Differences between boys and girls in ADR-related admissions do exist, but definitive conclusions cannot be drawn from this study.

From a regulatory perspective, these results emphasize the importance of surveillance of safe drug use in children. Drug use in the youngest children and use during pregnancy and lactation might require extra precaution.

Chapter 6

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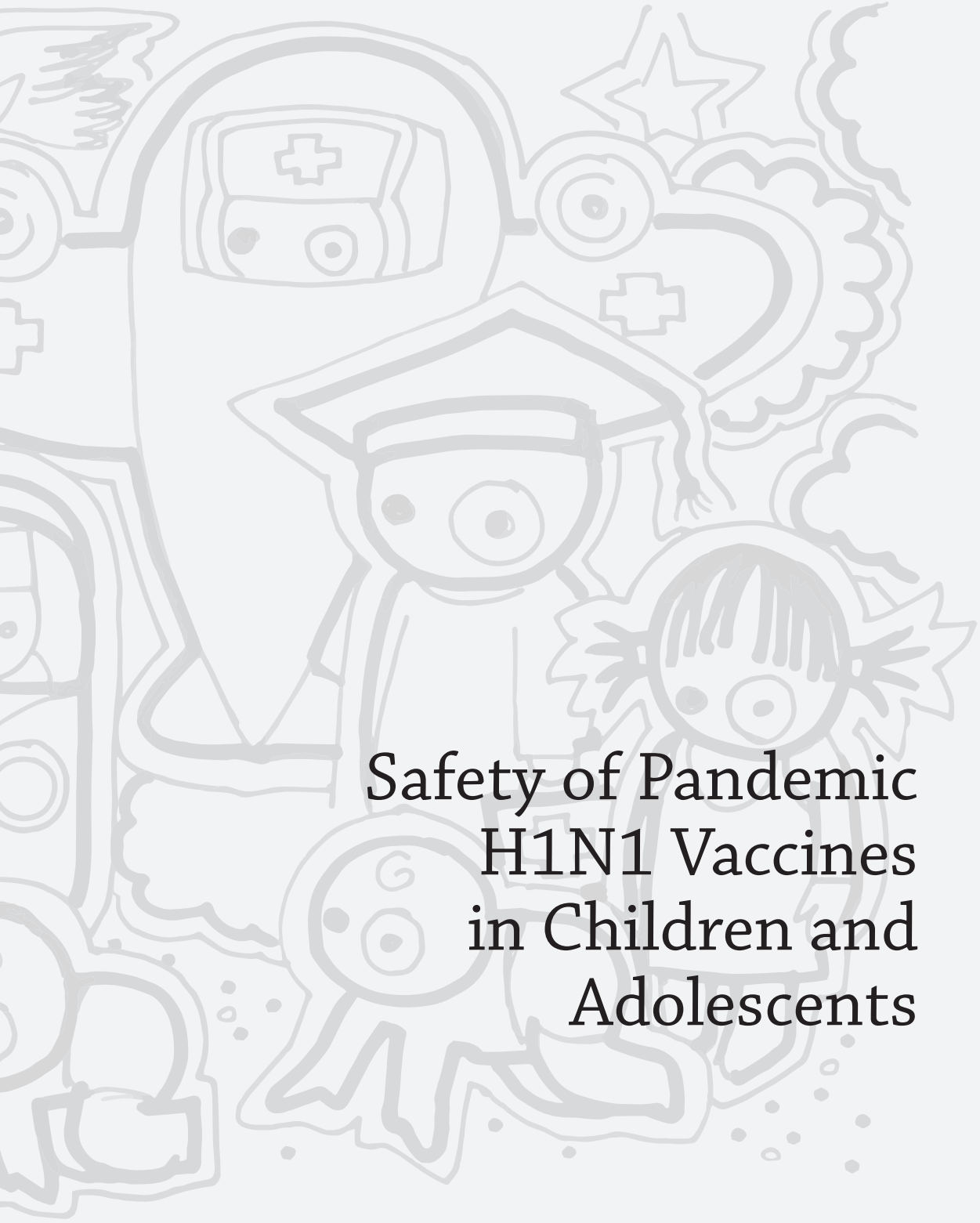

Safety of Pandemic H1N1 Vaccines in Children and Adolescents

Abstract

During the 2009 influenza A (H1N1) pandemic several pandemic H1N1 vaccines were licenced using fast track procedures, with relatively limited data on the safety in children and adolescents. Different extensive safety monitoring efforts were put in place to ensure timely detection of adverse events following immunisation. These combined efforts have generated large amounts of data on the safety of the different pandemic H1N1 vaccines, also in children and adolescents. In this overview we shortly summarise the safety experience with seasonal influenza vaccines as a background and focus on the clinical and post marketing safety data of the pandemic H1N1 vaccines in children. We identified 25 different clinical studies including 10,505 children and adolescents, both healthy and with underlying medical conditions, between the ages of 6 months and 23 years. In addition, large monitoring efforts have resulted in large amounts of data, with almost 13,000 individual case reports in children and adolescents to the WHO. However, the diversity in methods and data presentation in clinical study publications and publications of spontaneous reports hampered the analysis of safety of the different vaccines. As a result, relatively little has been learned on the comparative safety of these pandemic H1N1 vaccines - particularly in children. It should be a collective effort to give added value to the enormous work going into the individual studies by adhering to available guidelines for the collection, analysis, and presentation of vaccine safety data in clinical studies and to guidance for the clinical investigation of medicinal products in the paediatric population. Importantly the pandemic has brought us the beginning of an infrastructure for collaborative vaccine safety studies in Europe, the United States and globally.

Introduction

In the course of the 2009 influenza A (H1N1) pandemic, different pandemic H1N1 vaccines were made available to children and adolescents across the world at an unprecedented scale and speed. Several pandemic H1N1 vaccines were developed to mitigate the impact of the pandemic. All were based on the same isolate influenza A/California/7/2009 (H1N1)v. However, vaccines differed in the methods for virus propagation, purification, and inactivation, as well as antigen preparation, the amount of antigen in the vaccine, the presence and type of adjuvants, and the presence of other excipients. Most pandemic H1N1 vaccines were found to elicit a sufficient immune response after one dose for (healthy) persons aged 10 years and above. For children between 6 months and three years of age a second dose was recommended, and for some vaccines a second dose was also recommended for children between three and nine years of age.[150] Following official recommendations from the World Health Organisation (WHO),[151] Centers for Disease Control (CDC),[152] the European Union (EU)[153] and national health authorities, children in most countries were amongst the target groups of pandemic H1N1 vaccination campaigns. In some countries only children with underlying co-morbidities were targeted, in other countries also healthy children with or without age restrictions were vaccinated.[154]

Adjuvanted and non-adjuvanted monovalent pandemic H1N1 vaccines had been licenced in 2009 through fast track procedures in order to ensure availability.[155,156] Due to this fast track authorisation process, only limited safety data was available prior to wide spread distribution. The non-adjuvanted H1N1 vaccines were expected to have a similar safety profile to the well-established non-adjuvanted seasonal influenza vaccines for all age categories.[157,158] However in many countries in Europe and in Canada pandemic H1N1 vaccines with oil-in-water adjuvants (AS03, MF59) were used, also in children. At the time vaccination campaigns started, clinical data on these pandemic H1N1 vaccines in children was very limited. The safety profile for these vaccines was mostly based on non-clinical testing and on data derived from clinical studies with avian influenza mock-up vaccines, in addition to experience with an MF59 adjuvanted vaccine for over a decade in elderly in Italy.[155,159,160]

Due to the scale and scope of the pandemic H1N1 vaccination campaigns and the paucity of safety data, a stringent risk management plan including the capacity for early detection of adverse events was essential. Extensive monitoring of the safety of the vaccines was put in place through boosting of existing national and international passive surveillance systems (e.g. EudraVigilance, World Health Organisation-Uppsala Monitoring Centre (WHO-UMC), United States' (US) Vaccine Adverse Events Reporting System (VAERS), Canadian Adverse Events Following Immunisation Surveillance System (CAEFISS) and Immunisation Monitoring Program ACTive (IMPACT), and the Australian Adverse Drug Reactions System

(ADRS)) and through new active surveillance activities in the US and the EU.[161,162] Adverse events of special interest (AESIs), listed by the Committee for Human Medicinal Products (CHMP) in Europe and the Food and Drug Administration (FDA), included neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome (GBS), Bell's palsy, demyelinating disorders, and laboratory-confirmed vaccination failure. In the US, the FDA and Centers for Disease Control and Prevention (CDC) conducted active surveillance for the 2009 pandemic H1N1 vaccines through the newly established Post-Licensure Rapid Immunisation Safety Monitoring (PRISM) project and the existing Vaccine Safety Datalink (VSD).[162] Under the auspices of WHO, a global study was initiated on the association between pandemic H1N1 vaccines and GBS. The European Centre for Disease Prevention and Control (ECDC) funded the Vaccine Adverse Event Surveillance & Communication (VAESCO) project to investigate the background rates of AESIs and the association between pandemic H1N1 vaccines and GBS in European countries.[163]

The different passive and active surveillance efforts generated large amounts of information on the safety of the pandemic H1N1 vaccines, including in children. In this overview we shortly summarise the safety experience with seasonal influenza vaccines as a background and focus on the clinical and post marketing safety data of the pandemic H1N1 vaccines in children. Although the monovalent pandemic H1N1 vaccines are not expected to be used again on a large scale any time soon, the safety of these vaccines may have wider implications for the use of (adjuvanted) influenza vaccines in children, and lessons can be learned for future safety monitoring efforts in mass vaccination campaigns.

To find data on the safety of pandemic H1N1 vaccines in children we searched Pubmed using the MESH term [influenza vaccines] which was subsequently limited to 'All child (0-18 years)' and to articles published in the past three years. Further publications were derived from reference lists of identified articles and unpublished data was sought specifically to identify clinical studies, post marketing studies and case reports with data on the safety of pandemic H1N1 vaccines in children. In addition we searched websites of national health authorities and international health and regulatory organisation.[164-167]

Background: experience with seasonal influenza vaccines in children

Existing evidence on traditional trivalent inactivated vaccines shows that these vaccines are generally well tolerated, with a minority of recipients reporting mild transient systemic reactions such as fever, malaise and myalgia.[157,168-175] Systemic symptoms mostly occur in young children (6 months – 3 years). This may be related to the first exposure to the viral antigens as part of the vaccine.[172] In a review of the safety of trivalent inactivated vaccines in children under 2 years

from VAERS, the most frequently reported adverse events were fever, rash, injection-site reactions and febrile seizures.[176] A signal related to febrile seizures in young children following trivalent inactivated vaccines as detected in VAERS was not confirmed in further studies.[177] Live attenuated influenza vaccines have been found to be equally safe as inactivated influenza vaccines in children. However, in infants and toddlers under the age of 2 years an increase in wheezing or reactive airway disease occurred in association with live attenuated influenza vaccines. Therefore, the use has been restricted to children over 2 years, and not recommended for children between 2 and 3 years with asthma or with recurrent wheezing.[178-182]

Serious adverse reactions following seasonal influenza vaccination are rare,[170,174,183] and include (febrile) seizures, anaphylaxis, exacerbation or new onset of asthma, GBS, oculo-respiratory syndrome (ORS) and Bell's palsy.[174,176,184-187]

Safety of pandemic H1N1 vaccines in children: data from clinical studies

The safety data of inactivated influenza vaccines coming from clinical studies focus mostly on solicited and unsolicited local and systemic reactions, as other vaccine related adverse events are uncommon and clinical studies are generally too small to detect rare adverse events. Consequently, this section will mostly concentrate on the reactogenicity of the different vaccine formulations.

We identified 15 publications in peer reviewed journals regarding 13 clinical studies of different pandemic H1N1 vaccines which reported safety data in healthy children.[188-203] An overview of these studies is given in **table 6.1**.

Monovalent non-adjuvanted inactivated pandemic H1N1 vaccines

In total, nine publications on seven clinical studies were identified that reported data on the safety of monovalent inactivated pandemic H1N1 vaccines in healthy children.[188-193,196-198] These studies were conducted in Australia, China (N=2), Costa Rica, Korea, Taiwan and the US. Each study evaluated two doses with varying amounts of antigen. In total, the identified studies included 6,511 children between 6 months and 18 years of age who were exposed to inactivated split or subunit pandemic H1N1 vaccines. In none of the studies vaccine related serious adverse events, deaths or AESIs were reported.

All studies, except Liang *et al*., recorded events over a period of 7 days following vaccination and all studies examined two doses. There was, however, little consistency between studies regarding event definition and event types recorded.

Table 6.1 Overview of clinical studies evaluating pandemic H1N1 vaccines in children

Authors	Study type	Blinding	Random allocation	Registration	Country	Type of vaccine	Ages	N	Amount of antigen
Zhu *et al.* 2009 [192]	Placebo controlled	Double	Yes	NCT00975572	China	inactivated, split, AL adjuvanted	3y-17y	550	7.5 µg /15 µg /30 µg
						inactivated, split	3y-17y	440	15 µg / 30 µg
Arguedas *et al.* 2010 [197,198]	Parallel intervention	Open	Yes	NCT00973700	Costa Rica	MF59 adjuvanted egg based	3y-17y	108	7.5 µg
						Inactivated subunit	3y-17y	279	15 µg / 30 µg
Carmona *et al.* 2010 [202]	Parallel intervention	Open	Yes	NCT00971321	Spain	AS03 adjuvanted	6m-35m	104	1.9µg
							6m-35m	53	3.75µg
Liang *et al.* 2010 [196]	Parallel intervention	Double	Yes	NCT00956111/ NCT00975572*	China	inactivated, split	3y-18y	4572	7.5 µg /15 µg /30 µg
						inactivated, split AL adjuvanted	3y-18y	844	7.5 µg /15 µg /30 µg
Lu *et al.* 2010 [189]	Single intervention	Open	No	none	Taiwan	inactivated, split	1y-17y	180	7.5 µg / 15 µg
Mallory *et al.* 2010 [203]	Placebo controlled	Double	Yes	NCT00946101	United States	Live Attenuated	2-17y	259	10 e^7 FFU
Nolan *et al.* 2010 [193]	Parallel intervention	Single	Yes	NCT00940108	Australia	inactivated, split	6m-9y	369	15 µg / 30 µg
Oh *et al.* 2010 [188]	Single intervention	Open	No	none	Korea	inactivated, split	6m-18y	248	7.5 µg / 15 µg
Waddington *et al.* 2010 [194,195]	Parallel intervention	Open	Yes	NCT00980850	United Kingdom	Whole virion	6m-12y	466	7.5 µg
						AS03 adjuvanted	6m-12y	451	1.9µg
Yasuda *et al.* 2010 [199]	Parallel intervention	Single	Yes	NCT01000207	Japan	MF59 adjuvanted cell based	6m-19y	120	3.75µg / 7.5 µg
Garcia-Sicilia *et al.* 2011 [200]	Single intervention	Open	No	NCT00964158	Spain	AS03 adjuvanted	3y-17y	239	1.9µg
Garcia-Sicilia *et al.* 2011 [200]	Single intervention	Open	No	NCT00972517	Germany	AS03 adjuvanted	3y-17y	202	3.75µg
Plennevaux *et al.* 2011 [190,191]	Placebo controlled	Single	Yes	NCT00952419	United States	inactivated, split	6m-9y	423	7.5 µg / 15 µg
Scheifele *et al.* 2011 [201]	Parallel intervention	Single	Yes	NCT01000831	Canada	AS03 adjuvanted	6-35m	167	1.9µg

** of the 10 sites included 2 were registered at clinicaltrials.gov*

Lu *et al.* [189] is the only study reporting 'nasal congestion' with inactivated vaccines and reported this as the most common systemic reaction in all age categories. Liang *et al.* considered a body temperature of 37.1°C as fever, whilst other studies reported fever as a body temperature ≥38°C, and Plennevaux *et al.* only reported fever above ≥39.5°C for children up to two years of age and ≥39.0°C for older children. Moreover, studies were inconsistent in the age categories used to present their results. Because of the methodological differences between studies and the heterogeneity of safety reporting, comparisons of the frequency of reactogenicity to vaccination can only reliably be made within studies.

Two of the identified studies were placebo controlled studies.[190,196] Plennevaux *et al.* did not detect differences in reactogenicity between the inactivated pandemic H1N1 vaccine and placebo. Conversely, Liang *et al.* observed increased reactogenicity associated with the vaccine as compared to the placebo. The absolute reactogenicity in this study was lower than in the study of Plennevaux *et al.* This may possibly be due to the shorter observation period (3 days compared to 7 days) in the study by Liang *et al.*

Two studies detected higher reactogenicity associated with the first dose,[190,196] three studies did not find noticeable differences between the first and second dose[188,189,193] and one study found an increased reactogenicity associated with the second dose.[192]

The frequency of events per age category across studies ranged significantly. Local reactions were reported by 27% to 54% of children between 6 months and 3 years, by 15% to 61% of children between 3 and 12 years old and by 13% to 36% of children between 9 and 18 years old, dependent on the study. Systemic reactions following the first dose were reported in 31% to 58%, 17% to 35% and 16% to 58% of children respectively. This may also be due to differences in study methodology and data presentation.

Not all studies reported all local or systemic reactions per age category.[192,193,196] Zhu *et al.* [192] evaluated the effect of age on the safety of the vaccine, and found higher systemic reactogenicity for adolescents (12-17 years) as compared to children (3-11 years). However, they did not present numbers or types of reactions per age category. No clear effect of age was seen by Liang *et al.*[196] Other studies did not compare the reactogenicity between age categories.

None of the studies specifically evaluating the amount of antigen in the vaccine found either an increased or decreased reactogenicity with increasing amounts of antigen per dose.[190,192,193] The results from Liang *et al.* do point towards an increase in reactions with antigen dose. Unfortunately this data was not reported separately for children. Lu *et al.* reported increased pain at injection site associated with the 15µg formulation as compared to the 7.5µg formulation. However, the 7.5µg was given to children at 1 to 2 years of age whilst only older children received the 15

Table 6.2 Results of clinical studies evaluating (oil-in-water) adjunvanted pandemic H1N1 vaccines in children

Reference	Vaccine	Age	N	Antigen content	Solicited local adverse events			Solicited systemic adverse events			
					Total % reported after 1st dose	Pain after 1st dose	Pain after 2nd dose	Total % reported after 1st dose	Fever definition	Fever after 1st dose	Fever after 2nd dose
MF59 ADJUVANTED											
Yasuda *et al.* 2010 [199]	MF59 adj. cell based	6m-35m	10	3.75µg	*NR*	-	-	*NR*	≥38.0°C	10%	30%
	MF59 adj. cell based	6m-35m	11	7.5 µg	*NR*	-	-	*NR*	≥38.0°C	18%	18%
	MF59 adj. cell based	3y-19y	50	3.75µg	*NR*	64%	65%	*NR*	≥38.0°C	8%	2%
	MF59 adj. cell based	3y-19y	51	7.5 µg	*NR*	82%	63%	*NR*	≥38.0°C	10%	6%
Arguedas *et al.* 2010 [197,198]	MF59 adj. egg based	3y-8y	55	7.5 µg	25%	21%	15%	24%	≥38.0°C	*NR*	*NR*
	Inactivated subunit	3y-8y	84	15 µg	31%	25%	27%	28%	≥38.0°C	*NR*	*NR*
	Inactivated subunit	3y-8y	54	30 µg	20%	17%	16%	17%	≥38.0°C	*NR*	*NR*
	MF59 adj. egg based	9y-17y	53	7.5 µg	37%	32%	27%	24%	≥38.0°C	*NR*	*NR*
	Inactivated subunit	9y-17y	84	15 µg	36%	30%	30%	36%	≥38.0°C	*NR*	*NR*
	Inactivated subunit	9y-17y	57	30 µg	29%	25%	26%	16%	≥38.0°C	*NR*	*NR*
AS03 ADJUVANTED											
Carmona *et al.* 2010 [202]	AS03 adjuvanted	6m-35m	104	1.9µg	45%	36%	41%	*NR*	≥37.5°C	20%	67%
		6m-35m	53	3.75µg	50%	*NR*	*NR*	*NR*	≥37.5°C	*NR*	*NR*
Garcia-Sicilia *et al.* 2011 [200]	AS03 adjuvanted	3-5y	59	1.9µg	*NR*	66%	*NR*	*NR*	>37.5°C	*NR*	*NR*
		6-9y	63	1.9µg	*NR*	*NR*	*NR*	*NR*	>37.5°C	*NR*	*NR*
		10-17y	117	1.9µg	*NR*	*NR*	*NR*	*NR*	>37.5°C	*NR*	*NR*
		3-5y	53	3.75µg	*NR*	91%	*NR*	*NR*	>37.5°C	26%	50%
		6-9y	56	3.75µg	*NR*	*NR*	*NR*	*NR*	>37.5°C	*NR*	*NR*
		10-17y	93	3.75µg	*NR*	*NR*	*NR*	*NR*	>37.5°C	*NR*	*NR*
Scheifele *et al.* 2011 [201]	AS03 adjuvanted	6-35m	167	1.9µg	47%	44%	32%	*NR*	≥38.5°C	4%	9%
Waddington *et al.* 2010 [194,195]	AS03 adjuvanted	6m-5y	278	1.9µg	2%¥	31%	39%	5%*	≥38.0°C	9%	22%
	AS03 adjuvanted	5-12y	181	1.9µg	7%¥	75%	71%	3%*	≥38.0°C	8%	6%
	Whole virion cell culture	6m-5y	279	7.5 µg	0%¥	18%	17%	4.3%*	≥38.0°C	9.3%	12.5%
	Whole virion cell culture	5-12y	187	7.5 µg	1%¥	40%	42%	1.7%*	≥38.0°C	3.3%	2.9%

*NR = not reported; adj.=adjunvanted. * Only % with severe reactions reported.*

µg formulation and the expression of pain is subject to age specific differences. Considering the reactogenicity reported in the studies for inactivated non-adjuvanted pandemic H1N1 vaccines, no clear pattern of an age, dose or antigen related effect emerges. Overall, little can be concluded on the available data, besides that no alarming safety issues for the monovalent inactivated pandemic H1N1 vaccines have emerged from clinical studies. The limited comparability of pre-licensure vaccine safety data from published studies is a missed opportunity given that the issue is known, standardised case definitions and guidelines for data collection, analysis, and presentation are available for adverse events following immunisation (AEFI) of interest related to influenza vaccines and their use is recommended by regulatory authorities.[204-207]

Live attenuate pandemic H1N1 vaccines

One study was identified that evaluated a live attenuated pandemic H1N1 vaccine in children.[203] Mallory *et al.* randomised 326 children aged 2 to 17 years to either live attenuated pandemic H1N1 vaccine (N=261) or placebo (N=65), and did not see a significant difference in rates of solicited reactions or adverse events. Less solicited reactions and adverse events occurred following the second dose compared to the first. No vaccine related serious adverse events were reported.

Monovalent adjuvanted pandemic H1N1 vaccines

Nine studies were identified with pandemic H1N1 vaccines with either oil-in-water adjuvants (MF59, AS03) or aluminium adjuvants.[192,194-202] Safety data were reported for 230 children exposed to MF59, 1,224 exposed to AS03 (255 to AS03$_A$ and 969 to AS03$_B$), and 1,394 children exposed to aluminium adjuvanted vaccines. Local and systemic reactogenicity for the oil-in-water adjuvants is presented in **table 6.2**.

MF59

Two studies were identified reporting data on two different MF59 adjuvanted pandemic H1N1 vaccines.[198,199] Yasuda *et al.* compared a half dose versus a full dose of a cell culture-derived MF59 adjuvanted pandemic H1N1 vaccine in children aged 6 months to 19 years in Japan, given in two doses.[199] They found that the full vaccine dose (7.5µg) was more reactogenic than the half dose, and that the frequency and severity of reactions did not increase after the second dose. There were five serious adverse events reported in this study, all of which were considered unrelated to the vaccine. These concerned one fracture and four instances of influenza: three children who contracted influenza A infections and one child an influenza B infection. One child developed influenza A (H1N1) six days after receiving the first dose of the 3.75µg vaccine and two children who developed influenza A, seven and 25 days after the first dose of the 7.5µg vaccine.

Arguedas *et al.* evaluated the safety of an egg-based MF59 adjuvanted pandemic H1N1 vaccine and compared this to an inactivated split pandemic H1N1 vaccine in children aged 3 to 17 years.[198] The adjuvanted vaccine was more reactogenic than the non-adjuvanted vaccine, which was most apparent in children between 9 and 17 years. Similar local reactogenicity was seen following the first and second dose whereas systemic reactogenicity was lower with the second dose. Children aged 9 to 17 years reported more systemic reactions compared to children aged 3 to 8 years. Although fever (≥38°C) was solicited as adverse event, no information on fever was reported.[197,198]

AS03

Five different clinical studies were identified that evaluated the safety of AS03-adjuvanted pandemic H1N1 vaccines in children. Two compared 1.9µg AS03B with 3.75µg AS03A-adjuvanted vaccines,[200,202] a non-comparative study evaluated the 1.9µg AS03B formulation[201] and one study compared the 1.9µg AS03B adjuvanted vaccine with a whole virion cell culture-derived vaccine[194,195] in different age categories.

Carmona *et al.*[202] found that in children aged 6 months to 3 years local reactions increased with the 3.75µg AS03A-adjuvanted vaccine compared to the 1.9µg AS03B-adjuvanted vaccine, though not significantly. Similar observations were made by Garcia-Scilia *et al.* in children aged 3 to 17 years, where a higher amount of antigen and adjuvant was associated with higher reactogenicity.[200]

In the study by Carmona *et al.* mild, moderate and sever local and systemic reactions increased with the second dose, most notably for fever which was reported by approximately 20% following the first dose and around 70% following the second dose for both formulations.[202] Garcia-Scilia *et al.* also saw an increase in systemic reactions following the second dose compared to the first dose, however this was mainly with the 3.75 µg AS03A formulation and, unlike Carmona *et al.*, was not significant for local reactions (*not included in table 6.2 as information was not presented numerically*).[200]

Scheifele *et al.* reported much lower fever rates of 3.6% after the first dose and 8.6% after the second, y*et al*so showing a significant increase with the second dose in children aged 6 months to 3 years.[201] The lower rates could be the result of the difference in definitions of fever applied in the studies, although other factors might play a role as well. Waddington *et al.* also found the second dose to be more reactogenic than the first dose, most pronounced for fever in children between 6 months and 5 years (8.9% vs. 22.4%). They did not see an increase in fever following the second dose for children aged 5 to 12 years (7.7% vs. 6.3%).[195]

One AESI occurred in the study by Waddington *et al.* A child aged 11 months developed reactive arthritis following vaccination, which was judged possibly

related to the vaccine, and resolved within 10 days.[194,195] No AESIs or vaccine related serious adverse events were reported by the three other studies.

Aluminium

Two studies included aluminium adjuvanted pandemic H1N1 vaccines with different amounts of antigen in different age categories.[192,196] Solicited local adverse events following the first dose varied between 12% and 27.4%. There was no apparent relation between reactogenicity and amount of antigen or age for the aluminium adjuvanted formulations. Zhu *et al.* found that the adjuvant was associated with increased systemic reactogenicity. A similar trend can be seen in the data by Liang *et al.*, although this data was not presented for children separately.

Whole virion pandemic H1N1 vaccines

The study by Waddington *et al.* evaluated a whole virion cell culture-derived pandemic H1N1 vaccine in comparison to an AS03 adjuvanted vaccine.[195] The whole virion vaccine appears to be less reactogenic compared to the AS03 adjuvanted vaccine, as can be seen in **table 6.2**. For example, less severe local reactions were reported following the whole virion vaccine; 1.1% vs. 7.2% after the first dose in children over 5 years. This was seen over almost the entire range of solicited adverse events. No clear difference between the first and second dose was seen in children less than 5 years of age. In children between 5 and 12 years of age the second dose was associated with a reduced rate of 'feeling unwell' (15% vs. 25% after the first dose), yet an increase in nausea and vomiting (10% vs. 1% after the first dose), which was not seen for the AS03 adjuvanted vaccine.

Studies in children with underlying medical conditions

Ten studies were identified that evaluated different pandemic H1N1 vaccines in a total of 431 children and adolescents with underlying disease.[208-217] An additional study investigated pandemic H1N1 vaccination in 390 persons with asthma, including adolescents 12 years and above.[218] An overview of all studies is presented in **table 6.3**. Most were single intervention, observational studies.[208-211,218] Two studies included healthy controls,[213,215] and one study included hospital controls with different medical conditions.[216] The two remaining studies evaluated the effect of simultaneous vs. sequential administration of seasonal and pandemic H1N1 vaccines in paediatric kidney patients[214] and HIV-infected patients.[212] None of the studies compared adjuvanted and non-adjuvanted vaccine formulations. Two studies did not report any safety outcomes,[210,217] and the study in five paediatric heart transplant patients was too small for meaningful observations.[211] Torii *et al.* only reported that there were no systemic reactions and no allograft rejections in a cohort of renal trans-

Table 6.3 Overview clinical studies of pandemic H1N1 vaccines in children with underlying medical conditions

Reference	Country	Vaccine	Amount of antigen per dose	Number of doses evaluated	Number of children included	Age (range or mean ± SD)	Patients
Bate *et al.* 2010 [208]	United Kingdom	AS03 adjuvanted	1.9µg	2 doses	54	1y - 17y	Cancer
Busse *et al.* 2010 [218]	United States	Inactivated, split	15 µg	2 doses	NR	12y-79y	Asthma
			30 µg	2 doses	NR	12y-79y	Asthma
Esposito *et al.* 2010 [215]	Italy	MF59 adjuvanted	7.5 µg	1 dose	31	17.8 y ± 8.7y	β-thalassemia major
				1 dose	28	17.6 y ± 7.0y	Healthy
Alghisi *et al.* 2011 [209]	Italy	MF59 adjuvanted	7.5 µg	1 dose	48	8m-26y	Cystic Fibrosis
Altamirano-Diaz *et al.* 2011[211]	Canada	AS03 adjuvanted	3.75µg	1 or 2 doses	5	6m-8y	Heart transplant
Esposito *et al.* 2011[213]	Italy	MF59 adjuvanted	7.5 µg	2 doses	69	6m-23m	Preterm infants
					32	6m-23m	Healthy
Esposito *et al.* 2011 [214]	Italy	MF59 adjuvanted	7.5 µg	1 dose	16	15.4 y ± 5.6y	Renal transplant
		MF59 adjuvanted+seasonal	7.5 +3*15µg	1 dose	16	15.7 y ± 5.5y	Renal transplant
		MF59 adjuvanted	7.5 µg	1 dose	16	15.6 y ± 5.5y	Healthy
		MF59 adjuvanted+seasonal	7.5 +3*15µg	1 dose	16	15.4 y ± 5.7y	Healthy
Esposito *et al.* 2011 [212]	Italy	MF59 adjuvanted	7.5 µg	1 dose	19	9y-20y	HIV infected
		MF59 adjuvanted+seasonal	7.5 +3*15µg	1 dose	17	9y-20y	HIV infected
		MF59 adjuvanted	7.5 µg	1 dose	19	9y-20y	Healthy
		MF59 adjuvanted+seasonal	7.5 +3*15µg	1 dose	17	9y-20y	Healthy
Kelen *et al.* 2011 [210]	Hungary	Aluminium phosphate gel adjuvanted	6µg	1 dose	37	6y-23y	Renal transplant
Torii *et al.* 2011 [216]	Japan	Inactivated, subcutaneous	>15 µg	1 or 2 doses	13	1y-18y	Liver transplant
					31	1y-18y	Hospital controls (cerebral palsy, malformation syndrome, muscular dystrophy)
Okike *et al.* (*in press*) [217]	United Kingdom	AS03 adjuvanted	1.9µg / 3.75 µg	2 doses	31	11.2y (median)	HIV infected

plant patients,[216] and Busse *et al.* only reported safety findings by asthma severity in a cohort of asthma patients aged 12-79 years.[218] The studies that included healthy controls did not observe any difference in reactogenicity or safety in children and adolescents with underlying medical conditions. The study in paediatric cancer patients had a relatively low fever rate, however all participants with fever had to be hospitalised and treated with intravenous antibiotics and two became neutropenic.[208] No other significant adverse events were seen in any of the studies found.

Spontaneous reports, case reports, surveillance efforts

Several overviews on reported adverse events after administration of pandemic H1N1 vaccines have been published worldwide.[164-167,219-232] Reported events are mostly presented in stratified age categories, often including paediatric groups. Only few publications actually present age-specific reporting rates.[221-224] An overview of the number of reported events in children and adolescents reported by different sources is given in **table 6.4.** Importantly, many of the sources of spontaneous reports contain overlapping information as reports within national databases are also centrally collected by the WHO-UMC and, for European licenced vaccines in the EudraVigilance database. As a result of the overlap, comparisons between different publications are difficult to make.

Number of reports

The most complete overview of the number of spontaneous reports for children and adolescents after administration of pandemic H1N1 vaccines is published by the WHO-UMC.[220] Up to February 2011, 34,256 individual case safety reports (ICSRs) on 110,883 suspected AEFI were received from 31 countries worldwide spanning 11 different vaccine brands. Of these, 12,900 ICSRs (37.6%) were reported for children and adolescents. The majority of the reports are in children aged 2-≤11 years (N=7,650; 59.3% of reports on children). The most frequently suspected vaccine was the AS03 adjuvanted vaccine (Pandemrix, N=6,260; 48.5%), followed by reports for vaccines with unknown brand (N=5,249; 40.7%). For the AS03 adjuvanted vaccine 46.1% of the reports were reported for the paediatric population, of which 0.3% were related to neonates <28 days, 29.5% to infants/children 28 days to 23 months, 57.5% for children age 2-≤11 years, and 12.7% for adolescents 12-≤17 years of age. For each vaccine the WHO-UMC presented the number of reported events stratified by system organ class (SOC) and the number of reported adverse events of special interest. These results were not stratified by age category.

Table 6.4 Overview of postmarketing studies reporting the number of adverse event reported for pandemic H1N1 vaccines in children

Reports published on websites

Authors	Date	Data lock point	Source data	Type of data	Country	Type of vaccine	Age catagories	N of children	N of events	Remarks
WHO-UMC [220]	March 2011	Feb 2011	VigiBase	SR	Australia, Austria, Belgium, Brunei Darussalam, Canada, Chile, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malaysia, Malta, Mexico, Montenegro, Morocco, Netherlands, Norway, Peru, Saudi Arabia, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom and the United States.	Brand unknown	28d-23m	937		
							2y-11y	3,212		
							12y-17y	1,100		
						AS03-adjuvanted (Arepanrix)	2y-11y	2		
						AS03-adjuvanted (Arepanrix H1N1)	28d-23m	1		
						MF59-adjuvanted (Celtura)	2y-11y	2		
							12y-17y	3		
						Whole virion cell culture derived vaccine (Celvapan)	<28d	2		
							28d-23m	18		
							2y-11y	156		
							12y-17y	41		
						Whole virus, inactivated, aluminium adjuvated (Fluval P)	2y-11y	7		
							12y-17y	16		
						MF59-adjuvanted (Focetria)	<28d	1		
							28d-23m	97		
							2y-11y	391		
							12y-17y	136		
						Influenza A (H1N1) 2009 Pan. Mono. Vac. (Without Adju.)	2y-11y	1		
						AS03-adjuvanted (Pandemrix)	<28d	20		
							28d-23m	1,845		
							2y-11y	3,601		
							12y-17y	794		
						Non-adjuvanted inactivated split (Panenza)	28d-23m	2		
						Non-adjuvanted inactivated split (Panvax)	<28d	1		
							28d-23m	184		
							2y-11y	278		
							12y-17y	52		
MHRA [165]	01-Apr-2010	16-Mar-2010	MHRA	SR	United Kingdom	Whole virion cell culture derived vaccine; AS03-adjuvanted	0y-16y	440		4 fatal cases
Swedish Medical Products Agency [166]	02-Jun-2010	16-Apr-2010	Medical Products Agency	SR	Sweden	AS03-adjuvanted	Children			4 cases of lack of efficacy (4-13 years of age)

Reports published in literature

Carvajal *et al.* [231]	2011			SR	Spain	MF59-adjuvanted	14y-<18y	7	
				Follow-up study	Spain	MF59-adjuvanted	14y-<18y		
Folkenberg *et al.* [221]	2011	31-Mar-2010	Danish Pharmacovigilance database	SR	Denmark	AS03-adjuvanted	0y-4y	19	
							5y-14y	29	
							15y-64y	429	
Vellozzi *et al.* [222]	2010	31-Jan-2010	VAERS	SR	United States	Inactivated; Live, attenuated, unknown	0.5y-4y	1,358	4 cases of GBS
							5y-24y	3,415	21 cases of GBS
Wu *et al.* [223]	2010		Diary cards; telephone interviews		China	Non adjuvated monovalent split-virion vaccine	4y-11y	42	9/42 vaccine-related
							12y-17y	69	28/69 vaccine-related
Liang *et al.* [224]	2011	21-Mar-2011	Chinese CDS	SR	China	Nonadjuvant, split-virion vaccins	≤9y	1,669	137 serious
							10y-19y	3,436	293 serious, 3 cases of GBS < 15 years
Kurz *et al.* [219]	2011	30-Apr-2010	EudraVigilance	SR	EEA(98.2%)	Whole virion cell culture derived vaccine	< 3y	31	
							3y-8y	58	
							9y-17y	57	
						MF59-adjuvanted	< 3y	90	
							3y-8y	148	
							9y-17y	107	
						AS03-adjuvanted	< 3y	2,601	
							3y-8y	1,908	
							9y-17y	632	
Banzhoff *et al.* [226]	2011	Mar-2010	Novartis	SR (97%), trials (2.8%), lit. (0.3%)	Europe	MF59-adjuvanted	< 18y	805	
Parretta *et al.* [225]	2011	30-Jun-2010	Italian Pharmacovigilance Adverse Event Spontaneous Reporting System	SR	Italy	MF59-adjuvanted	0,5y-<2y	37	5 serious
							2y-11y	162	12 serious
							12y-17y	59	3 serious
Mahajan *et al.* [227]	2010	31-Dec-2009	Australian Adverse Drug Reactions System database	SR	Australia (New South Wales)	Unknown	< 7y	10	0 serious

Adju.=adjuvant; EEA=European Economic Area; GBS= Guillain-Barré syndrome; Lit=literature; SR=spontaneous reports.

Reporting rates

We identified three studies that calculated reporting rates based on the number of reported adverse events and the number of vaccinated persons.[221,222,224] An overview of the rates is given in **table 6.5**. These three studies were all based on spontaneous reporting. Reporting rates for serious adverse events ranged from 6.8 to 10.7 per 1,000,000 doses or vaccinated persons. The number of exposed persons per vaccine has not been published. Rates for non-serious events ranged from 82 to 120 per 100,000 doses or vaccinated persons. Reporting rates for serious events tend to be higher in the younger children compared to adolescents and adults. Vellozzi *et al.* compared the reporting rates for the pandemic H1N1 vaccines with the events for seasonal vaccines in the previous seasons using the VAERS data. The rate for serious events was significantly higher for the pandemic H1N1 vaccines for all age categories except for children under the age of 5 years.[222]

Wu *et al.*[223] calculated reporting rates based on stimulated surveillance. This resulted in higher reporting rates: 0.77% (95% CI 0.54-1.01) for children aged 4 to 11 years and 0.28% (95% CI 0.22-0.35%) for adolescents aged 12 to 17 years.

Differences in reporting rates acquired through spontaneous reporting and those observed with active surveillance were also seen in the Spanish study by Carvajal *et al.*[231] Comparing spontaneous reporting rates with rates based on a follow-up study it was estimated by the authors that the spontaneous reporting rates were 322-fold lower than the study rates. For serious events the rate of spontaneous reports was 37-fold lower.

Figure 6.5 Reporting rates of adverse events based on spontaneous reporting for pandemic H1N1 vaccines in children

Author	Country	Vaccine	Agegroup in years	Serious adverse events	Non-serious adverse events	Total
Folkenberg *et al.* [221]	Denmark	Pandemrix	0-4			30.61 / 1,000,000 *
			5-14			27.02 / 1,000,000 *
			15-64			22.55 / 1,000,000 *
Vellozzi *et al.* [222]	United States	Inactivated; Live, attenuated, unknown	0.5-4	8.1/1,000,000 *	113.2/1,000,000 *	
			5-24	6.8/1,000,000 *	120.4/1,000,000 *	
Liang *et al.* [224]	China	nonadjuvant, split-virion vaccins	≤9	10.7/1,000,000 **	119.9/1,000,000 **	130.6 / 1,000,000 **
			10-19	7.7/1,000,000 **	82.4/1,000,000 **	90.1 / 1,000,000 **

Rates were transformed to 1/100,000 administered doses (*) or vaccinated persons (**) to enhance comparisons

Types of events

Parretta *et al.* presented the number of reported events on a SOC level for three paediatric age categories from Italy, all concerning the MF59 adjuvanted vaccine. For children aged 0.5-<2 years and 2-11 years, most reports were reported for the SOCs 'General disorders and administration site conditions' (59.5% resp. 63.6%), 'Skin and subcutaneous tissue disorders' (24.3% resp. 18.5%) and 'Nervous system disorders' (24.3% resp. 25.3%). For adolescents aged 12-17 years the reports were within 'General disorders and administration site conditions' (66.1%), 'Nervous system disorders' (32.2%) and 'Respiratory, thoracic and mediastinal disorders' (8.5%).

For the pandemic H1N1 vaccines licenced centrally in Europe the most frequently reported adverse events in children and adolescents per vaccine were published by EMA.[167] For the AS03 adjuvanted pandemic H1N1 vaccine produced in Canada (Arepanrix) these were anaphylactic reaction, cough, cyanosis, dyspnoea, angioedema, urticaria, throat tightness, pyrexia, nausea, erythema, rash, pallor, flushing, anaphylactic shock, hypersensitivity, depressed level of consciousness and wheezing. For AS03 adjuvanted pandemic H1N1 vaccine (Pandemrix) produced in Europe, the most frequently reported events were pyrexia, hyperpyrexia, vomiting, injection-site pain, headache, diarrhoea, cough, fatigue, rash, decreased appetite, nausea, abdominal pain, malaise, injection-site erythema, crying, somnolence, pallor, injection site swelling, listlessness, syncope, dyspnoea, pain in extremity, febrile convulsion, influenza-like illness, myalgia, urticaria, dizziness, erythema, tearfulness and erythema. The only difference between the two AS03 adjuvanted vaccines is the production site, they can otherwise be considered identical.[233,234] For the whole virion cell culture derived vaccine, dizziness, medication error, vomiting, nausea, pallor, pyrexia, headache, hypersensitivity, syncope, underdose, injection site pain, rash, fatigue, malaise, diarrhoea, vision blurred, feeling hot and wrong technique in drug usage process. For the MF59 adjuvanted pandemic H1N1 vaccine the following adverse events were most frequently reported in children: drug exposure during pregnancy, pyrexia, headache, premature baby, hyperpyrexia, vomiting, cough, small for dates baby, nausea, abdominal pain, diarrhoea, injection-site pain, myalgia, fatigue, influenza like illness, large for dates baby, dyspnoea, rash, malaise, urticaria, infection and convulsion.

Case reports

Six published case-reports were identified on children and adolescents experiencing adverse events after administration of a pandemic H1N1 vaccine. Two reports from Canada were identified. A 2-year old boy experienced bilateral optic neuritis and acute disseminated encephalomyelitis (ADEM) after two doses of AS03 adjuvanted pandemic H1N1 vaccine,[235] and an 11-year old boy was diag-

nosed with GBS 13 days after vaccination with AS03 adjuvanted pandemic H1N1 vaccine.[236] Two reports after vaccination with unadjuvanted pandemic H1N1 vaccines were reported from China. A 17-year old Chinese girl experiencing bilateral sudden hearing loss 14 hours after vaccination[237] and a 13-year old boy diagnosed with acute transverse myelitis 5 days after vaccination.[238] One report concerned a 9-year old boy from the United States with papular acrodermatitis of childhood, or Gianotti-Crosti syndrome following vaccination with a live attenuated intranasal pandemic H1N1 vaccine.[239] The final report concerned a 6-year old boy from France experiencing cytophagic histiocytic panniculitis 1 week after the second injection of unadjuvanted pandemic H1N1 vaccine.[240]

Observational studies, active surveillance

Few observational studies evaluating potential adverse effects of pandemic H1N1 vaccination been published so far, although several are still ongoing. A German study compared adverse events following pandemic H1N1 vaccination in 72 children and adolescents (1 to 19 years) after liver transplantation with 27 vaccinated healthy siblings and 243 from a database.[241] Most common adverse events reported were local symptoms. There was no significant difference in the frequency of adverse events between patients and controls, except for headache, diarrhoea, fatigue and muscle pain which were reported at lower rates in the transplantation group. Another prospective cohort study, monitoring immunocompromised and immunocompetent children and adolescents either immunised with AS03 or MF59 adjuvanted pandemic H1N1 vaccine, or with confirmed influenza infection, found that adverse events increased with age and were more frequent following exposure to AS03 adjuvanted vaccine than to MF59 adjuvanted vaccine.[242] In the Netherlands, a study into the occurrence of fever following vaccination with the AS03 adjuvanted pandemic H1N1 vaccine in children between 6 months and 4 years of age was conducted.[232] In this study, all parents or caregivers reporting fever to the adverse drug reaction reporting database of the Netherlands Pharmacovigilance Center (Lareb) following the first dose of pandemic H1N1 vaccine were sent questionnaires. They found that 44% of children who experienced fever following the first dose did not develop fever following the second dose and that those with fever following the second dose experienced a less severe course. Unfortunately, this study did not consider those who did not develop fever following the first dose but did develop fever following the second dose. The EMA published a warning on their website concerning the risk of fever in young children after with the second dose of the AS03-adjuvanted pandemic H1N1 vaccine.[243]

Following the experience with swine flu vaccination in 1976 in the US, much attention has gone out GBS in the active surveillance studies. The potential association with pandemic H1N1 vaccination has been evaluated in different studies in the US,[244] Europe,[245,246] and Korea.[229] All these studies included cases in chil-

dren or adolescents. For the overall population no association between GBS and pandemic H1N1 vaccination was detected. Numbers were too low to draw conclusions for the paediatric population specifically. Preliminary results from a US based study indicate a small excess risk of 0.8 cases per 1 million vaccinations.[244]

In August 2010, reports of a possible association between exposure to AS03 adjuvanted pandemic H1N1 vaccine and occurrence of narcolepsy-cataplexy in children and adolescents emerged first in Sweden and later in Finland, leading to the recommended discontinuation of this vaccine in these countries and a review of this vaccine within the EMA.[247,248] At the same time, France reported 6 cases, 5 following the AS03 adjuvanted vaccine and 1 following an inactivated split pandemic H1N1 vaccine.[249] In November 2010 a publication appeared discussing 14 cases of narcolepsy after H1N1 vaccination, and 2 after H1N1 infection cases from 3 sleep centres in the US, Canada and France.[250] Since then more cases have been identified, mostly in children and adolescents. A registry study in Finland, published in February 2011, found a 9-fold increase in narcolepsy in association with the AS03 adjuvanted pandemic H1N1 vaccine.[251] Two Swedish studies also strengthened the signal by observing a relative risk of 4.19,[252] and 6.6.[253] A causal association between the onset of narcolepsy and exposure to a pandemic H1N1 vaccine has not been established. Alternative explanations accounting for the observed epidemiological association have not been fully investigated so far. This includes effect modification by circulating pandemic virus, other circulating infections, or seasonal influenza vaccine. It also includes diagnostic bias by preferential shortening of the time to diagnosis in exposed cases due to increased awareness of narcolepsy and the potential relation with the vaccine. Currently, extended epidemiological assessments of the association between narcolepsy and pandemic H1N1 influenza vaccination are underway.[122,254] An investigation of narcolepsy following exposure to MF59 adjuvanted pandemic H1N1 vaccines did not identify any cases.[255] In July 2010 the CHMP reviewed the European marketing authorisation of the AS03-adjuvanted pandemic H1N1 vaccine and concluded that the vaccine should only be given to persons below the age of 20 if seasonal trivalent vaccines are absent.[256]

Concluding remarks

Much has been published on the safety of pandemic H1N1 vaccines in children. There have been several studies with different vaccines spanning all age categories and several studies in children and adolescents with underlying medical conditions. In addition, large monitoring efforts have resulted in much data, with almost 13,000 individual case reports in children and adolescents to the WHO. However, both differences in study methodology and data presentation render meta-analytic safety analyses of the pandemic H1N1 vaccines in the different, relevant, age categories difficult. Especially the diversity in the clinical studies for inactivated non-adjuvanted pandemic H1N1 vaccines re-emphasizes the need

for harmonisation of study protocols and presentation of safety data in clinical study publications.[207,257] The added value of publications of spontaneous report analyses from overlapping source populations could be increased by crystallizing differences between populations and age categories. With the currently published information this is impossible. Thus, although a large amount of data has been generated, relatively little has been learned on the comparative safety of these pandemic H1N1 vaccines – particularly in children. It should be a collective effort to give added value to the enormous work going into the individual studies by adhering to available guidelines for the collection, analysis, and presentation of vaccine safety data in clinical studies,[205,258] and to guidance for the clinical investigation of medicinal products in the paediatric population.[259]

The 2009 H1N1 pandemic has shown that although spontaneous reporting of AEFI is necessary for the monitoring of vaccine safety, it is useful to enhance surveillance by methods and infrastructures to verify signals and test hypothesis. Observed over expected analyses to verify signals rely on accurate background incidence rates of disease within targeted age categories. Both in the US and in Europe these rates were provided though coordinated action and use of health care databases. In Europe data were provided from 8 countries on a population of more than 50 million subjects. Several hypothesis testing studies were implemented to be able to assess the potential association of pandemic influenza vaccine with GBS and narcolepsy. All required multinational collaboration to meet the need. The pandemic has brought us the beginning of an infrastructure for collaborative vaccine safety studies in EU, the US and globally.

Chapter 7

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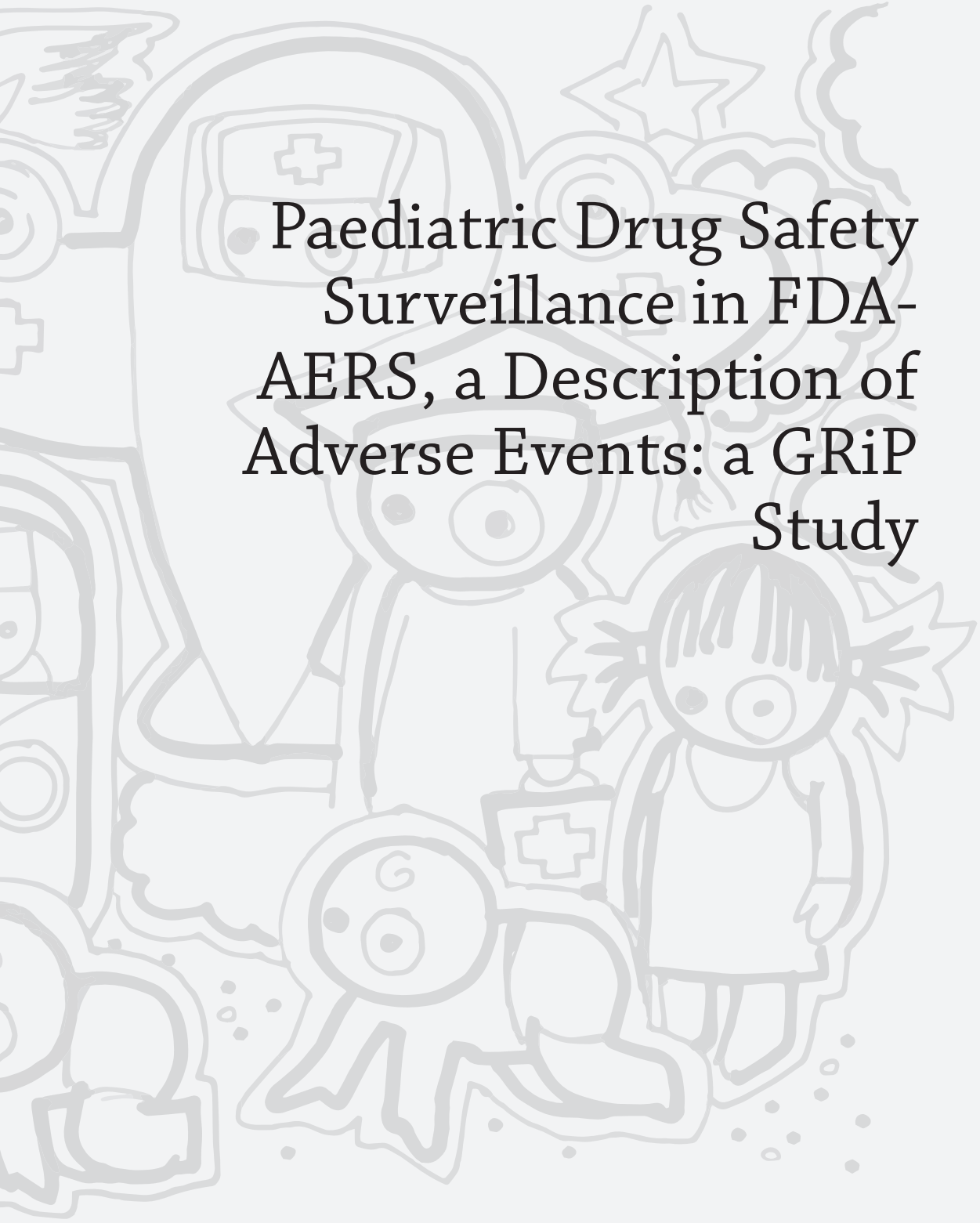


Paediatric Drug Safety Surveillance in FDA-AERS, a Description of Adverse Events: a GRiP Study

Abstract

Purpose

Individual case safety reports (ICSRs) are a cornerstone in drug safety surveillance. The knowledge on using these data specifically for children is limited. Therefore we studied characteristics of paediatric ICSRs reported to the United States (US) Food and Drug Administration (FDA) Adverse Event Reporting System (AERS).

Methods

Public available ICSRs reported in children (0-18 years) to AERS were downloaded from the FDA-website for the period January 2004 to December 2011. Characteristics of these ICSRs, including the reported drugs and events, were described and stratified by age-groups.

Results

We included 106,122 paediatric ICSRs (55% boys) (58% US) with a median of 1 drug [range 0-157] and 3 events [1-94] per ICSR. Mean age was 9.1 years. 90% was submitted through expedited (15-days) (65%) or periodic reporting (25%) and 10% by non-manufacturers. The proportion and type of paediatric ICSRs reported were relatively stable over time. Most commonly reported drug classes by decreasing frequency were 'neurological' (58%), 'antineoplastic' (32%) and 'anti-infectives' (25%). Most commonly reported system organ classes were 'general' (13%), 'nervous system' (12%) and 'psychiatric' (11%). Duration of use could be calculated for 19.7% of the reported drugs, of which 14.5% concerned drugs being used long-term (>6 months).

Conclusions

Knowledge on the distribution of the drug classes and events within AERS is a key first step in developing paediatric specific methods for drug safety surveillance. Analysis of the reported drugs indicates disproportionate safety reporting of neurological/psychiatric and antineoplastic agents. Studying multiple databases is useful because of worldwide differences in drug utilisation and type of reports.

Introduction

The limited knowledge about the effects of drugs in children has boosted initiatives by the World Health Organisation (WHO) and triggered new legislation in recent years.[13,14] The Global Research in Paediatrics Network of Excellence (GRiP) is an European Commission-funded consortium, which aims to implement an infrastructure facilitating the development and safe use of medicines in children. This entails the development of a comprehensive educational programme and integrated use of existing research capacity, whilst reducing the fragmentation and duplication of efforts.[48,49]

Post-marketing drug safety surveillance using spontaneous reporting systems is essential in studying drug safety.[19] An important part of the GRiP project is evaluating current and developing new methodology for post-marketing drug safety studies specifically for the paediatric population. Typical large spontaneous reporting systems include VigiBase of the WHO Uppsala Monitoring Center (WHO-UMC), the Adverse Event Reporting System (AERS), maintained by United States (US) Food and Drug Administration (FDA), the Vaccine Adverse Effect Reporting System (VAERS), maintained by FDA and CDC (Centers for Disease Control and Prevention), and EudraVigilance of the European Medicines Agency (EMA).[25-28]

While these spontaneous reporting databases were predominantly used by regulatory authorities to monitor drug safety and to perform safety signal detection, these data are increasingly available for research purposes. The FDA databases offer publicly downloadable datasets,[31,260] the EMA published their access policy for EudraVigilance in 2011,[261] and WHO-UMC is preparing summary VigiBase data to be made accessible via their website.[262] Understanding the structure and scope of these datasets and their respective strengths and limitations is essential for their correct use and interpretation and a first and important step for evaluating current and developing new methodology. In 2011 an overview of paediatric ICSRs reported to WHO-UMC was published.[263] Published descriptions on the paediatric reports within AERS include the number of reports, their outcome, and the most frequently reported drugs.[135,264,265] However, studies rarely reported on the reported type of adverse events within AERS.

In the current study we aimed to describe the paediatric ICSRs as reported within AERS. Specific attention was given to describing adverse events occurring after long-term drug use or with delayed onset after cessation of treatment.

Methods

Data source

AERS is a database that contains information on adverse event and medication error reports submitted to the FDA. It is a passive surveillance system that relies on voluntary reporting 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.[31]

AERS data is publicly available and files containing the raw data of individual case safety reports (ICSRs) as contained within the database are available.[31] The information include: patient demographic and administrative information; drug/biologic information; preferred terms of MedDRA (Medical Dictionary for Regulatory Activities) of the events; patient outcomes for the event; report sources for the event; therapy start dates and end dates; and indications of use (diagnosis) for the reported drugs.

Data preparation

We extracted all ICSRs for the period January 2004 till December 2011 and included all ICSRs on children, aged 0 to <18 years. We excluded the following reports from the analyses; adults reports (≥18 years); reports in which the age was missing; reports in which the reported drug or event was missing; duplicate reports (e.g. in a follow-up report, were only included once). All reported events are coded in preferred terms of MedDRA. To facilitate high level descriptive we recoded the reported terms to a single System Organ Classes (SOCs) of MedDRA. The reported drugs are described either as a valid trade name or as unstructured narrative. As far as possible the reported drug names were recoded to Anatomical Therapeutic Chemical (ATC) drug classes using drug dictionaries.[30,266-268] This recoding was possible for >90% of the reported drugs reported in the selected ICSRs. The entries for which recoding was not possible included reports without a specified drug name and spelling errors. For the analyses on type of reported drugs, only those records with a known ATC-code were included.

Analysis

Each of the included ICSRs was classified by the age at time of the event, sex, number of drugs and number of events. Results were stratified by age categories

in which age at onset was categorised based on the ICH (International Conference on Harmonisation) age-groups: neonates (≤27 days), infants (28 days-≤23 months), children (2-≤11 years), and adolescents (12-≤17 years).[111]

The role of the reported drugs, being either primary suspect, secondary suspect, concomitant or interacting was provided. The most frequently reported drugs and events were described. In addition, the reported events were stratified with respect to the outcome of the event. The outcome was registered in terms of the seriousness criteria: death, life-threatening, hospitalisation (initial or prolonged), disability, congenital anomaly, requiring intervention to prevent permanent impairment or damage or other. Using the primary suspect and secondary suspect drugs only, the most frequently reported drug-event combinations were described.

For those drugs for which the starting date of the drug and the date of the event were known, the time to event was calculated. An event occurred after *long-term use* if it occurred at least 6 months after starting of therapy.[269] We also studied *delayed events*. For those records with a known stopping date of therapy and date of the event, the type of reported events occurring >3 months after drug cessation were compared with the type of events occurring during drug use.

Characteristics of the ICSRs were compared using χ^2 analysis to compare proportions and either students-t test, if variable was normally distributed or Mann-Whitney tests if the variable was not normally distributed to compare means. A *p*-value <0.05 was considered to be statistical significant.

Results

The overall publicly available dataset of AERS included 3,691,417 ICSRs; 106,122 (2.9%) ICSRs occurred in children 0-<18 years and were included in the analyses. The mean age of the children in these reports was 9.1 years. 10.5% of the ICSRs were on children up to one year of age, after which this decreased to 3.6% at 4 to 5 years of age and gradually increased again to 8.9% at 17-18 years of age (**figure 7.1**). The majority of the ICSRs (54.5%) were reported for boys, reports for boys exceeded those for girls up to the age of 11 years (54.1-59.9%) and this reversed from the age of 12 years onwards (47.7%), the mean age in the female reports was higher than for male reports (p=0.000) (**table 7.1**). The number of ICSRs reported by calendar year is increasing, with a small dip in 2010 (**figure 7.2**). The majority of the reports originated from the US (58%), followed by Japan (7.0%) and the United Kingdom (6.6%).

Of the included ICSRs, 10.0% (N=10,576) concerned 'Direct' reporting, defined as ICSRs being voluntary submitted by 'non-manufacturers'. The majority of the ICSRs were submitted by manufacturers; 64.9% (N=68,886) were expedited re-

Table 7.1 General characteristics of paediatric ICSRs (N=106,122) within AERS

Number of included paediatric ICSRs	N (%)	Males
0 - 27 days	4,717 (4.4%)	2,114 (54.1%)
28 days - 23 months	16,096 (15.2%)	7,921 (55.3%)
2 - 11 years	47,248 (44.5%)	27,075 (59.9%)
12 - 17 years	38,061 (35.9%)	17,658 (47.7%)
Total	106,122 (100%)	54,768 (54.5%)
Mean age	Mean (95% CI)	
Male	8.9 (95% CI 8.8-8.9)	
Female	9.7 (95% CI 9.6-9.8)	
Total	9.1 (95% CI 9.0-9.1)	
Number of reported drugs	Total no. of drugs N(%)	No. of drugs/ICSR Median(range)
0 - 27 days	12,180 (5.2%)	1 (0-36)
28 days - 23 months	34,575 (14.6%)	1 (0-55)
2 - 11 years	103,988 (44.0%)	1 (0-75)
12 - 17 years	85,748 (36.3%)	1 (0-61)
Total	236,491 (100%)	1 (0-157)
Number of reported events	Total no. of events N(%)	No. of events/ICSR Median(range)
0 - 27 days	21,265 (5.4%)	1 (1-15)
28 days - 23 months	59,306 (14.9%)	1 (1-15)
2 - 11 years	173,395 (43.7%)	1 (1-19)
12 - 17 years	143,254 (36.1%)	1 (1-30)
Total	397,220 (100%)	3 (1-94)
Type of report	N (%)	
Direct reporting	10,576 (10.0%)	
Expedited reports ('15 day reports')	68,886 (64.9%)	
Periodic reports	26,660 (25.1%)	
Reporter	N(%)	
Physician	33,990 (32.0)	
Consumer/non-health professional	26,378 (24.9)	
Other health professional	21,193 (20.0)	
Pharmacist	6,159 (5.8)	
Lawyer	1,301 (1.2)	
Unspecified	17,101 (16.1)	
Initial source	N(%)	
Foreign	10,290 (9.7%)	
Study	164 (0.2%)	
Literature	882 (0.8%)	
Consumer	10,123 (9.5%)	
Health Professional	11,196 (10.6%)	
User Facility	14 (0.0%)	
Company representative	3,964 (3.7%)	
Distributor	229 (0.2%)	
Other	554 (0.5%)	
Unknown	68,706 (64.7%)	
Country	N(%)	
United States	50,625 (47.7%)	
Japan	6,119 (5.8%)	
United Kingdom	5,722 (5.4%)	
France	4,656 (4.4%)	
Germany	2,758 (2.6%)	
Unknown	18,827 (17.7%)	

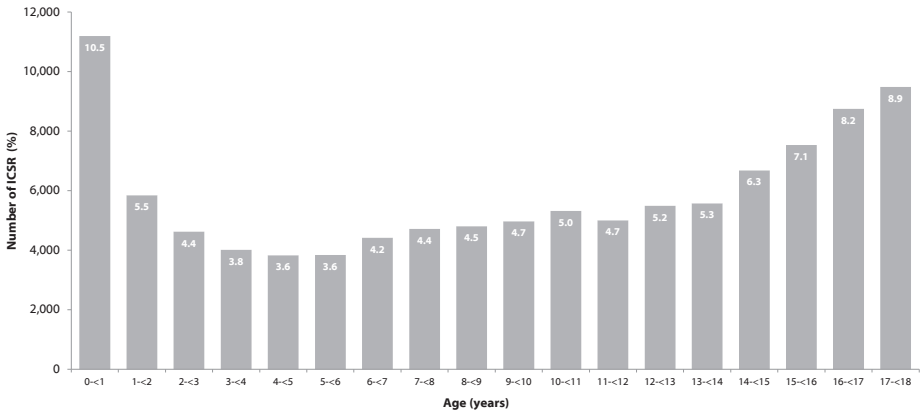
ports and 25.1% (N=26,660) were periodic reports (**table 7.1**). The reporter was a physician in 32.0% of the ICSRs, a consumer in 24.9% and another health professional in 20.0%.

The ICSRs comprised a total of 236,491 drug records (median 1 drug/ICSR) (**table 7.1**). Of these, 35% were indicated as the primary suspected drug and 21% as secondary suspected drug. The other drugs were either indicated as concomitant (45%) or interacting (0.3%).

Nervous system drugs were the most frequently reported drug class in all age categories (**figure 7.3**). These were mainly antiepileptic drugs and analgesics in the youngest children and drugs to treat ADHD (attention deficit hyperactivity disorder) in the older children (**table 7.2**). Anti-infectives were an important group of the reported drugs for the youngest children, covering 22% of the reported drugs in children 0 to 27 days of age (antiretroviral drugs and antibiotics) and 20% of the drugs in children aged 28 days to 23 months (specific immunoglobulins and antibiotics). In the older children the anti-infectives covered a smaller proportion of the drugs and antineoplastic drugs became of more importance; 17% in children aged 2 to 11 years and 16% in children aged 12 to 17 years.

The ICSRs comprised a total 397,220 event records (median 3 events/ICSR) (**table 7.1**). The outcome in terms of seriousness criteria was: 33% hospitalisation (initial or prolonged); 12% death; 3% life-threatening; 3% disability; 2% congenital anomaly; 1% required intervention to prevent permanent impairment or damage; 31% other and was missing in 15%. In **figure 7.4** the reported events are

Figure 7.1 Number of reported ICSRs within AERS stratified by age



Number of reported ICSRs stratified by age. Within the bars the proportion of ICSRs within this age stratum of the total reported paediatric ICSRs is given.

Table 7.2 Most frequently reported drugs

0-27 days	N (%)	28 days - 23 months	N (%)	2-11 years	N (%)	12-17 years	N (%)	Total	N (%)
Zidovudine	310 (2.9%)	Palivizumab	1,025 (3.3%)	Atomoxetine	4,680 (4.9%)	Isotretinoin	2,634 (3.4%)	Atomoxetine	6,597 (3.1%)
Vitamines	229 (2.1%)	Paracetamol, combinations	905 (3.0%)	Methylphenidate	3,557 (3.8%)	Atomoxetin	1,897 (2.4%)	Methylphenidate	5,224 (2.4%)
Ampicillin	170 (1.6%)	Paracetamol	746 (2.4%)	Montelukast	2,067 (2.2%)	Methylphenidate	1,637 (2.1%)	Paracetamol	3,704 (1.7%)
Valproic acid	160 (1.5%)	Ibuprofen	611 (2.0%)	Fluticasone	1,705 (1.8%)	Paracetamol	1,304 (1.7%)	Methotrexate	3,192 (1.5%)
Dopamine	140 (1.3%)	Ranitidine	501 (1.6%)	Methotrexate	1,669 (1.8%)	Methotrexate	1,207 (1.5%)	Montelukast	3,015 (1.4%)
Furosemide	138 (1.3%)	Mitoxantrone	372 (1.2%)	Paracetamol	1,546 (1.6%)	Lamotrigine	1,165 (1.5%)	Valproic acid	2,887 (1.3%)
Gentamicin	137 (1.3%)	Furosemide	342 (1.1%)	Valproic acid	1,524 (1.6%)	Drospirenone and estrogen	1,077 (1.4%)	Ibuprofen	2,881 (1.3%)
Lamivudine	136 (1.3%)	Amoxicillin	328 (1.1%)	Somatropin	1,392 (1.5%)	Infliximab	1,038 (1.3%)	Isotretinoin	2,810 (1.3%)
Insulin	130 (1.2%)	Amoxicillin / clavulanic acid	310 (1.0%)	Ibuprofen	1,331 (1.4%)	Aripriprazole	1,012 (1.3%)	Fluticasone	2,590 (1.2%)
Nitric oxide	130 (1.2%)	Choline salicylate	309 (1.0%)	Salbutamol	1,260 (1.3%)	Valproic acid	940 (1.2%)	Lamotrigine	2,483 (1.2%)

Table 7.3 Most frequently reported events

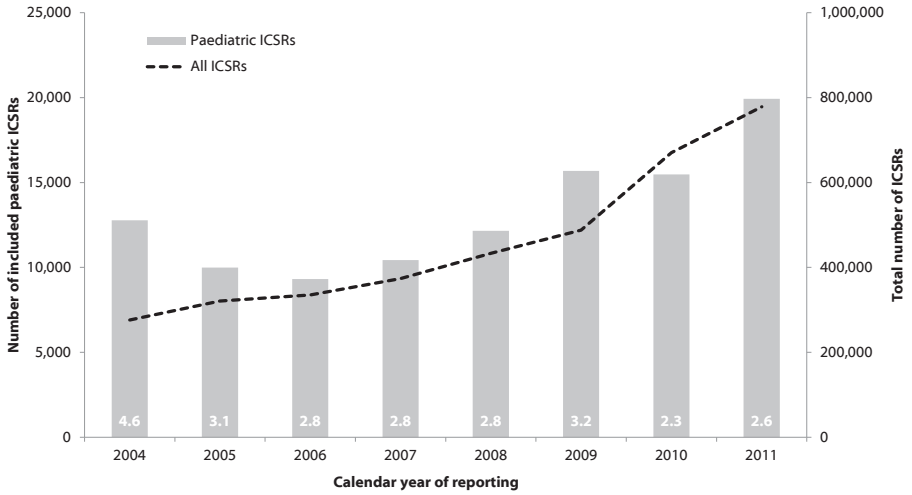
0-27 days	N (%)	28 days - 23 months	N (%)	2-11 years	N (%)	12-17 years	N (%)	Total	N (%)
Drug Exposure During Pregnancy	1,350 (6.3%)	Pyrexia	1,068 (1.8%)	Vomiting	2,818 (1.6%)	Vomiting	1,878 (1.3%)	Vomiting	5,827 (1.5%)
Premature Baby	562 (2.6%)	Vomiting	1,046 (1.8%)	Pyrexia	2,425 (1.4%)	Headache	1,747 (1.2%)	Pyrexia	4,880 (1.2%)
Maternal Drugs Affecting Foetus	484 (2.3%)	Convulsion	895 (1.5%)	Drug Ineffective	2,394 (1.4%)	Nausea	1,641 (1.1%)	Convulsion	4,720 (1.2%)
Neonatal Disorder	381 (1.8%)	Accidental Drug Intake By Child	789 (1.3%)	Convulsion	2,334 (1.3%)	Depression	1,581 (1.1%)	Drug Ineffective	4,392 (1.1%)
Drug Withdrawal Syndrome Neon.	333 (1.6%)	Diarrhoea	645 (1.1%)	Abnormal Behaviour	2,261 (1.3%)	Convulsion	1,399 (1.0%)	Headache	3,531 (0.9%)
Caesarean Section	328 (1.5%)	Accidental Exposure	622 (1.0%)	Aggression	1,755 (1.0%)	Drug Ineffective	1,365 (1.0%)	Abnormal Behaviour	3,264 (0.8%)
Maternal Exp. During Pregnancy	158 (0.7%)	Drug Ineffective	548 (0.9%)	Headache	1,733 (1.0%)	Pyrexia	1,322 (0.9%)	Nausea	3,093 (0.8%)
Neonatal Resp. Distress Syndr.	140 (0.7%)	Somnolence	544 (0.9%)	Somnolence	1,392 (0.8%)	Suicidal Ideation	1,140 (0.8%)	Somnolence	2,903 (0.7%)
Drug Exposure Via Breast Milk	134 (0.6%)	Product Quality Issue	541 (0.9%)	Nausea	1,330 (0.8%)	Overdose	1,118 (0.8%)	Overdose	2,713 (0.7%)
Patent Ductus Arteriosus	122 (0.6%)	Overdose	540 (0.9%)	Product Quality Issue	1,238 (0.7%)	Suicide Attempt	1,113 (0.8%)	Aggression	2,710 (0.7%)

Table 7.4 Most frequently reported drug-ADR combinations (primary and secondary suspected drugs only)

0-27 days (N=3,274)	N (%)	28 days - 23 mo (N=21,356)	N (%)	2-11 years (N=146,094)	N (%)	12-17 years (N=129,699)	N (%)	Total (N=548,640)	N (%)
Buprenorphine – Drug withdrawal syndrome neonatal	32 (1.0%)	Valproate - Drug exposure during pregnancy	84 (0.4%)	Atomoxetine – Prescribed overdose	473 (0.3%)	Isotretinoin - Depression	472 (0.4%)	Isotretinoin - Depression	669 (0.1%)
Heparin - Maternal drugs affecting foetus	29 (0.9%)	Fluoxetine- Drug exposure during pregnancy	49 (0.2%)	Atomoxetine –Drug Ineffective	462 (0.3%)	Isotretinoin -Inflammatory bowel disease	337 (0.3%)	Atomoxetine –Drug Ineffective	664 (0.1%)
Heparin - Premature baby	21 (0.6%)	Valproate – Foetal anticonvulsant syndrome	40 (0.2%)	Atomoxetine – Abnormal behaviour	396 (0.3%)	Isotretinoin -Colitis Ulcerosa	257 (0.2%)	Atomoxetine – Prescribed overdose	654 (0.1%)
Levetiracetam - Maternal drugs affecting foetus	17 (0.5%)	Olanzapine - Drug exposure during pregnancy	39 (0.2%)	Methylphenidate – Product quality issue	393 (0.3%)	Isotretinoin -Crohn's disease	234 (0.2%)	Atomoxetine – Abnormal behaviour	579 (0.1%)
Heparin – Caesarean section	14 (0.4%)	Fentanyl – Accidental drug intake by child	38 (0.2%)	Atomoxetine – Somnolence	356 (0.2%)	Isotretinoin -Suicidal ideation	225 (0.2%)	Methylphenidate – Product quality issue	573 (0.1%)

Presented proportions are based on the total number of 'primary suspect' and 'secondary suspect' reported drugs. The number of unique drug-event combinations was 180,100 and within the age categories: 2,606 (0-27 days); 14,800 (28 days-23 months); 62,788 (2-11 years); 59,101 (12-17 years).

Figure 7.2 Number of reported ICSRs within AERS over time

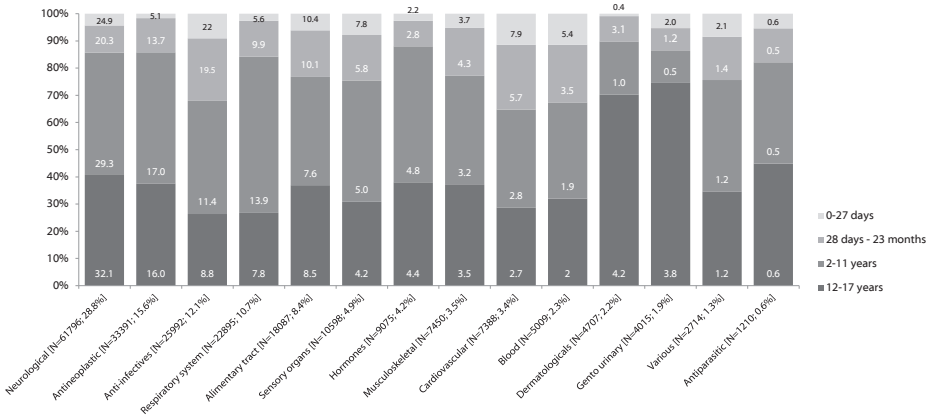


Number of reported ICSRs over time. The number of included paediatric ICSRs are plotted on the left X-axis. The total number of ICSRs within the database is plotted on the right X-axis. Within the bars the proportion of paediatric ICSRs of the total number of reported ICSRs is given.

stratified by their SOCs and by age categories. The ten most frequently reported events are presented in **table 7.3**. The reported events were most frequently situated in the SOCs '*General disorders and administration site conditions*' (13%) (e.g. vomiting and pyrexia), '*Nervous system disorders*' (12%) (e.g. convulsion and headache), and '*Psychiatric disorders*' (11%) (e.g. abnormal behaviour and aggression). In the youngest group of children '*Pregnancy, puerperium and perinatal conditions*' (16%) and '*Congenital, familial and genetic disorders*' (11%) covered a large part of the reported events (*drug exposure during pregnancy, premature baby and maternal drugs affecting foetus*). The proportion of '*Psychiatric disorders*' increased with age from 5% at 0-27 days of age to 13% at 12 to 17 years of age. Also reporting of '*Nervous system disorders*' increased with age, incrementing from 7% at 0-27 days of age to 12-13% at 2-17 years of age. The number of reported drug-event pairs was calculated using the primary and secondary suspected drugs only. The number of unique drug-event combinations was 180,100 and within the age categories: 2,606 (0-27 days); 14,800 (28 days-23 months); 62,788 (2-11 years); 59,101 (12-17 years).

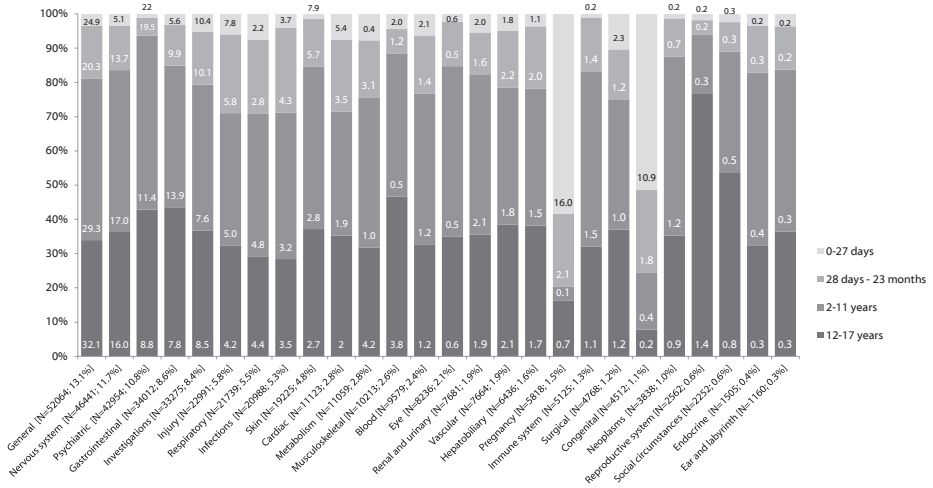
Duration of drug use could be calculated for 63,311 drug records (26.8%). The median duration of use was 10 days (range 0-6,209). The starting and event date were equal in 28.4% of the records, 19.1% were reported after 1-7 days since starting. Time to event was 8-30 days in 14.4% of the records, 31-182 days in 17.8% and >182 days (defined as long-term use) in 20.2% of the records. The proportion of drugs being used long-term increased with age; 0.0% (0-27 days); 7.8% (28 days-23 months); 22.0% (2-11 years) and 24.1% (12-17 years). The drugs used

Figure 7.3 Number of reported drugs stratified by anatomical main group



Distribution of the number of reported drugs over anatomical main group (1st level ATC), stratified by age-categories. The reported ATC classes are presented at the X-axis including the number of reports and the percentage of total. On the y-axis the distribution of the age-categories within each ATC class is presented, counting up to 100%. Within the bars the proportion of this ATC class within the total number of reported drugs within the specified age-category is presented. Only those drugs with a recoded ATC code are included (N=214,327).

Figure 7.4 Number of reported events stratified by system organ class



Distribution of the number of reported events over system organ classes (SOCs), stratified by age-categories. The reported SOCs are presented at the X-axis including the number of reports and the percentage of total. On the y-axis the distribution of the age-categories within each SOC is presented, counting up to 100%. Within the bars the proportion of this SOC within the total number of reported events within the specified age-category is presented.

long-term use more often concerned drugs within the drug groups '*Systemical hormonal preparations*' (10.1% vs. 2.9%; *p*=0.000), '*Alimentary drugs*' (10.8% vs. 5.8%; *p*=0.000) and '*Antineoplastic and immunomodulating agents*' (16.5% vs. 13.9%; *p*=0.000). The most frequently reported drugs after long-term use were '*Somatropin*' (N=955; 7.5%), '*Atomoxetine*' (N=507; 4.0%), and '*Methylphenidate*' (N=462; 3.6%). Also the type of reported events differed; events within the SOCs '*Neoplasms benign and malignant*' (2.1% vs. 0.5%; *p*=0.000), '*Infections and infestations*' (7.0% vs. 4.8%; *p*=0.000) and '*Musculoskeletal, connective tissue and bone disorders*' (3.8% vs. 2.3%; p=0.000) were more often reported after long-term use. The most frequently reported events after long-term use were '*Vomiting*' (N=415; 1.2%), '*Convulsion*' (N=412; 1.2%), and '*Pyrexia*' (N=389; 1.2%).

For 47,301 drug records (20.0%) the time between ceasing of therapy and occurrence of the event was known. The event occurred prior to stopping of the drug in 42.1% of the records, on the day of stopping of the drug in 31.5% and after stopping of therapy in 26.4%. Of the drugs occurring after stopping therapy, 45.2% occurred within 1-7 days, 27.0% occurred within 8-30 days, 11.3% within 31-90 days, 5.4% within 91-182 days, 5.1% within 183-365 days and 6.0% after 365 days. The most frequently reported drugs after delayed use (>3 months) were '*Isotretinoin*' (N=184; 8.8%), '*Palivizumab*' (N=95; 4.5%), and '*Infliximab*' (N=75; 3.6%). SOCs '*Neoplasms benign and malignant*' (2.9% vs. 0.6%; *p*=0.000), '*Gastrointestinal disorders*' (14.8% vs. 9.8%; *p*=0.000), and '*Infections and infestations*' (7.5% vs. 4.6%; *p*=0.000) were more frequently reported 3 months after stopping. The most frequently reported delayed events were '*Crohn's disease*' (N=106; 1.7%), '*Inflammatory bowel disease*' (N=98; 1.6%), and '*Depression*' (N=89; 1.4%). When comparing the drug classes reported >90 days of ceasing of therapy with those drug classes reported during drug use, the largest differences, with higher proportion for delayed effects, were present for '*Antineoplastic and immunomodulating agents*' (26.6% vs. 9.9%; *p*=0.000), '*Dermatologicals*' (10.8% vs. 5.1%; *p*=0.000), and '*Hormones*' (6.1% vs. 3.7%; *p*=0.000).

Discussion

Signal detection within spontaneous reporting databases is the first step in the detection of a safety signal, which may be followed by signal prioritisation and evaluation.[24] The GRiP network aims to create an infrastructure that supports this workflow and active safety surveillance in children. Knowledge about the available data in systems as AERS is a key first step in the development of paediatric specific methodology for post-marketing drug safety studies. Signal detection is influenced by the type of ICSRs that are reported; in a previous study we demonstrated the influence of the proportion of vaccines within VigiBase on the sensitivity of data mining algorithms.[270] Also the distribution of other factors including the type of reporter and year of reporting can influence the results. Knowledge on the difference in the distribution of reported drugs and events within the dif-

ferent databases, like AERS and VigiBase, gives insight on which factors might be of influence on the results but also helps choosing the right database for a specific research hypothesis.

The paediatric ICSRs reported within VigiBase were studied by Star *et al*.[263] Although US reports make up the largest proportion of the ICSRs both within AERS (58%) and within VigiBase (39%), striking differences between the datasets are present. First, the type of reporters differed. While more than half of the ICSRs of VigiBase were reported by physicians, only a third of the AERS ICSRs were reported by physicians. The most notable difference was for consumer reports; 24.9% of the AERS reports versus 4.3% within VigiBase. This difference might be due to different time-periods; consumer reporting is increasing in latest years.[271] Second, only a small proportion of the AERS ICSRs concerned reporting by non-manufacturers. The majority was either reported as part of expedited reporting (65%) or as part of periodic reporting. Earlier it was shown that the US reports within VigiBase are mainly reported by manufacturers, while these form only a small proportion of the reports from the other continents.[26] Third, the reported drug groups and events differed. VigiBase reports more often concerned anti-infective and dermatological drugs, while within AERS neurological drugs and antineoplastic drugs were most frequently reported. This also reflects utilisation differences between the US and Europe, with high rates of prescriptions of methylphenidate in US adolescents in recent years.[272] Choosing an appropriate time-period to study these kinds of drugs is essential since the utilisation of neurological drugs and especially for the treatment of ADHD has changed tremendously since the start of VigiBase in 1968.[272,273]

Describing of ICSRs reported after long-term drug use was a topic of special interest. Long-term drug use and long-term adverse events are of importance during childhood because of possible effects on growth and development. However, they are difficult to study. Studies often lack sufficient time of follow-up and adverse events occurring long after initiating therapy are not easily recognised. Especially for drugs being used chronically, studies investigating long-term safety should be performed. The reported types of drugs before and after 6 months of use differed significantly. '*Systemical hormonal preparations*', '*alimentary drugs*' and '*antineoplastic/immunomodulating agents*' were prominently reported after long-term treatment, while '*anti-infective drugs*', '*musculoskeletal system drugs*' and '*sensory organ drugs*' were reported mostly with short term use. These findings are in line with drugs known to be used short-term or are known to be used for long periods of time.[50] New onset neoplasms are an important concern and were more often reported after long-term drug use. It is not possible to infer any causal association based on spontaneous reporting data. However, the distribution of the drug classes and events reported after long-term drug use are in line with what is expected and therefore a complete dataset of paediatric ICSRs might be a suitable additional source to generate signals on delayed events and new onset chronic events.

The use of spontaneous reporting data has many well known limitations.[24] Since the publically available datasets often do not include all variables there are analytic limitations and since case-narratives are lacking it is difficult to draw inferences on causality. For example, the non-availability of case-narratives implies a loss of potentially important information not otherwise coded in the ICSR. Another well-known, limitation is the volume of duplicates.[274] Duplicate reports are present in all spontaneous reporting databases.[275] The identification and elimination of duplicates from analyses is advantageous for using the data and is important for a correct interpretation of the data. However, so far, few easy to use duplicate-detection methods are currently available and enhanced methods of duplicate detection are being developed.[274] For this study, we dealt with the issue of duplicate reports by only including unique ICSRs. However it is inevitable that duplicate reports are still present within the used database.

Conclusions

Knowledge on the distribution of the drug classes and events within AERS is a key first step in developing paediatric specific methods for drug safety surveillance. Studying multiple databases is useful because global differences in drug utilisation and type of reports.

Methods in Paediatric Safety Signal Detection

Chapter 8

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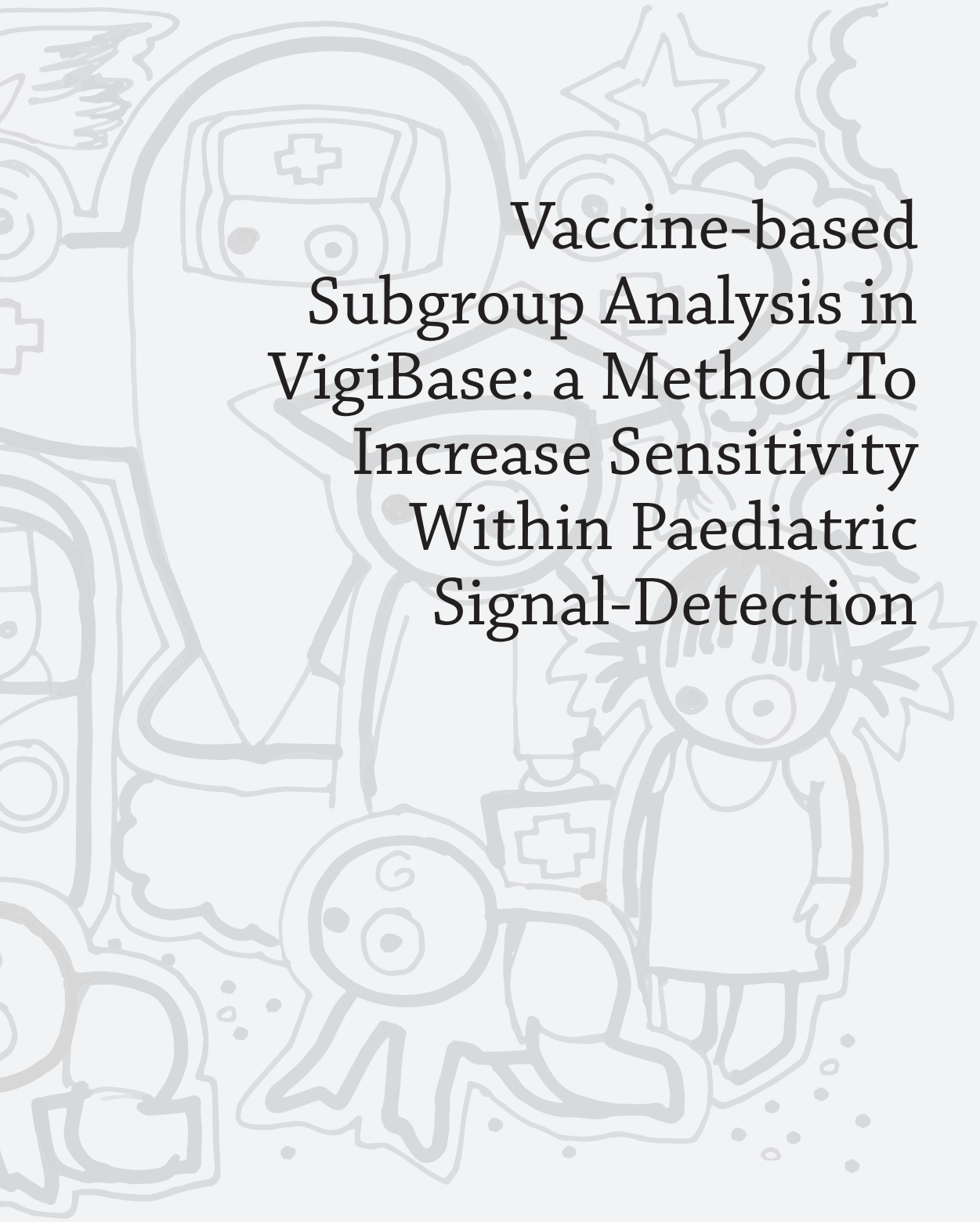


Vaccine-based Subgroup Analysis in VigiBase: a Method To Increase Sensitivity Within Paediatric Signal-Detection

Abstract

Background

Data mining of spontaneously reported adverse drug reactions (ADRs), using measures of disproportionality, is a valuable first evaluation step for drug safety signal-detection. Of all ADRs reported for children within VigiBase, vaccine-ADR pairs comprise more than half of the reports. ADRs concerning vaccines differ with respect to type and seriousness from other drugs, and therefore may influence signal-detection for non-vaccine drugs if not accounted for appropriately. The potential influence of vaccines on safety signal-detection for drugs was recently raised by the CIOMS (Council for International Organizations of Medical Sciences) working group VIII. 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. However, it has not described for which types of ADRs or drugs, subgroup analysis is beneficial.

Objective

To study the methodological aspects concerning the influence of a high prevalence of vaccine-related ADRs on signal-detection within paediatric ADR data.

Methods

We analysed all paediatric Individual Case Safety Reports (ICSRs) received by VigiBase between 2000 and 2006 and calculated the reporting odds ratio (ROR) for all unique drug-ADR pairs with at least 3 reports. The ROR was additionally calculated in subgroups of vaccine-ADR pairs and non-vaccine-ADR pairs and further in different age-groups. A proportional change in the ROR for the different subgroups was calculated and the change in the number of signals of disproportional reporting (SDRs) after subgroup analysis was assessed.

Results

Of all paediatric ICSRs (N=218,840; 54% vaccines) a total of 26,203 unique drug-ADR pairs were eligible for inclusion (21% vaccines). Subgroup analysis for vaccines and non-vaccines revealed 494 new SDRs for vaccines (+30%) and 821 new SDRs for non-vaccines (+6%). Subgroup analyses are only beneficial for non-vaccines if the ADR of interest is reported uncommon for non-vaccines and beneficial for vaccines if the ADR is reported uncommon for vaccines. Subgroup analy-

sis for ADRs that are reported commonly for either vaccines or non-vaccines led to the disappearance of 272 SDRs for vaccines and 2,721 SDRs for non-vaccines. We could empirically derive a model that predicts the change in ROR in the subgroups based on the proportion of vaccines within the total dataset.

Conclusions

The high proportion of vaccine-related reports within paediatric ADR data has a large and mathematically predictable impact on signal-detection in paediatric ADR data. Subgroup analysis reveals new SDRs that potentially represent genuine safety signals. The most inclusive and sensitive signal detection method would be the combination of a crude and a subgroup-based data mining approach, based on the ratio between the proportion of vaccines within the ADR of interest and within all other ADRs.

Introduction

Spontaneously reported adverse drug reactions (ADRs) are an important source for identifying drug safety signals.[18] For efficient signal-detection, data mining methods have been developed that mostly are based on measures of disproportionality. Well known examples are the Reporting Odds Ratio (ROR), the Proportional Reporting Ratio (PRR), the Information Component (IC), and the Empirical Bayes Geometric Mean (EBGM).[36-40] These data mining methods are used as a first signal identifying method. Subsequently, further case evaluation is necessary to determine whether the signal of disproportionality is a real safety signal.[24,41]

Although useful, data mining methods are subject to bias and confounding. Effort has been put to allow for dealing with possible confounding factors such as age, sex and time, but with varying results.[40,276-278] Other factors that might influence the disproportionality estimates include; the number of serious versus non-serious individual case safety reports (ICSRs), consumer versus health care professional reported ICSRs, company owned databases versus databases of national competent authorities and differences in the distribution of the population characteristics within the different databases or of the different outcomes.[36,279] All these factors might lead to a relative increase of specific groups of reports by type of ADR, drug class, or age-group. Such clusters of reports may influence the distribution of drugs and ADRs within the data and thereby jeopardise the assumption that reporting should be non-differential in order to guarantee unbiased estimates of measures of disproportionality.

The phenomenon of clusters of reports of a specific group of drugs is very clearly observed in paediatric safety signal-detection. Within national compilations of paediatric ICSRs, vaccines make up 45-69% of the suspected drugs within the ADR reports.[280,281] ADRs reported for vaccines differ from non-vaccines with respect to seriousness and type.[280-282] Many studies already addressed issues around data mining within vaccine-related ADRs, mostly boosted by the work on the United States' (US) specific Vaccine Adverse Event Reporting System (VAERS) database.[276,278,283,284] Little is however known about the influence of vaccines on safety signal-detection for non-vaccines and vice versa in a mixed ADR database, containing both vaccines and non-vaccines. Due to the high exposure to vaccines in the paediatric age category, this influence will be most pronounced when data mining is applied to paediatric ADR reports.

The potential influence of vaccines on safety signal-detection for drugs was recently raised in the report of the CIOMS (Council for International Organizations of Medical Sciences) working group VIII.[24] 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. However, it has not described for which types of ADRs or drugs, subgroup analysis is beneficial.

Therefore, we studied the methodological aspects of signal detection within paediatric ADR data where the prevalence of vaccine-related ADRs is high. We studied how restriction to either vaccine or non-vaccine related ADRs influences disproportionality analyses, whether this affects the number of detected signals of disproportional reporting and for which ADRs subgroup analysis using restriction is beneficiary.

Methods

Setting

We used data from the VigiBase database of suspected ADRs. This World Health Organisation (WHO) global ICSR database system was established in 1968 and in June 2006, it held more than 3.7 million ICSRs.[29] VigiBase is maintained on behalf of the WHO Programme by the Uppsala Monitoring Centre (UMC). At the time, more than 80 countries participated in the WHO International Drug Monitoring program and another 17 countries were associate members who did not actively contribute data yet. ICSRs are submitted through the national pharmacovigilance centres. The WHO Programme member countries submit ICSRs to the UMC on a regular basis; preferably once a month, but at least every quarter.[26]

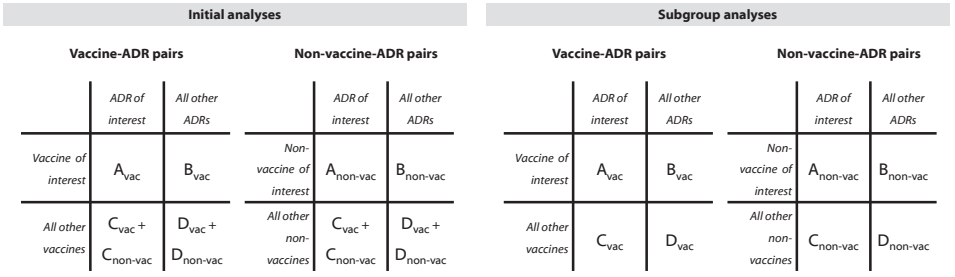
At the time of data extraction in 2006, all ADRs within VigiBase were coded using preferred terms of the WHO-Adverse Reaction Terminology (WHO-ART) coding dictionary. Reported drugs were recoded using the WHO Drug dictionary, and were also coded according to the Anatomical Therapeutic Chemical (ATC) classification system of the WHO Collaborating Centre for Drug Statistics Methodology.[30]

Selection of ICSRs and drug-ADR pairs

From VigiBase we extracted all ICSRs on children, aged 0-≤18 years, which were received or occurred between January 2000 and December 2006. Only ICSRs received through spontaneous reporting and where the drug was reported as suspected were included. The information in these reports include country of origin, type of reporter, age at onset, year of onset, sex, suspected drugs, ADRs, starting and stopping date of the suspected drugs, starting and stopping date of the ADRs, dosing regimen of the drugs, administration route, and causality assessment of the event. We excluded ICSRs where the reported drug or ADR could not be coded in the WHO drug dictionary or WHO-ART.

An ICSR can contain more than one suspected drug, or more than one ADR. We defined a drug-ADR pair as a unique combination of a single drug and a single

Figure 8.1 Distribution of vaccine-ADR and non-vaccine-ADR pairs within the two-by-two contingency table



ADR=adverse drug reaction. A_{vac}=vaccine-ADR pair of interest, $A_{non-vac}$=non-vaccine-ADR pair of interest, B_{vac}=All other ADRs for vaccine of interest, $B_{non-vac}$=All other ADRs for non-vaccine of interest; C_{vac}=ADR of interest for all other vaccines, $C_{non-vac}$= ADR of interest for all other non-vaccines, D_{vac}=all other vaccine-related ADRs, $D_{non-vac}$=all other non-vaccine related ADRs.

ADR. Hence, an ICSR containing two ADRs with one suspected drug for both ADRs counted as two pairs.

Vaccine-ADR pairs were defined as drug-ADR pairs in which a vaccine, coded using the ATC-code J07, was reported as the suspected drug. All other drug-ADR pairs were considered as non-vaccine related drug-ADR pairs.

Statistical analysis

Disproportionality calculations and subgroup analysis

For all possible, unique, drug-ADR pairs with at least 3 records within the database we calculated the reporting odds ratios (RORs) with 95% confidence intervals (95% CI).[38,39] All disproportionality analyses were conducted on a drug-ADR pair level. Calculation of the ROR is based on a two-by-two contingency table, containing all drug-ADR pairs within the dataset, in which cell A represents the number of pairs for the combination of interest, cell B all other ADRs for the drug of interest, cell C the number of pairs for the ADR of interest for other drugs and cell D all other pairs without the ADR and without the drug of interest (**figure 8.1**). When the drug-ADR pair of interest concerns a non-vaccine, cells A and B of the two-by-two table in a mixed ADR database as VigiBase will only contain non-vaccine-ADR pairs while cells C and D will contain both vaccine-ADR and non-vaccine-ADR pairs. For vaccine-related combinations, cells A and B consist solely of vaccine-ADR pairs and cells C and D will be mixed with non-vaccines.

To explore the effect of vaccine-ADRs pairs on the number of detected SDRs we performed first a crude analysis (independent of the type of drug) and subse-

quently subgroup analyses where we split the total ADR dataset in vaccine-ADR pairs or non-vaccine-ADR pairs (**figure 8.1**). In this subgroup analyses we calculated the ROR for all vaccine-ADR pairs after restriction to vaccine-ADR pairs and for non-vaccine ADRs, the calculation was restricted to non-vaccine ADR pairs.

RORs, both in the initial crude analyses and within the subgroup analyses, were additionally calculated within predefined subgroups of age in order to observe whether the effect differed across age categories. Age at the time of the event was categorised according to the guidelines of the International Conference on Harmonisation (ICH) into three categories; 0-<2 years, 2-≤11 years and 12-≤18 years.[111] The ROR was only calculated within those age-groups that contained at least 3 reports of the unique drug-ADR pair of interest.

Vaccine and non-vaccine proportion ratio

Subgroup analysis of vaccine-ADR pairs or non vaccine-ADR pairs only influences cells C and D of the two-by-two contingency table (**figure 8.1**). For each drug-ADR pair in this study the proportion of vaccine-ADR pairs and the proportion of non-vaccine-ADR pairs within cells C and D was calculated. The ratio between the proportion of vaccine-related pairs in cell C and the proportion of vaccine-related pairs in cell D was defined as the 'vaccine-proportion ratio'. The 'non-vaccine proportion ratio' was defined as the ratio between the proportion of non-vaccine related pairs in cell C and the proportion of non-vaccine related pairs in cell D.

Effect of subgroup analysis on ROR

In order to compare the subgroup specific ROR estimates with the crude overall ROR, a proportional change in the ROR was calculated. This change was calculated as follows; $[(ROR_{subgroup}/ROR_{crude})-1] \times 100\%$. A mathematical model was constructed to describe the relationship between the change in ROR and the proportion-ratio of vaccines or non-vaccines. To compare the change in ROR based on the mathematical model with the observed change in ROR, an R-square statistic was calculated (R^2).

Signals of disproportional reporting

For all unique drug-ADR pairs with at least 3 records it was determined whether the combination was a signal of disproportional reporting (SDR), defined as an ROR with a lower limit of the 95% confidence interval>1.[39] Evaluation of potential SDRs was performed both during the crude analysis and after restriction to vaccines or non-vaccines.

For SDRs that were newly detected after the subgroup analysis a random sample of 10% was taken to evaluate whether this was a false positive or a true positive association. This was obtained by evaluating whether the ADR was listed or cov-

ered in the summary of product characteristics (SPC) of the drug or vaccine of interest. For SDRs that disappeared after subgroup analysis a random sample of 5% was taken for comparison with the SPC to evaluate whether these disappearing SDRs were false negative or true negative SDRs.

Comparisons

Characteristics of the vaccine-ADR pairs and non-vaccine-ADR pairs (and within the age categories) were compared using χ^2 analysis (to compare proportions) and Mann-Whitney tests (to compare means). A *p*-value <0.05 was considered to be statistical significant.

Results

Individual Case Safety Reports (ICSRs)

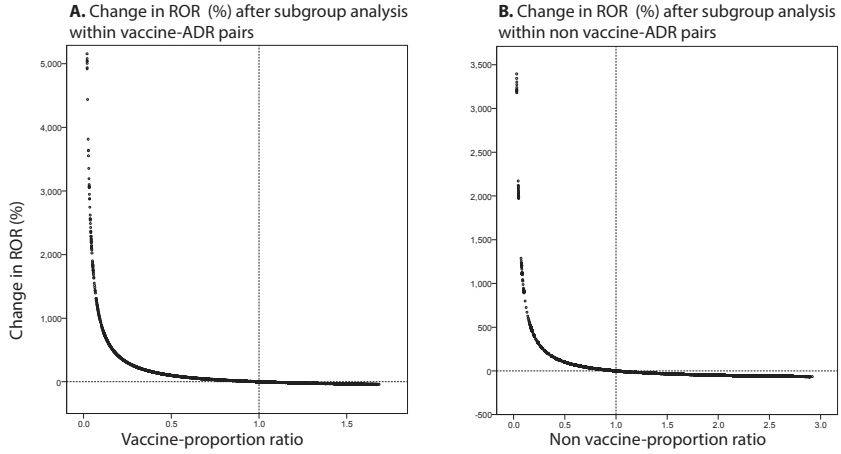
In the period between January 2000 and December 2006, 221,508 ICSRs on children aged ≤18 years were received by the WHO-UMC. ICSRs that lacked information on the reported drug or reported ADR were excluded (N=2,668; 1.2%). The remaining ICSRs (N=218,840) contained 812,415 drug-ADR pairs, with a median of 2 pairs per ICSR (**table 8.1**).

Table 8.1 Characteristics of the Individual Case Safety Reports (ICSRs)

	ICSRs N (%)	Drug-ADR pairs N (%)	# pairs / ICSR *
N	218,840 (100)	812,415 (100)	3.7
Sex; male	110,271 (50.4)	417,463 (51.4)	3.8
Age (years)			
Median (range)	5.0 (0.0-18.0)	3.0 (0.0-18.0)	
0-<2 years	74,735 (34.2)	366,023 (45.1)	4.9
2-≤11 years	84,744 (38.7)	261,488 (32.2)	3.1
12-<18 years	59,361 (27.1)	184,904 (22.8)	3.1
Vaccine-related†	117,877 (53.9)	517,642 (63.7)	4.4
0-<2 years	58,835 (78.7)	320,814 (87.6)	5.5
2-≤11 years	42,505 (50.2)	146,784 (56.1)	3.5
12-<18 years	16,537 (27.9)	50,044 (27.1)	3.0
Non–vaccine related†	100,963 (46.1)	294,773 (36.3)	2.9
0-<2 years	15,900 (21.3)	45,209 (12.4)	2.8
2-≤11 years	42,239 (49.8)	114,704 (43.9)	2.7
12-<18 years	42,824 (72.1)	134,860 (72.9)	3.1

**Mean number of drug-ADR pairs within an ICSR. †Percentage of vaccines or non-vaccines in this group relative to all ICSRs or drug-ADR pairs in this age category. Abbreviations: ADR=Adverse Drug Reaction; ICSR=Individual Case Safety Report*

Figure 8.2 Change in ROR (%) after subgroup analysis



All unique vaccine-ADR pairs with at least three records are included. On the x-axis the vaccine proportion ratio is given: the proportion of vaccines in cell C of the two-by-two table divided by the proportion of vaccines in cell D of the two-by-two table. The y-axis has been cut off at 5,000%; the actual data on the y-axis ranges from -41% to 19,055% for vaccines

All unique non-vaccine-ADR pairs with at least three records are included. On the x-axis the non-vaccine proportion ratio is given: the proportion of non-vaccines in cell C of the two-by-two table divided by the proportion of non-vaccines in cell D of the two-by-two table. The y-axis has been cut off at 3,500%; the actual data on the y-axis ranges from -66% to 6,990%.

The median age in the reported ICSRs was 5.0 years. The distribution of the ICSRs within the three predefined age categories was 34.2% in 0-<2 years, 38.7% for children aged 2-≤11 years, and 27.1% in children aged 12-≤18 years. More drug-ADR pairs per ICSR were reported for the youngest children (0-<2 years) than for the two other age categories (mean 4.9 vs. 3.1 record per ICSR) (p=0.000). Consequently, the highest proportion of drug-ADR pairs is present in the youngest category (45.1%) (p=0.000).

Vaccines were reported as suspected drug in 53.9% of all ICSRs. Vaccine-related reports had a higher number of drug-ADR pairs per ICSR than non-vaccine-related reports (4.4 vs. 2.9) (p=0.000). None of the ICSRs had both a vaccine and a non-vaccine reported as the suspected drug.

Vaccines accounted for 63.7% of the total number of drug-ADR pairs. In the youngest children (0-<2 years) the proportion of vaccine-ADR pairs was highest at 87.6% (p=0.000). This proportion decreased with age to 56.1% in children aged 2-≤ 11 years, and 27.1% in children aged 12-≤18 years (**table 8.1**).

Table 8.2 Number of signals of disproportional reporting

		Vaccines				Non-vaccines				Overall			
		Total database	0-<2 years	2-≤11 years	12-<18 years	Total database	0-<2 years	2-≤11 years	12-<18 years	Total database	0-<2 years	2-≤11 years	12-<18 years
Crude analyses													
Unique drug-ADR pairs	N	11,478	7,865	6,166	3,999	78,963	19,320	37,561	44,371	90,441	27,185	43,727	48,370
	(%) [a]	(12.7)	(28.9)	(14.1)	(8.3)	(87.3)	(71.1)	(85.9)	(91.7)	(100.0)	(100.0)	(100.0)	(100.0)
Unique drug-ADR pairs with at least 3 reports	N	5,586	3,757	2,699	1,626	20,617	3,061	8,375	10,033	26,203	6,818	11,074	11,659
	(%) [a]	(21.3)	(55.1)	(24.4)	(13.9)	(78.7)	(44.9)	(75.6)	(86.1)	(100.0)	(100.0)	(100.0)	(100.0)
Number of SDRs	N	1,637	1,053	811	716	13,375	2,468	5,518	6,016	15,012	3,521	6,329	6,732
	(%) [a]	(10.9)	(29.9)	(12.8)	(10.6)	(89.1)	(70.1)	(87.2)	(89.4)	(100.0)	(100.0)	(100.0)	(100.0)
Subgroup analyses													
Vaccine or non-vaccine proportion ratio <1 [b]	N	2,879	1,749	1,302	591	15,291	2,285	6,458	7,060				
	(%) [c]	(51.5)	(46.6)	(48.2)	(36.3)	(74.2)	(74.6)	(77.1)	(70.4)				
Vaccine or non-vaccine proportion ratio >1 [b]	N	2707	2,008	1,397	1,035	5,326	776	1,917	2,973				
	(%) [c]	(48.5)	(53.4)	(51.8)	(63.7)	(25.8)	(25.4)	(22.9)	(29.6)				
Became SDR	N	494	153	202	115	821	159	306	327				
Vaccine or non-vaccine proportion ratio <1 [b]	N	494	153	202	115	821	159	306	327				
	(%) [c]	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)				
Vaccine or non-vaccine proportion ratio >1 [b]	N	0	0	0	0	0	0	0	0				
	(%) [c]	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)				
Became non-SDR	N	272	89	205	306	2721	370	833	439				
Vaccine or non-vaccine proportion ratio <1 [b]	N	0	0	0	0	0	0	0	0				
	(%) [c]	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)				
Vaccine or non-vaccine proportion ratio >1 [b]	N	272	89	205	306	2721	370	833	439				
	(%) [c]	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)				
Increase in number of SDRs [d]	%	(30.2)	(14.5)	(24.9)	(16.1)	(6.1)	(6.4)	(5.5)	(5.4)				

All pairs with at least three records are included in the analyses. Since a drug-ADR pair can occur in either of the age categories, age categories add up above 100% of the database.
*[a] Relative frequency within vaccines or non-vaccines compared to total. [b] Vaccine proportion ratio: proportion of vaccines in cell C of the two-by-two table divided by the proportion of vaccines in cell D of the two-by-two table; Non-vaccine proportion ratio: proportion of non-vaccines in cell C of the two-by-two table divided by the proportion of non-vaccines in cell D of the two-by-two table [c] Frequency based on the total number of SDRs within this category [d] Increase in number of SDRs (%) = (newly detected SDRs)/initial SDRs*100%*
Abbreviations: ADR=Adverse Drug Reaction; SDR=signal of disproportional reporting; non-SDR=not a signal of disproportional reporting

Unique drug-ADR pairs and signals of disproportional reporting

The 218,840 ICSRs included in the analyses contained 90,441 unique drug-ADR pairs, of which 13% (N=11,478) concerned vaccine-ADR pairs. Of the unique pairs, 26,203 (29%) were reported at least three times and were included in the subgroup analyses. The number of unique pairs with at least 3 records per age-stratum was 6,818 (25.1%) for age category 0-<2 years, 11,074 (25.3%) for age category 2-≤11 years, and 11,659 (24.1%) for age category 12-≤18 years (**table 8.2**).

Within the records with at least 3 records, 21% (N=5,586) concerned vaccines. The proportion of unique vaccine-ADR pairs within the combinations with at least three records decreased with age; 55.1% (N=3,757) within children aged 0-<2 years, 24.4% (N= 2,699) within children aged 2-≤11 years, and 13.9% (N=1,626) within children aged 12-≤18 years.

In the crude analysis, 15,012 unique drug-ADR pairs with at least 3 records (57.3%) were considered a signal of disproportional reporting (SDR). These concerned 1,637 vaccine-ADR pairs (10.9% of all SDRs) and 13,375 non-vaccine-ADR pairs (89.1% of all SDRs) (**table 8.2**).

Change in ROR and SDRs after subgroup analyses

The mean proportion of vaccines in cell D of the two-by-two contingency table for the unique vaccine-ADR pairs was 63.8% (95% confidence interval (95% CI); 63.8-63.8%). For the unique non-vaccine ADR pairs, the mean proportion of non-vaccines in cell D was 36.2% (95% CI; 36.2-36.2%). The median vaccine proportion ratio was 0.98 and ranged from 0.01 to 1.68. The median non-vaccine proportion ratio was 1.89 and ranged from 0.01 to 2.92. The proportional change in ROR after restriction to either vaccine-related pairs or non-vaccine related pairs depended on the vaccine-proportion and non-vaccine proportion ratio, respectively (**figure 8.2**).

When the vaccine- or non-vaccine proportion ratio was smaller than one, the ROR increased after subgroup analysis, when the ratio was greater than one, the ROR after subgroup analysis decreased in comparison to the crude ROR. The shape of the relationship between the proportional change in ROR and the proportion of vaccines within the data was modelled mathematically (**figure 8.3 and appendices 8.I and 8.II**). The observed RORs after subgroup analyses were perfectly predicted by the model (R^2=1.0).

The shape of the relationship between the change in ROR after subgroup analysis and the vaccine- and non-vaccine proportion ratios is similar for all age categories, although the mean proportion of vaccines in cell D of the two-by-two

Figure 8.3 Estimation of proportional change in ROR and ROR after subgroup analyses

Vaccine-ADR pairs:

Change in ROR (%) after restriction to vaccine-ADR pairs =

$$100\% \times \left(\frac{D\ vac/D}{C\ vac/C} - 1\right)$$

ROR after restriction to vaccine-ADR pairs =

$$\frac{D\ vac/D}{C\ vac/C} \times ROR_{crude}$$

Non vaccine-ADR pairs:

Change in ROR (%) after restriction to non-vaccine-ADR pairs only =

$$100\% \times \frac{D\ non\ vac/D}{C non\ vac/C} - 1)$$

ROR after restriction to non-vaccine related pairs only =

$$\frac{D\ non\ vac/D}{C non\ vac/C} \times ROR_{crude}$$

C_{vac} / C=*proportion of vaccines in C*
$C_{non\ vac}$ / C=*proportion of non-vaccines in C*
D_{vac} / D=*proportion of vaccines in D*
$D_{non\ vac}$ / D=*proportion of non-vaccines in D*

table, and consequently the point where the proportion ratio equals 1 differed. The point of equality was 87.2% (95% CI 87.2-87.2%) for children aged 0-<2 years, 55.8% (95% CI 55.8-55.9%) for children aged 2-≤11 years and for children aged 12-≤18 years the point of equality was 26.9% (95% CI 26.9-26.9%). The mean proportions of non-vaccines were 12.8% (95% CI 12.6-12.8%), 44.2% (95% CI 44.1-44.2%) and 73.1% (95% CI 73.1-73.1%) for the increasing age categories (*data not shown*).

Consequently to the change in the ROR upon subgroup analyses, the number of detected SDRs changed. Of the unique vaccine-related pairs that were no SDR in the crude analysis, 494 (12.5%) became an SDR in the vaccine specific analysis, while 272 (16.6%) of the initial vaccine-related SDRs no longer were an SDR. Within the non-vaccine-ADR pairs 821 (11.3%) became an SDR and 2,721 (20.3%) no longer were an SDR after subgroup analysis. The effect of subgroup analysis on the number of detected or disappeared SDRs depended on vaccine- and non-vaccine proportion ratios (**table 8.2**). When the vaccine or non-vaccine reporting ratio was less than one, additional SDRs were detected after subgroup analysis while no SDRs disappeared. When the ratio was greater than one, SDRs disappeared after subgroup analysis while no additional SDRs were detected. When subgroup analysis is restricted to ADRs with a proportion ratio smaller than one, 30.2% more SDRs were detected for vaccines and 24.9% more SDRs were detected for non-vaccines.

Characteristics of newly detected and disappearing SDRs

A random sample of 10% of the newly detected SDRs (N=134) concerned 50 vaccine-related and 84 non-vaccine related SDRs. For the vaccines 40.0% (N=20) of the newly detected SDRs after subgroup analysis were true positives, associations that were listed in the SPC of the vaccine. For the non-vaccines 63% (N=53) of the newly detected SDRs after subgroup analysis concerned associations that were true positives.

A random sample of 5% of the SDRs (N=139) that disappeared after subgroup analysis was reviewed. These concerned ADRs of 14 vaccines of which 8 were listed in the SPC (57%) (false negatives) and ADRs of 125 non-vaccines of which 67 were listed in the SPC (54%) (false negatives).

Within all newly detected vaccine-related SDRs, the following ADRs were most frequently reported: 'Oedema periorbital' (N=10; 2.0%), 'Rash erythematous' (N=10; 2.0%), and 'Abdominal pain' (N=8; 1.6%). Of the non-vaccine related SDRs, 'Fever' (N=94; 11.4%), 'Agitation' (N=52; 6.3%), and 'Rash' (N=37; 4.5%) were most frequently reported.

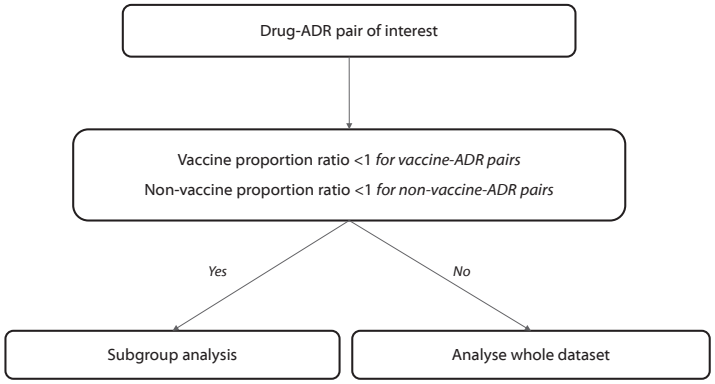
For the disappearing vaccine-related SDRs after subgroup analysis, the following ADRs were most frequently reported: 'Fever' (N=22; 8.1%), 'Injection site reaction' (N=18; 6.6%), and 'Injection site mass' (N=13; 4.8%). Of the non-vaccine related SDRs that disappeared, 'Medication error' (N=92; 3.4%), 'Death' (N=65; 2.4%), and 'Coma' (N=56; 2.1%) were the most frequently reported ADRs.

Discussion

In this study we explored methodological aspects concerning signal-detection for non-vaccine drugs and vaccines within a mixed dataset of paediatric ADR-data and how this is influenced by the proportion of vaccines within the data. For vaccine-related ADRs that were less frequently reported for vaccines compared to all other ADRs in the dataset, subgroup analysis by restriction to vaccine-related pairs led to an increase in the ROR, resulting in new vaccine-related SDRs. Equally, for non-vaccine related ADRs, additional SDRs were detected for ADRs that were less reported for non-vaccines compared to all other ADRs in the dataset.

In 2008 both Hopstadius *et al.*[277] and Woo *et al.*[278] studied the impact of stratification as a method to deal with confounding within data mining for signal-detection. Hopstadius *et al.* used VigiBase to study the effect of stratification as a method to adjust for possible confounding by age, sex, time of reporting, and country of origin. Based on their results, they concluded that the possible improvement of the data mining methods by stratification is smaller than previ-

Figure 8.4 Flowchart: A method to determine when to perform subgroup analysis



For non-vaccine ADR pairs subgroup analysis by restriction to non-vaccine ADR-pairs is beneficial if the non-vaccine proportion ratio less than one. For vaccine-ADR pairs, subgroup analysis by restriction to vaccine-ADR pairs is beneficial if the vaccine proportion ratio is less than one.

ously assumed. Woo *et al*. used the Vaccine Adverse Event Reporting System (VAERS) database for their study. Stratification by age and sex did reveal some signals that previously were undetected.

In a comment on the studies of Hopstadius and Woo, Evans touched upon the differences between conventional drugs (non-vaccines) and vaccines and highlighted the differences in health, population and spectrum of adverse events between the two groups of drugs.[285] Evans concluded that data mining within vaccine-data only has gains and losses since reactions that are commonly reported for other vaccines might be missed as a potential safety signal if they are mined in a vaccine stratum solely. An issue touched upon in the recently published report on 'Practical aspects of signal detection in pharmacovigilance' of the CIOMS VIII working group, which also considers the impact of vaccines on signal-detection.[276] In their report, the CIOMS working group states that restricting to vaccines probably does not solve all problems that are related to signal-detection within vaccines and proposed that it may be appropriate to undertake automatic signal-detection using both medicines and vaccines, and some analysis using vaccines only.

Evans' concern on the risk to miss vaccine-related signals when restricting to vaccine-related pairs, especially for ADRs commonly reported for vaccines is confirmed in our study. Using measures we defined as the 'vaccine proportion ratio', the proportion of vaccine-related pairs in cell C divided by the proportion of vaccine-related pairs in cell D, and the 'non-vaccine proportion ratio', the proportion of non-vaccine related pairs in cell C divided by the proportion of non-vaccine related pairs in cell D, we were able to identify subsets of reports for which subgroup analysis by restriction to either vaccine-related or non-vaccine

related pairs is either harmful or beneficiary.

In the current study, ADRs that were commonly reported for either vaccines or non-vaccines were reflected by a vaccine- or non-vaccine proportion ratio greater than one. For these ADRs, subgroup analysis led to a decrease in the ROR resulting in the disappearance of SDRs that were detected in the crude analysis. This can be regarded as harmful since, based on a random sample of 5%, a majority of the vaccine-related pairs and non-vaccine related pairs are included in the SPC and might represent real associations. ADRs that were reported less frequent for either vaccines or non-vaccines were reflected by a vaccine- or non-vaccine proportion ratio smaller than one. For these ADRs, the ROR increased after subgroup analysis, resulting in SDRs that were not detected in the crude analysis. This can potentially be regarded as beneficiary since, based on a random sample of 10%, 40% of the vaccine-related pairs and 63% of the non-vaccine related pairs are included in the SPC and might represent real associations.

The potential gain or loss of SDRs should be kept in mind when applying safety signal-detection in databases containing both vaccines and conventional drugs. Ignoring subgroup analysis will decrease the sensitivity of the data mining algorithm due to false negative SDRs. Restricting to subgroup analysis only will also increase the number of false negative SDRs, resulting in a lower sensitivity.

We explored under which conditions this approach, both crude analysis and subgroup analysis, is most efficient (no loss of SDRs) and will increase the sensitivity (**figure 8.4**). In this method, subgroup analyses are applied only to ADRs with a vaccine- or non-vaccine reporting ratio smaller than one, while for ADRs with a ratio greater than one the ROR is calculated using the whole dataset. Following this approach will lead to additional SDRs to be detected while no SDRs will be lost and will increase the sensitivity of the data mining algorithm.

Subgroup analysis for ADRs with a vaccine or non-vaccine proportion ratio greater than one will lead to a decrease in ROR and SDRs, but can however be informative to compare the magnitude of class effects for the individual drugs in the class. Studying fever convulsions using vaccines only will give an estimate of the disproportionality compared to the other vaccines. In other words, for which vaccines are fever convulsions most frequently reported compared to all other vaccines.

Strengths and limitations of this study

To our knowledge our study is the first to present a method which identified groups of drug-ADR pairs for which subgroup analysis using restriction is beneficiary and can increase the sensitivity of the data mining algorithm. We used a large sample size and were able to precisely predict the change in ROR due

to restriction to either vaccines or non-vaccines. Paediatric pharmacovigilance is still in its infancy and more studies and research is needed to further develop pharmacovigilance tools that can be applied within this special population.

Our study also has limitations. First, we only investigated the influence of the proportion of vaccines within the database on the estimates of the ROR. We did not study any of the other data mining algorithms for signal-detection. However, given the relatedness of analyses and dependence on the same underlying data it is likely that the results would be comparable. Second, in this study we did stratify by age, but we did not take other important confounding factors such as sex, time of reporting, country of origin, and seriousness of the reports into account. These factors are also to be considered when studying individual safety signals. Third, it should be emphasized that we used paediatric ADR data only. When applying similar methods to adult data, clustering factors might be less important resulting in fewer newly detected SDRs after subgroup analysis. Studying the influence of other factors, such as seriousness of the report, might also influence the number of detected SDRs within adult data. This might have a larger impact and implication on the daily practice of signal-detection. Fourth, subgroup analysis as performed in our study was only possible since we used ADR data on a drug-ADR pair level, which allowed us to make two mutually exclusive datasets. When performing the analysis on an ICSR level, division of the data into two strict groups might not be possible. Fifth, the data used for this study dates back to 2006. More up to date data is currently available however, using more recent data would not have influenced the methodological approach and conclusions of this study apart from the comparisons of SDRs with information from the SPCs. Finally, a subgroup analysis by restriction to either vaccines or non-vaccines has an influence on the number of drug-ADR pairs that can be used to calculate an ROR. Since restriction decreases the number of pairs included this also has its effect on the 95% CI of the estimates. This can in part explain why certain genuine drug-ADR pairs were no longer SDR after subgroup analysis (false negatives).

Conclusions

The high proportion of vaccine-related reports within paediatric ADR data has a large and mathematically predictable impact on signal-detection in paediatric ADR data. Subgroup analysis reveals new SDRs that potentially represent genuine safety signals. However, depending on the distribution of vaccine/non-vaccine reports, SDRs can also disappear after subgroup analysis. The most inclusive and sensitive signal detection method would be the combination of a crude and a subgroup-based data mining approach based on the vaccine- or non-vaccine proportion ratio.

Acknowledgements

Data from the WHO Collaborating Centre for International Drug Monitoring was used. The information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction. The opinions and conclusions expressed in this article are not necessarily those of the Uppsala Monitoring Centre, the various national centres, or the WHO.

This paper was greatly improved by the comments and extensive review of the anonymous reviewers.

Appendix 8.I. Calculation of proportional change in ROR after restriction

The calculation of the reporting odds ratio (ROR) is based on the following two-by-two table in which all drug-ADR pairs are included:

	ADR of interest	All other ADRs
Drug of interest	A	B
All other drugs	C	D

The ROR is calculated analogous to an odds ratio:

$$\text{ROR} = \frac{A \cdot D}{C \cdot B}$$

After restriction to either vaccine-ADR pairs or non-vaccine-ADR pairs we calculated the proportional change in ROR:

$$\text{Change in ROR (\%)} = 100\% \times \left(\frac{ROR2}{ROR1} - 1\right)$$

The initial crude ROR (ROR_1) and the ROR after restriction (ROR_2) only differ with respect to the number of records within cells C and D. With C_{vac} and D_{vac} being the number of records within cells C and D that are vaccine-related and $C_{non\text{-}vac}$ and $D_{non\text{-}vac}$ being the number of records within cells C and D that are non-vaccine related.

Subgroup analyses

Vaccine-ADR pairs

	ADR of interest	*All other ADRs*
Vaccine of interest	A_{vac}	B_{vac}
All other vaccines	C_{vac}	D_{vac}

Non-vaccine-ADR pairs

	ADR of interest	*All other ADRs*
Non-vaccine of interest	$A_{non\text{-}vac}$	$B_{non\text{-}vac}$
All other non-vaccines	$C_{non\text{-}vac}$	$D_{non\text{-}vac}$

In the following example the difference between the initial ROR and the ROR after restriction is given for non-vaccine related drug-ADR combinations:

$$ROR_1 = \frac{A \cdot D}{C \cdot B} = \frac{A \cdot (Dvac + Dnon\ vac)}{(Cvac + Cnon\ vac) \cdot B}$$

$$ROR_2 = \frac{A \cdot D}{C \cdot B} = \frac{A \cdot (Dnon\ vac)}{(Cnon\ vac) \cdot B}$$

When we fill in these fractions within the proportional change in ROR formula we get the following:

$$\text{Change in ROR (\%)} = 100\% \text{ x } (\frac{ROR2}{ROR1} - 1)$$

$$= 100\% \text{ x } (\frac{\frac{A \cdot (Dnon\ vac)}{(Cnon\ vac) \cdot B}}{\frac{A \cdot (Dvac + Dnon\ vac)}{(Cvac + Cnon\ vac) \cdot B}} - 1)$$

$$= 100\% \text{ x } (\frac{A \cdot (Dnon\ vac) \cdot (Cvac + Cnon\ vac) \cdot B}{(Cnon\ vac) \cdot B \cdot A \cdot (Dvac + Dnon\ vac)} - 1)$$

As A and B are both in the numerator and in the denominator, we can cross these away:

$$\text{Change in ROR (\%)} = 100\% \text{ x } (\frac{(Dnon\ vac) \cdot (Cvac + Cnon\ vac)}{(Cnon\ vac) \cdot (Dvac + Dnon\ vac)} - 1)$$

$$= 100\% \text{ x } (\frac{\frac{(Dnon\ vac)}{(Dvac + Dnon\ vac)}}{\frac{(Cnon\ vac)}{(Cvac + Cnon\ vac)}} - 1)$$

The proportion of non-vaccines related combinations within C is $\frac{Cnon\ vac}{Cvac + Cnon\ vac}$, and the proportion of non-vaccines related combinations within D is $\frac{Dnon\ vac}{Dvac + Dnon\ vac}$. Therefore the proportional change in ROR for non-vaccine related combinations can be re-written as:

$$\text{Change in ROR (\%)} = 100\% \text{ x } (\frac{\text{prop of non-vac rel. records in D}}{\text{prop of non-vac rel. records in C}} - 1)$$

Analogously the proportional change in ROR for vaccine-related combinations can be written as:

$$\text{Change in ROR (\%)} = 100\% \text{ x } (\frac{\text{prop of vaccine-rel. records in D}}{\text{prop of vaccine-rel. records in C}} - 1)$$

Appendix 8.II. Prediction of ROR after restriction

As deducted in appendix 8.I, the proportional change in ROR after restriction can be written as:

For non-vaccine related drug-ADR combinations:

$$\text{Change in ROR (\%)} = 100\% \times \left(\frac{\text{prop of non-vac rel.records in D}}{\text{prop of non-vac rel.records in C}} - 1 \right)$$

For vaccine related drug-ADR combinations:

$$\text{Change in ROR (\%)} = 100\% \times \left(\frac{\text{prop of vaccine-rel.records in D}}{\text{prop of vaccine-rel.records in C}} - 1 \right)$$

Using these formulas, the absolute ROR after restriction can also be predicted. Therefore we re-write the formula for change in ROR. In this example again the non-vaccine-ADR pairs are given.

$$\text{Change in ROR (\%)} = 100\% \times \left(\frac{\text{prop of non-vac rel.records in D}}{\text{prop of non-vac rel.records in C}} - 1 \right)$$

$$= 100\% \times \left(\frac{ROR2}{ROR1} - 1 \right)$$

This can be written as:

$$100\% \times \left(\frac{\text{proportion of non-vaccine related records in D}}{\text{proportion of non-vaccine related records in C}} - 1 \right) =$$

$$100\% \times \left(\frac{ROR2}{ROR1} - 1 \right)$$

This equals:

$$\frac{\text{proportion of non-vaccine related records in D}}{\text{proportion of non-vaccine related records in C}} = \frac{ROR2}{ROR1}$$

The ROR after restriction (ROR_2) to non-vaccine related drug-ADR combinations can consequently be written as:

$$ROR_2 = \left(\frac{\text{proportion of non-vaccine related records in D}}{\text{proportion of non-vaccine related records in C}} \right) \times ROR_1$$

Analogously, the ROR after restriction (ROR_2) to vaccine-ADR combinations can consequently be written as:

$$ROR_2 = \left(\frac{\text{proportion of vaccine-related records in D}}{\text{proportion of vaccine-related records in C}}\right) \times ROR_1$$

Estimation of ROR after subgroup analysis in general

In general, the effect of restriction based on a cluster of drugs within a database on the ROR can be described with similar mathematical models. An important assumption for applying these formulas is that the drug-ADR combination of interest can only be present in one of the strata.

The ROR after subgroup analysis based on a cluster of reports that influences the distribution of the reported drugs within the database equals:

$$ROR_2 = \left(\frac{\text{proportion of records for restriction factor in D}}{\text{proportion of records for restriction factor in C}}\right) \times ROR_1$$

The ROR after subgroup analysis based on a cluster of reports that influences the distribution of the reported ADRs within the database equals:

$$ROR_2 = \left(\frac{\text{proportion of records for restriction factor in D}}{\text{proportion of records for restriction factor in B}}\right) \times ROR_1$$

Chapter 9

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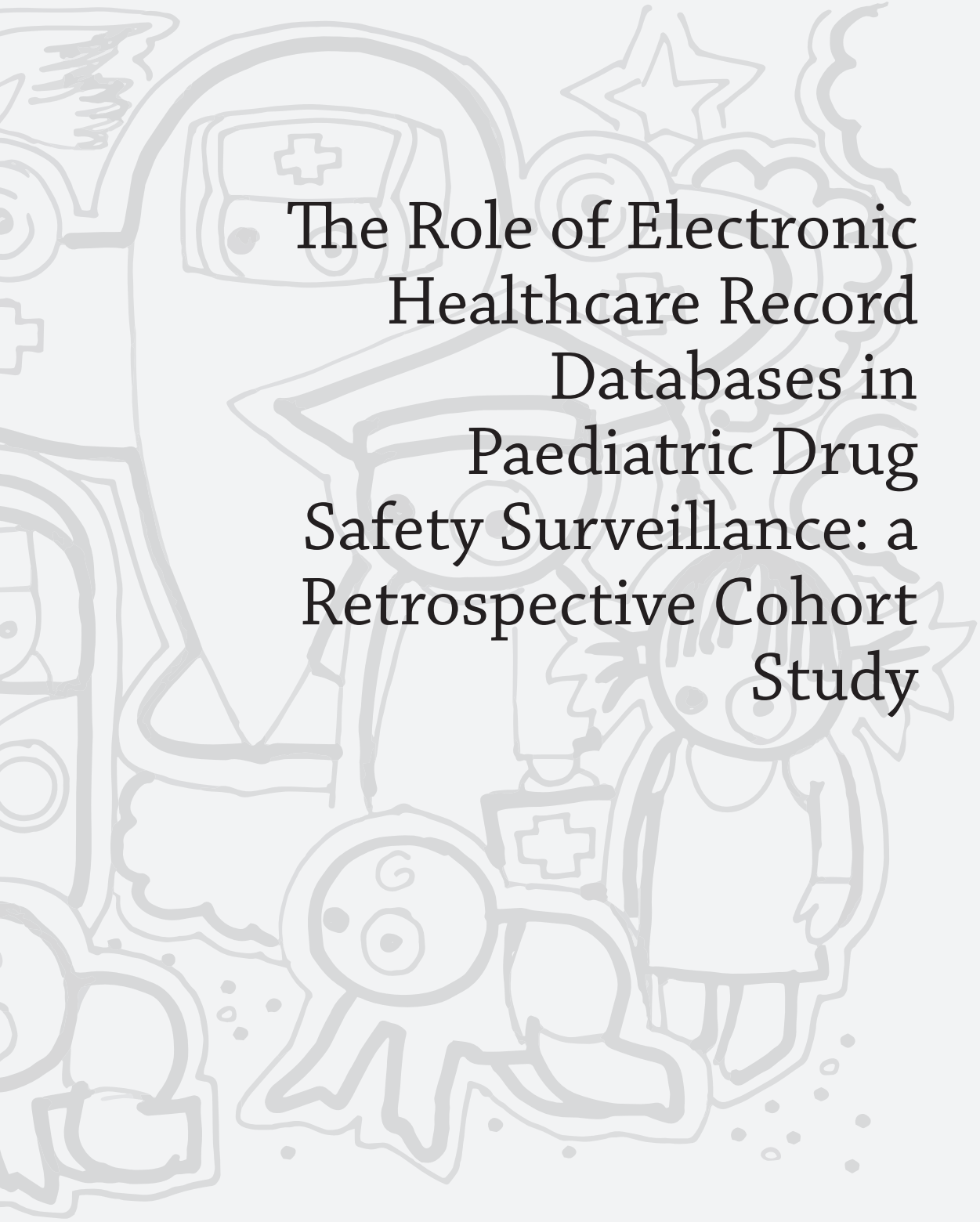


The Role of Electronic Healthcare Record Databases in Paediatric Drug Safety Surveillance: a Retrospective Cohort Study

Abstract

Background

Traditional drug safety surveillance activities do not focus specifically on children. The EU-ADR network (*Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge*) aims to use information from various electronic healthcare record (EHR) databases to produce a computerised integrated system for the early detection of drug safety signals.

Objectives

To provide estimates on the number of drugs and incidence rates (IRs) of adverse events that can be monitored in children and adolescents.

Methods

Data were obtained for children and adolescents (0-18 years) from seven population-based EHR databases of the EU-ADR network from Denmark, Italy, and the Netherlands (1996-2010). We estimated the number of drugs for which specific adverse events can be monitored as a function of actual drug use, minimally detectable relative risk (RR), and empirically-derived IRs for 10 events of interest.

Results

The paediatric population comprised 4,838,146 individuals contributing 25,575,132 person years (PY) of follow-up, being prescribed 2,170 drugs (1,610,631 PY drug-exposure). Eighteen drugs (0.8%) comprised half of the total drug exposure in PY; with 90% of the total drug exposure being represented by 158 drugs (7.3%). For a relatively frequent event such as upper gastrointestinal bleeding (IR=14.4/100,000 PY) there were 39 drugs for which an association with a RR≥4, if present, can be investigated. For rare events such as anaphylactic shock there were 8 drugs for which an association of same magnitude can be investigated.

Conclusions

Drug use in children is rare and shows little variation since only a few drugs cover the majority of the prescriptions. The number of drugs with enough exposure to detect safety signals within EHRs for rare events is limited. The use of EHR databases is particularly promising for events with a high background incidence and for drugs with a high prevalence of exposure.

Introduction

Since very few pre-approval clinical trials are performed in children and adolescents, safety monitoring of drugs in this population relies, even more than in adults, on the post-marketing phase. Currently, spontaneously reported adverse drug reactions and post-marketing safety studies are the most important sources to identify safety signals both in children and in adults.[18,286] Although there is a fair amount of experience with using spontaneous reporting systems (SRS) to study vaccine safety in children,[276,278,282,283,287,288] the use of such systems for routine safety surveillance of conventional medicines in children is limited. And although SRS have proven their value for safety surveillance, there are well recognised limitations and biases such as selective underreporting, stimulated reporting and the lack of exposure data.[24,42,43]

To complement SRS and other traditional monitoring systems, initiatives in the United States (US) and in Europe have set up population-based surveillance systems that make use of longitudinal healthcare data.[44-46] In Europe, the EU-ADR Project (*Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge*) was initiated in 2008 and is a collaboration of 18 public and private institutions. EU-ADR aims to exploit information from various electronic healthcare records (EHR) and other biomedical databases in Europe to produce a computerised integrated system for the early detection of drug safety signals.[44] A previous study within EU-ADR showed that safety surveillance in the general population using EHR databases is possible but the statistical power might be low for infrequently used drugs or for rare outcomes.[289] This study included paediatric data, although no specific analyses were performed on the paediatric population.

In this study, we aimed to provide estimates of the number of drugs that have enough exposure to be monitored in children and adolescents for events currently being investigated within the EU-ADR network using incidence rates (IRs) empirically-derived within the study. Furthermore, we aimed to provide information on the frequency range of events that can be monitored based the on actual drug-exposure in the cohort and we speculate how large a network should be to monitor drug safety in children.

Patients and Methods

Data sources and setting

We performed a retrospective cohort study using data from the EU-ADR network, of which a detailed description has been published earlier.[44,290] In sum-

mary, the EU-ADR platform currently comprises data from eight EHR databases in four European countries. For the current study we used paediatric data from the seven of the databases from three European countries: Health Search/CSD Longitudinal Patient Database (Italy), Integrated Primary Care Information (the Netherlands) and Pedianet (Italy) are population-based general practice databases, in which clinical information and medication prescriptions are recorded. Aarhus University Hospital Database (Denmark), PHARMO Network (the Netherlands), and the regional Italian databases of Lombardy and Tuscany are all comprehensive record-linkage systems in which drug dispensing data of regional/national catchment area are linked to a registry of hospital discharge diagnoses and other registries. The majority of healthcare services, including pharmaceutical services, are provided for, or subsidised by, the state in Italy and Denmark and covered by obligatory health insurance in the Netherlands. In all of these countries general practitioners or family paediatricians function as gatekeepers of the healthcare system.

Study population

The study population included children and adolescents aged 0 to 18 years within these databases. The study period ran between January 1st 1996 and December 31st 2010. Follow up started after a run-in period of 365 days. This run-in period was required to determine the first occurrence of an event. The run-in period was omitted for children younger than one year at the start of observation; these children started to contribute follow-up person time from the date of birth or the date of registration on, whichever came first.

Data from the different databases were pooled using a distributed network approach, in which data holders maintain control over their original data and only aggregated data are shared with the rest of the network. This was done through generation of the data into a common format followed by local aggregation using custom-built software, Jerboa©.[44]

Drug exposure

Drug use was categorised using the World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system.[30] Drug exposure was measured in terms of person-years (PY). We further analysed drug use by anatomical main groups (ATC 1st level), and by chemical substances (ATC 5th level).

To study the distribution of the drugs over classes of drug exposure, drugs were subsequently categorised based on the total amount of drug exposure in PY as follows: <10 PY; >10-≤50 PY; >50-≤100 PY; >100-≤500 PY; >500-≤1,000 PY; >1,000-≤5,000 PY; >5,000-≤10,000 PY; and >10,000 PY. Furthermore, the number

of drugs that accounted for 50% and 90% of the total drug exposure in the study population were calculated.

Events

The identification of the events of interest and the process of mapping and harmonisation of event coding terminologies across the various databases within EU-ADR have been described in more detail in other publications.[44,290-292] In summary, events of interest, considered to be most serious and most relevant (generally within the context of safety monitoring in adults), were included and were identified in the databases using an iterative process that included defining events based on clinical criteria established from literature, using diagnosis codes and free text as well as laboratory findings, when available. The different event coding terminologies within the databases were first mapped using the UMLS1 (Unified Medical Language System1).[293] Currently, there are 13 events that have been mapped and harmonised in the EU-ADR platform and for which age-specific incidence rates (IRs) have been estimated. The following 10 events, occurring with an annual IR of >1/100,000 PY in children were included in this study: (1) acute liver injury, (2) acute renal failure (3) anaphylactic shock; (4) bullous eruptions; (5) cardiac valve fibrosis; (6) hip fractures; (7) neutropenia; (8) acute pancreatitis; (9) pancytopenia; and (10) upper gastrointestinal bleeding (UGIB).

Statistical analysis

Given the pooled empirically derived IRs of the 10 included events, we calculated the total amount of PY of exposure that would be required to detect an association between a particular drug and a particular event over varying magnitudes of relative risk (RR) of 2 (weak signal), 4 (moderate signal), and 6 (strong signal) using a one-sided significance level $\alpha=0.05$ and power of 80% ($\beta=0.2$) using the methodology as described previously.[289] We subsequently determined the number of drugs for which there would be sufficient data for safety monitoring. The number of drugs was expressed as the number of unique chemical substances (ATC 5th level). For the drugs with enough exposure to detect the RR of interest, the proportion of the PY of exposure to these drugs, compared to the total PY of exposure for all drugs, was calculated. Analogously we calculated the range of IRs of events that can be monitored to detect weak ($RR\geq2$), moderate ($RR\geq4$) or strong ($RR\geq6$) associations based on the actual drug exposure within the cohort. These results were stratified within categories of drug exposure (as specified under 'drug exposure') and age.

Based on the actual exposure and hypothetical incidences of adverse events (1/100,000 PY; 10/100,000 PY; 50/100,000 PY; 100/100,000 PY; and 500/100,000

Table 9.1 Amount of required drug exposure to identify potentially drug-induced adverse events

		Weak association (RR≥2)			Moderate association (RR≥4)			Strong association (RR≥6)		
Event Type	IR/ 100,000 PY	Required exposure (PY)	Drugs N	% of Exp	Required exposure (PY)	Drugs N	% of Exp	Required exposure (PY)	Drugs N	% of Exp
Hip fracture	15.31	52,501	6	29.5	8,039	42	67.8	3,589	81	80.4
Upper GI bleeding	14.42	55,725	5	26.2	8,532	39	66.3	3,810	79	79.9
Neutropenia	8.10	99,259	2	13.0	15,198	25	56.9	6,786	48	70.5
Acute liver injury	3.96	202,733	0	0	31,041	9	37.3	13,860	26	57.8
Pancytopenia	3.73	215,469	0	0	32,991	9	37.3	14,730	25	56.9
Bullous eruption	3.58	224,394	0	0	34,358	9	37.3	15,341	24	56.0
Anaphylactic shock	3.23	248,526	0	0	38,053	8	35.0	16,990	20	52.1
Cardiac valve fibrosis	2.91	275,840	0	0	42,235	8	35.0	18,858	15	46.6
Acute renal failure	1.55	517,050	0	0	79,168	3	17.9	35,348	9	37.3
Acute pancreatitis	1.55	519,664	0	0	79,568	3	17.9	35,527	9	37.3

Drugs (N): Number of drugs at 5th ATC, chemical substance level that have enough PY of exposure to detect a potential signal (total 2,170). % of Exp: Proportion of PY of exposure of the drugs with enough exposure compared to the total PY of exposure for all drugs. Abbreviations: IR=incidence rate; PY=person years; RR=relative risk; Upper GI bleeding=upper gastrointestinal bleeding

PY) we also calculated for how many drugs within specific drug groups (ATC 1st level) would there be enough exposure to detect associations with varying magnitudes.

Stratification by age

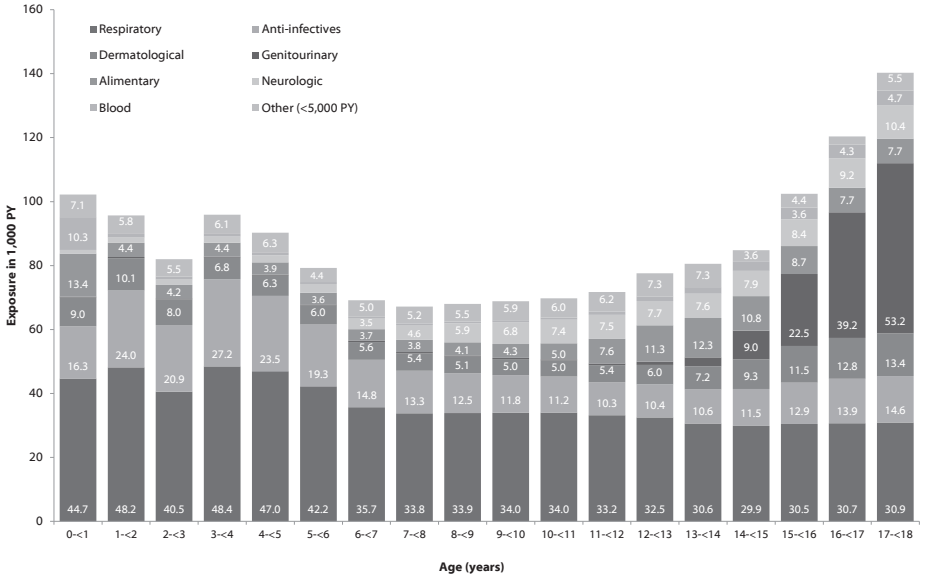
Results were stratified in one-year age categories and according to four age categories: 0-<2 years, 2-≤5 years; 6-≤11 years and 12-<18 years.[111]

Results

The paediatric population (aged 0 to 18 years) of the EU-ADR network comprised 4,838,146 individuals contributing 25,575,132 PY of follow-up (1996-2008). Of these PY, 12.8% were for children aged 0-<2 years, 22.2% for children aged 2-≤5 years, 32.7% for children aged 6-≤11 years and 32.3% for adolescents aged 12-<18 years.

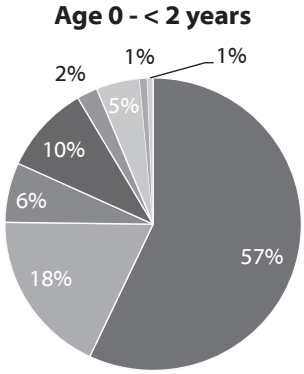
A total of 2,170 drugs were used (i.e. prescribed or dispensed) during the study period with a total exposure of 1,610,631 PY. An overview of drug exposure, at the anatomical level of the ATC classification across different age categories is

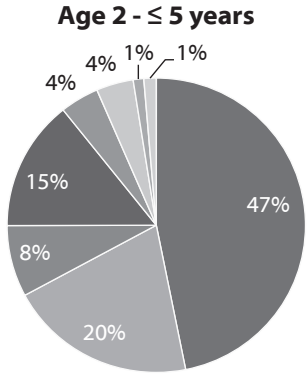
Figure 9.1 Drug exposure in person-years stratified by age

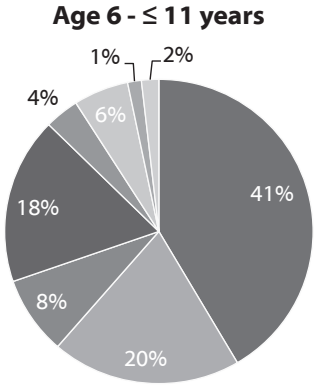


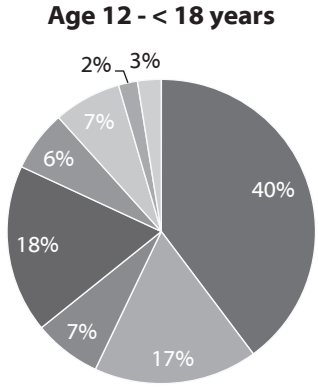
NOTE: Drug exposure is aggregated on the 1st ATC level (anatomical main group). 'Other' represents all other drug groups with a total exposure of <5,000 PY

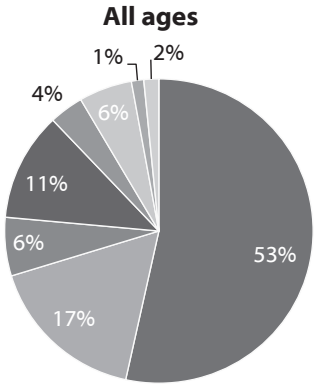
Figure 9.2 Distribution of exposure in PY by age-groups (5th ATC level)











	Range PY	Incid /1,000 PY RR≥2	Incid /1,000 PY RR≥4	Incid /1,000 PY RR≥6
	<10	<765	<12	<5.2
	>10 - ≤50	<160	<2.4	<1.1
	>50 - ≤100	<80	<1.2	<0.55
	>100 - ≤500	<16	<0.25	<0.11
	>500 - ≤1,000	<8.0	<0.12	<0.055
	>1,000 - ≤5,000	<1.6	<0.02	<0.011
	>5,000 - ≤10,000	<0.8	<0.01	<0.0055
	>10,000	≥0.8	≥0.01	≥0.0055

The range in PY is given with the corresponding incidence rates of events that can be monitored. PY=person-years; incid=incidence.

illustrated in **figure 9.1**. Up to 12 years of age, the drug classes with the highest exposure are respiratory drugs (32,200-48,400 PY) and anti-infective drugs (10,300-27,200 PY). From age of 14 years on, genitourinary drugs, mainly oral contraceptives were increasingly prescribed up to 17-<18 years, with 53,200 PY of exposure. For the entire paediatric population the drug classes with the highest exposure were respiratory drugs (661,000 PY); anti-infective drugs (279,000 PY), dermatological drugs (138,000 PY), genitourinary drugs (132,000 PY) and alimentary drugs (121,000 PY). The remaining drug classes had a total exposure of <100,000 PY (*data not shown)*.

The number of drugs that have enough exposure to detect, if present, weak (RR≥2), moderate (RR≥4) or strong (RR≥6) associations for the 10 events are presented in **table 9.1**. Since the numbers are low, these results were not further stratified by age. The stronger the association to be studied, the higher is the number of drugs that can be studied. Also more drugs can be studied for frequently occurring events. For a relative frequent event such as upper gastrointestinal bleeding (UGIB) (IR=14.4/100,000 PY), five drugs had the minimal exposure of 55,725 PY required to detect a weak association (RR≥2). These five drugs comprised 26.2% of the total drug exposure in PY. Thirty-nine drugs (66.3% of the total drug exposure) had the minimal required exposure of 8,532 PY to detect a moderate association (RR≥4) with UGIB and 79 drugs (79.9% of the total exposure) had the minimal exposure of 3,810 PY required to assess a strong association (RR≥6). On the other hand, for the rare event acute pancreatitis (1.6/100,000 PY) none of the drugs had enough exposure to detect a weak signal (RR≥2), 3 drugs (17.9% of exposure) had enough exposure to detect a moderate signal (RR≥4), and 9 drugs (37.3% of exposure) had enough exposure to detect a strong signal (RR≥6).

The number of drugs, stratified at the anatomical level of the ATC classification, with enough exposure to study hypothetical IRs to detect weak, moderate or strong associations is given in **table 9.2**. Respiratory drugs and anti-infectives were among those drugs having enough exposure to monitor associations of RR≥2, RR≥4 and RR≥6 for events having (hypothetical) IRs 10/100,000 PY and higher. None of the drugs rarely used in the study population (e.g., antineoplastic, antiparasitic, and cardiovascular drugs), had enough exposure to monitor an association with RR≥2 for any of the hypothetical incidences ranging from 1 to 500/100,000 PY.

As illustrated in **figure 9.2**, only a small proportion of drugs that are being used in the EU-ADR paediatric population of around 5 million subjects, have a high exposure in PY. About half of the drugs have a total exposure of less than 10 PY. This is most pronounced in the youngest children, for which 75% of the drugs have a total exposure of <10 PY. In the table accompanying **figure 9.2**, the minimal detectable IRs for the exposure-categories for each RR is given: for drugs with an exposure of 10 PY, IRs of 765/1,000 PY and higher can be detected for

Table 9.2 Number of drugs (5th ATC level) by class with enough exposure to study the given incidences with the given RRs

1st ATC class *		≤1/100,000 PY			≤10/100,000 PY			≤50/100,000 PY			≤100/100,000 PY			≤500/100,000 PY		
		RR≥2	RR≥4	RR≥6	RR≥2	RR≥4	RR≥6	RR≥2	RR≥4	RR≥6	RR≥2	RR≥4	RR≥6	RR≥2	RR≥4	RR≥6
Alimentary [N=391]	N (%)	-	-	-	-	1 (0.3)	2 (0.5)	1 (0.3)	11 (2.8)	21 (5.4)	2 (0.5)	20 (5.1)	37 (9.5)	14 (3.6)	52 (13.3)	66 (16.9)
Respiratory [N=160]	N (%)	-	-	3 (1.9)	2 (1.3)	15 (9.4)	21 (13.1)	12 (7.5)	29 (18.1)	37 (23.1)	18 (11.3)	35 (21.9)	47 (29.4)	30 (18.8)	54 (33.8)	63 (39.4)
Dermatological [N=203]	N (%)	-	-	-	-	2 (1.0)	8 (3.9)	1 (0.5)	14 (6.9)	23 (11.3)	5 (2.5)	23 (11.3)	35 (17.2)	19 (9.4)	48 (23.6)	62 (30.5)
Anti-infectives [N=232]	N (%)	-	-	2 (0.9)	1 (0.4)	5 (2.2)	8 (3.4)	3 (1.3)	12 (5.2)	22 (9.5)	6 (2.6)	19 (8.2)	28 (12.1)	17 (7.3)	40 (17.2)	58 (25.0)
Neurologic [N=269]	N (%)	-	-	-	-	2 (0.7)	2 (0.7)	1 (0.4)	9 (3.3)	19 (7.1)	2 (0.7)	19 (7.1)	27 (10.0)	14 (5.2)	41 (15.2)	57 (21.2)
Sensory organs [N=169]	N (%)	-	-	-	-	-	1 (0.6)	-	5 (3.0)	12 (7.1)	-	12 (7.1)	19 (11.2)	11 (6.5)	34 (20.1)	42 (24.9)
Cardiovascular [N=192]	N (%)	-	-	-	-	-	-	-	-	5 (2.6)	-	3 (1.6)	9 (4.7)	-	18 (9.4)	33 (17.2)
Genitourinary [N=153]	N (%)	-	-	1 (0.7)	-	2 (1.3)	4 (2.6)	2 (1.3)	5 (3.3)	8 (5.2)	3 (2.0)	8 (5.2)	11 (7.2)	8 (5.2)	24 (15.7)	32 (20.9)
Hormones [N=72]	N (%)	-	-	-	-	2 (2.8)	8 (11.1)	-	10 (13.9)	14 (19.4)	4 (5.6)	14 (19.4)	18 (25.0)	14 (19.4)	24 (33.3)	30 (41.7)
Musculoskeletal [N=104]	N (%)	-	-	-	-	-	-	-	2 (1.9)	5 (4.8)	-	4 (3.8)	7 (6.7)	3 (2.9)	8 (7.7)	18 (17.3)
Blood [N=97]	N (%)	-	-	-	-	-	2 (2.1)	-	3 (3.1)	6 (6.2)	2 (2.1)	5 (5.2)	7 (7.2)	3 (3.1)	11 (11.3)	16 (16.5)
Antiparasitic [N=35]	N (%)	-	-	-	-	-	-	-	-	1 (2.9)	-	1 (2.9)	1 (2.9)	-	5 (14.3)	11 (31.4)
Antineoplastics [N=76]	N (%)	-	-	-	-	-	-	-	-	2 (2.6)	-	2 (2.6)	5 (6.6)	-	6 (7.9)	10 (13.2)
Total [N=2,170]	N (%)	-	-	6 (0.3)	3 (0.1)	29 (1.3)	56 (2.6)	20 (0.9)	100 (4.6)	175 (8.1)	42 (1.9)	165 (7.6)	251 (11.6)	133 (6.1)	365 (16.8)	498 (22.9)

**First ATC level 'Various' [N=35] had no drugs with enough exposure for any of the incidences and is not presented.*

RR≥2, 12/1,000 PY and higher for RR≥4 and 5.2/1,000 PY and higher for RR≥6. The proportion of the drugs with an exposure of more than 1,000 PY (necessary to detect IRs of up to 16/1,000 PY with a RR≥2) is less than 5% within the age categories, and is only 8.4% for the total paediatric population

Eighteen of the 2,170 drugs (0.8%) make up 50% of the total drug-exposure in PY (0-<18 years) (**table 9.3**). For 0-<2 years, 2-≤5 years; 6-≤11 years and 12-<18 years there were 8 (0.6%), 8 (0.5%), 14 (0.9%) and 20 (1.0%) drugs, each of the 18 drugs had drug-exposures of ≥18,236 PY. Based on these exposures, events with IR>44/100,000 PY (RR≥2), IR>6.7/100,000 PY (RR≥4) and IR>3.0/100,000 PY (RR≥6) can be detected (*data not shown)*.

Data from 90% of the total drug exposure is represented by 158 drugs (0-<18 years). For 0-<2 years, 2-≤5 years; 6-≤11 years and 12-<18 years there were 67 (3.1%), 86 (4.0%), 125 (5.8%) and 165 (7.6%) drugs. Each of the 158 drugs had drug-exposures of ≥1,334 PY, allowing detection of events with IR>603/100,000 PY (RR≥2), IR>92/100,000 PY (RR≥4) and IR>41/100,000 PY (RR≥6) (*data not shown*).

Discussion

The number of initiatives evaluating the use of EHR databases as a source for drug safety surveillance is growing.[45,46,294,295] Some of these include data on children and adolescents; however, none of these initiatives have yet focused on the paediatric population, for which safety data are actually lacking most.

Despite the fact that almost 5 million children and adolescents are included in the EU-ADR network, the number of drugs that have enough exposure to study weak, moderate or strong associations with the events currently monitored in EU-ADR network is limited. For a rare but serious event like anaphylactic shock there were no drugs with enough exposure to study a weak association (RR≥2) and only 20 drugs to study a strong association (RR≥6). These numbers are low compared to the total of 2,170 drugs prescribed. It is mainly for drugs that are known to be chronically used in children (i.e., anti-infectives, respiratory drugs and hormones)[50] that there was enough exposure to monitor a wide range of IRs for varying magnitudes of risks. An important group of drugs for which safety alerts concerning the use in children and adolescents have been issued in recent years are central nervous system drugs like ADHD (attention deficit-hyperactivity disorder)-drugs.[12] Methylphenidate was the only neurological drug among the 18 of drugs that covered 50% of the total drug exposure in PY. Thus, safety concerns regarding methylphenidate can be studied within the EU-ADR network, but this may not be possible for other neurological drugs where the total exposure might be too low for a potential risk to be detectable.

Table 9.3 Drugs that cover 50% of the total drug exposure in person years

Age 0 to < 2 years *	Age 2 to ≤ 5 years*	Age 6 to ≤ 11 years*	Age 12 to< 18 years *	Total *
Beclometasone [R03BA01] (13.1)	Beclometasone [R03BA01] (12.5)	Salbutamol [R03AC02] (6.8)	Levonorgestrel and estrogen [G03AA07] (11.9)	Beclometasone [R03BA01] (6.8)
Salbutamol [R03AC02] (10.5)	Salbutamol [R03AC02] (9.1)	Beclometasone [R03BA01] (6.4)	Sodium fluoride [A01AA01] (3.9)	Salbutamol [R03AC02] (6.2)
Amoxicillin [J01CA04] (6.5)	Amoxicillin / Clavulanic acid [J01CR02] (7.9)	Amoxicillin / Clavulanic acid [J01CR02] (5.2)	Amoxicillin / Clavulanic acid [J01CR02] (3.4)	Amoxicillin/ Clavulanic acid [J01CR02] (4.9)
Amoxicillin / Clavulanic acid [J01CR02] (4.9)	Amoxicillin [J01CA04] (5.0)	Fluticasone [R03BA05] (4.8)	Salbutamol [R03AC02] (3.2)	Levonorgestrel and estrogen [G03AA07] (4.6)
Phytomenadione (vitamin K) [B02BA01] (4.4)	Fluticasone [R03BA05] (5.0)	Cetirizine [R06AE07] (4.1)	Cyproterone and estrogen [G03HB01] (3.2)	Amoxicillin [J01CA04] (3.6)
Fluticasone [R03BA05] (3.8)	Budesonide [R03BA02] (4.3)	Budesonide [R03BA02] (3.5)	Cetirizine [R06AE07] (2.5)	Fluticasone [R03BA05] (3.4)
Budesonide [R03BA02] (3.6)	Clarithromycin [J01FA09] (3.8)	Amoxicillin [J01CA04] (3.4)	Beclometasone [R03BA01] (2.4)	Budesonide [R03BA02] (2.9)
Flunisolide [R03BA03] (3.6)	Flunisolide [R03BA03] (3.1)	Methylphenidate [N06BA04] (3.2)	Amoxicillin [J01CA04] (2.3)	Cetirizine [R06AE07] (2.6)
		Salmeterol and other drugs for obstructive airway diseases [R03AK06] (2.7)	Ferrous sulfate [B03AA07] (2.1)	Clarithromycin [J01FA09] (2.2)
		Clarithromycin [J01FA09] (2.7)	Methylphenidate [N06BA04] (1.8)	Sodium fluoride [A01AA01] (1.9)
		Desmopressin [H01BA02] (2.3)	Salmeterol and other drugs for obstructive airway diseases [R03AK06] (1.7)	Flunisolide [R03BA03] (1.7)
		Montelukast [R03DC03] (1.7)	Desloratadine [R06AX27] (1.6)	Methylphenidate [N06BA04] (1.6)
		Fluticasone (nasal) [R01AD08] (1.7)	Budesonide [R03BA02] (1.6)	Salmeterol and other drugs for obstructive airway diseases [R03AK06] (1.6)
		Terbutaline [R03AC03] (1.6)	Fluticasone [R03BA05] (1.6)	Terbutaline [R03AC03] (1.5)
			Levocetirizine [R06AE09] (1.4)	Cyproterone and estrogen [G03HB01] (1.2)
			Gestodene and estrogen [G03AA10] (1.4)	Fluticasone [R01AD08] (1.1)
			Clarithromycin [J01FA09] (1.3)	Montelukast [R03DC03] (1.1)
			Fluticasone (nasal) [R01AD08] (1.3)	Salbutamol and other drugs for obstructive airway diseases [R03AK04] (1.1)
			Terbutaline [R03AC03] (1.2)	
			Mometasone [R01AD09] (1.1)	

** drug [5th ATC level] (% of total exposure in person years)*

This study showed that within the paediatric population of the EU-ADR network, the amount of drug exposure time is low and a limited number of drugs cover the majority of the person time of exposure. The 1.6 million PY of exposure were distributed over 2,170 individual drugs, compared to 2,289 for the overall population (all ages) in EU-ADR (95%). Of these, only 18 represented 50% and 158 drugs covered 90% of the total drug exposure time. This knowledge places the number of drugs having enough exposure to detect weak, moderate or strong associations in another context. The 20 drugs that have enough exposure to study a strong association with anaphylactic shock (at RR≥6) represent 52.1% of the total drug exposure. As illustrated in the current study, moderate associations can be studied for half of the total drug exposure, for events having IRs of ≥10/100,000 (29 drugs), while for events having IRs of ≥50/100,000 also weak associations can be studied (20 drugs). It should be noted that these results have not been corrected for multiple testing.

The number of drugs that can be investigated is also limited by the low IRs in the paediatric population of the 10 events of interest in EU-ADR. The low IRs were not surprising, since the events were chosen based on safety issues, which were more relevant in adults. Events occurring more frequently in children need less PY of exposure to study a potential association. For example the incidence of febrile seizures in young children has been estimated at 14 / 1,000 PY.[296] Based on this literature-derived incidence a total of 132 drugs within EU-ADR have enough exposure to detect a possible association at RR≥4. Therefore, in future initiatives to set up drug surveillance systems for the paediatric population using EHRs, it is very important to choose age-appropriate events and definitions.

An important unaddressed question is whether the positive predictive value of mining longitudinal healthcare database for safety surveillance will be higher than data mining in spontaneous reporting systems.[24] Trifirò and colleagues compared potential signals derived from the EU-ADR network with signals derived from spontaneous reporting systems (SRSs).[297] SRSs were more likely to detect potential associations for events with a low incidence in the general population and commonly regarded as drug-induced like Stevens Johnson syndrome and anaphylactic shock. EU-ADR may complement traditional SRS in the detection of adverse events that are frequent in the general population and are not commonly regarded to be drug-related. This is in line with the results we obtained. For events with a low IR and a high probability to be drug-induced only a small number of drugs had enough exposure to detect potentially drug-induced events. For events with a high IR a larger number of drugs could be studied. This makes EU-ADR and other healthcare data-based systems an important supplement to the existing SRS. It is also important to note that although the number of drugs that can be studied for rare events is low, the drugs that can be studied have a relatively large exposure within the population and hence, EHR databases appear to be able to detect associations for drugs that are frequently used. It is known that ADRs have the highest chance to be detected (and reported) at

the beginning of the drug therapy, since at this time both the treating physician and the patients are most aware of potential adverse events. Because of the longitudinal nature of the data collection in EHR databases, signals may also be detected after long-term use of drugs, possibly even for rare diseases.

Limitations and Future directions

Our study illustrates that the capacity of EHR databases as a source for drug safety surveillance is not primarily limited by the size of the population, but is mainly hampered by the fact that the majority of the drugs are prescribed very rarely or for a very short period of time. We emphasize that the results should be interpreted within the context of the data which gave rise to these results. Since the majority of the databases are primary care-based, specialist prescriptions (e.g., for antineoplastic drugs) are only captured in the system if continued by the general practitioner. Expansion of the database network to include other populations would be necessary to capture all drugs prescribed in the population not only to increase the size of the studied population, but also to increase the variation in prescribing patterns.

Other possible sources of paediatric data include the Mini-Sentinel and the Observational Medical Outcomes Partnership (OMOP).[46,294] The paediatric population within Mini-Sentinel comprises ~27 million children and adolescents up to 19 years (21.6% of total)[298] OMOP comprises ~39.5 million children and adolescents up to 18 years. If it would be possible to combine these data sources altogether, the current study population will be enlarged with a factor of 14.7. Assuming similar patterns of follow-up and patterns of exposure to drugs in all databases, this (hypothetical) population will have a total drug exposure of ~23.7 million PY. Consequently, for an event like anaphylactic shock the number of drugs having enough exposure to study a moderate association (RR≥4) will increase from 8 to 100 and for a more frequent event like UGIB 242, instead of 39, drugs could be investigated to study a moderate association. Global collaboration will be necessary for further development of paediatric drug safety monitoring systems using EHRs, although such collaborations may still be incapable of studying the majority, if not all, drugs used in children and adolescents. Collaboration with other currently ongoing worldwide initiatives using healthcare data for safety surveillance (such as OMOP and Sentinel Initiative) will also be important for external validation of newly identified safety signals.

Conclusions

Drug use in children is rare and only 18 out of the total 2,170 prescribed or dispensed drugs (<1%) make up half of the total exposure to drugs in the paediatric population in EU-ADR. The number of drugs with enough exposure to detect po-

tentially drug-induced adverse events using EHR for rare events in children and adolescents is limited. Mining within EHR databases seems especially promising for events that have a high background incidence in the paediatric population and for drugs with a large amount of exposure. Inter-continental collaboration will be necessary to gain enough statistical power for paediatric safety surveillance.

Signal Detection and Safety Warnings

Chapter 10

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Signal Detection for Upper Gastro-Intestinal Bleeding in Children: a Comparison Between a Spontaneous Reporting System and Electronic Healthcare Records

Abstract

Background

There is a growing number of initiatives exploring the use of electronic healthcare records (EHR) for drug safety signal detection. It is currently unknown what the capabilities of these systems are for signal detection in children and whether there are differences in the type of signals being detected using EHR or spontaneous reporting systems (SRSs).

Objectives

To compare statistical signals detected for upper gastro-intestinal bleeding (UGIB) in children and adolescents using data from EHR and SRS.

Methods

A cohort of individuals of 0-<20 years of age was obtained from seven population-based EHR databases of the EU-ADR network in 3 countries (1996-2010). A signal was defined both for the LGPS (Longitudinal Gamma Poisson Shrinker) and the SCCS (Self-Controlled Case Series) methods as a RR with lower limit of the 95% confidence interval (95% CI)>1. SRS data was derived from VigiBase and the following measures calculated: i. reporting odds ratio (ROR); ii. proportional reporting ratio (PRR); and iii. Empirical Bayes Geometric Mean (EBGM) for all drugs with ≥3 reports for UGIB. Within VigiBase, a signal was defined as having i. ROR≥2 and 95% CI>1, or ii. PRR≥2 and χ^2≥4, or iii. 5% of the EBGM quantile of the empirical Bayesian posterior distribution (EB05)≥2. For all identified signals it was checked if they were new using both the EU-ADR platform and by summaries of product characteristics.

Results

In total, 142 different signal were identified. There were 17 signals identified in both data sources; 87 signals were identified in VigiBase only and 38 in EU-ADR only. VigiBase identified more signals for drugs prescribed by specialists and used in-hospital, such as biologicals and chemotherapeutic agents. EU-ADR identified more signals for drugs with a high prevalence of use in outpatients.

Conclusions

The overlap between the number of signals identified within EU-ADR and VigiBase for UGIB in children and adolescents is limited. The ability to identify safety signals in children using EHR data is limited by the amount of exposure in the databases. Signal detection on EHR is technically possible but would profit from large collaborations with heterogeneity in exposure.

Introduction

There is a growing number of initiatives exploring the use of electronic healthcare records (EHRs) for drug safety signal detection. Population-based surveillance systems that make use of longitudinal healthcare data are being set up to complement spontaneous reporting systems (SRS).[44-46,299] In Europe, the EU-ADR Project (*Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge*) was initiated in 2008 and is a collaboration of 18 public and private institutions. The objective of EU-ADR Project was to exploit information from various EHR and other biomedical databases in Europe to produce a computerised integrated system for the early detection of drug safety signals.[44] Primarily because EHR databases comprise data collected routinely for actual medical care, their use for signal detection is not subject to biases known to affect SRS such as selective underreporting, stimulated reporting and the lack of exposure data.[24,42,43]

Now that EHR-based surveillance systems are being established it is important to know how the value of mining these longitudinal healthcare database compares to data mining in SRSs.[24] A preliminary study comparing potential signals identified from the EU-ADR network with signals derived from SRSs showed that adverse events having a very low incidence in the general population and commonly regarded as drug-induced were more likely to be identified in SRSs while events that are frequent in the general population and are not commonly regarded to be drug-related were more likely detected in EU-ADR.[297] Thereby it is believed that signal detection within EHR databases like EU-ADR may complement traditional SRS. Although EU-ADR was not set up particularly for data mining in children and adolescents we investigated in an earlier study the statistical power of the EU-ADR system to perform signal detection in this paediatric subpopulation of about 5 million individuals.[300] Our findings showed that for a relatively frequent event such as upper gastrointestinal bleeding (UGIB) there were five drugs (0.23% of total database) for which a weak association (RR≥2) and 39 drugs (1.8% of total database) for which a moderately strong association (RR≥4), if present, could be investigated.

In a sequel to this study we investigated the performance of the EU-ADR network in identifying drug safety signals for UGIB. We compared the number and type of signals identified within the EU-ADR network and a SRS (VigiBase) within a population of children and adolescents (0-<20 years).

Methods

We performed a retrospective evaluation of drug safety signals identified from EHR data in the EU-ADR network, and a spontaneous reporting system, using VigiBase, for UGIB in children and adolescents (0-<20 years).

Data sources, setting and study population

Electronic Health Records – EU-ADR network

We assembled a retrospective cohort from the network of databases of the EU-ADR Project, of which a detailed description has been published earlier.[44,290] In summary, the EU-ADR database network currently comprises data from eight EHR databases in four European countries. For the current study we used paediatric data from seven of these databases from three European countries. Health Search/CSD Longitudinal Patient Database (Italy), Integrated Primary Care Information (the Netherlands) and Pedianet (Italy) are population-based general practice databases, in which clinical information and medication prescriptions are recorded. Aarhus University Hospital Database (Denmark), PHARMO Network (Netherlands), and the regional Italian databases of Lombardy and Tuscany are all comprehensive record-linkage systems in which drug dispensing data of regional/national catchment area are linked to a registry of hospital discharge diagnoses and other registries. The majority of healthcare services, including pharmacy services, are provided for, or subsidised by, the state in Italy and Denmark and covered by obligatory health insurance in the Netherlands. In all of these countries general practitioners, or family paediatricians, function as gatekeepers of the healthcare system.

The study population in this retrospective cohort included children and adolescents aged 0 to <20 years within the abovementioned databases. The study period ran between January 1st 1996 and December 31st 2010. Follow up started after a run-in period of 365 days. This run-in period was required to determine the first occurrence of an event. The run-in period was omitted for children younger than one year at the start of observation; these children started to contribute follow-up person-time from the date of birth or the date of database registration, whichever came first. Age was divided in strata of five years to allow for correction for age in the analyses.

Data from the different databases were pooled using a distributed network approach, preserving local control by database holders over their respective data and only aggregated, de-identified results were shared with the rest of the network. This was done through generation of the data into a common format followed by local aggregation using custom-built software, Jerboa©.[44]

Spontaneous reporting system – VigiBase

We used data from the VigiBase repository of suspected ADRs as source for the spontaneous reporting system data. This World Health Organisation (WHO) global individual case safety report (ICSR) database system was established in 1968 and contained more than 5.0 million ICSRs by 2010.[29] VigiBase is maintained on behalf of the WHO International Drug Monitoring Programme by the Uppsala Monitoring Centre (WHO-UMC). As of 2010, there are more than 80 countries participating in the programme and another 17 associate member countries that have yet to actively contribute data. ICSRs are submitted to the WHO-UMC through the national pharmacovigilance centres on a regular basis, at least every quarter or, more often, once a month.[26] From the VigiBase data released in the last quarter of 2010 we extracted all ICSRs on children aged 0-20 years. Both suspect and co-occurring drugs were included.

Drug exposure

In both EU-ADR and VigiBase drug use was categorised using the WHO Anatomical Therapeutic Chemical (ATC) classification system,[30] at the 5th level (chemical substance).

Selection of events

EU-ADR

This analysis focused on UGIB. The identification of UGIB and the process of mapping and harmonisation of event coding terminologies across the various databases within EU-ADR has been described in more detail in other publications.[291,292,301] In summary, events of interest, considered to be most serious and most relevant (generally within the context of safety monitoring in adults), were included and were identified in the databases using an iterative process that included defining events based on clinical criteria established from literature, using diagnosis codes and free text as well as laboratory findings, when available. The different event coding terminologies within the databases were first mapped using the UMLS1 (Unified Medical Language System1).[293]

VigiBase

Reports were selected based on preferred terms (PTs) of MedDRA. Reports with the following PTs were included: *chronic gastrointestinal bleeding*; *duodenal ulcer haemorrhage*; *duodenitis haemorrhagic*; *gastric haemorrhage*; *gastric occult blood positive*; *gastric ulcer haemorrhage*; *gastric ulcer haemorrhage obstructive*; *gastric varices haemorrhage*; *gastritis haemorrhagic*; *gastroduodenal haemorrhage*; *gas-*

troduodenitis haemorrhagic; *gastrointestinal haemorrhage*; *gastrointestinal ulcer haemorrhage*; *haematemesis*; *haematochezia*; *haemorrhagic erosive gastritis*; *melaena*; *occult blood positive*; *oesophageal haemorrhage*; *oesophageal ulcer haemorrhage*; *oesophagitis haemorrhagic*; *peptic ulcer haemorrhage*; *ulcer haemorrhage*; *upper gastrointestinal haemorrhage*.

Statistical analysis – Statistical signals

The definition of a statistically significant signal depends on the statistical method used and the thresholds defined. In both the EHR-data and the SRS data at least 3 reports of an event occurring during exposure were needed to be classified as a potential signal.

EU-ADR

The EU-ADR system has not established a fixed way to establish signals but developed methods for signal generation, bias and confounding assessment plus signal substantiation in a recognition that temporal statistical associations on electronic health care records alone would yield too many false positives. For signal generation we used the Longitudinal Gamma Poisson Shrinker (LGPS),[302,303] and the self-controlled case series analyses (SCCS). LGPS is developed within EU-ADR and is a modification of the Gamma Poisson Shrinker that uses person-time rather than case counts for estimating the expected number of events. SCCS uses information from cases only and thereby controls for stable confounding within a person.

In an additional analysis we filtered signals that are potentially due to protopathic bias using a method developed in EU-ADR: the Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs (LEOPARD).[302] We defined a statistically significant signal for the LGPS and the SCCS as a RR with a lower limit of the 95% confidence interval (95% CI) >1.

VigiBase

For VigiBase we applied three different data mining algorithms. We applied two frequency-based methods, the reporting odds ratio (ROR) and the proportional reporting ratio (PRR), and one Bayesian-based method, the Empiric Bayes Geometric Mean (EBGM). The EBGM is, just as the ROR and PRR, based on disproportionality of reporting, but uses Bayesian statistics to shrink estimates of risks. A signal was considered significant for i.ROR≥2 and 95% CI>1, or ii. PRR≥2 and chi-square (χ^2)≥4, or iii. the 5% quantile of the empirical Bayesian posterior distribution (EB05) ≥2.[38,39,304] Since vaccines are included in VigiBase, whereas they are not systematically captured in all EU-ADR databases, we removed the vaccine-related events from the results to make the two systems more comparable.

Statistical analysis – Substantiation of signals

All signals identified in either EU-ADR or VigiBase were evaluated for their occurrence in literature. All identified events were processed through the EU-ADR Web Platform, a workflow that integrates information on targets and proteins with the drugs and suggests possible biological pathways that connect the drug and the event.[305] It is an open workspace for the integrated analysis of pharmacovigilance datasets. Drug–event pairs can be substantiated and statistically analysed within the platform's working environment (*https://bioinformatics.ua.pt/euadr/*). Using the EU-ADR Web Platform, for each identified signal it was checked if it was known in literature. For signals not known in EU-ADR it was checked whether they were listed in the summary of product characteristics (SPC) of the drug.

Statistical analysis – Comparisons

For each event we compared the number of signals identified within the type of data source (EHR or SRS) using the different methods. We also determined how many signals were identified in both systems and described the characteristics of the signals identified by each method.

Results

Incidence rates

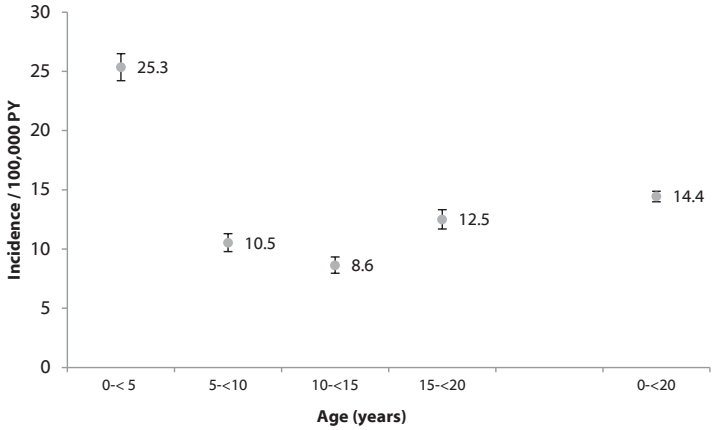
The EU-ADR network cohort (age 0-20 years) contributed a total of 28,777,287 person years (PY) of follow-up (1996-2010) and 1,921,359 PY of drug-exposure. The incidence rate of UGIB is presented in **figure 10.1**.

Signals

The number of identified statistical signals for UGIB using the different methods in EU-ADR and VigiBase is presented in **table 10.1.** An overview of the identified signals is presented in **table 10.2.**

Within EU-ADR there were 55 signals with a RR≥1 for UGIB based on the LGPS and 30 signals for SCCS. Filtering with LEOPARD reduced the number of potential signals to 15 for LGPS (27.2%) and 5 for SCCS (16.7%). Out of the 15 signals identified after applying LPGS and LEOPARD-filtering, three were known associations based on the EU-ADR web platform (*ibuprofen, diclofenac and acetylsalicylic acid*) and two were included in the SPC (*baclofen and ursodeoxycholic acid*) (**figure 10.2**).

Figure 10.1 Incidence rates of upper gastro-intestinal bleeding in EU-ADR



Incidence number of events per 100,000 person years with 95% confidence interval (Poisson regression) by age categories

In VigiBase there were 206 drugs with at least 3 reports of UGIB. Using the ROR we identified 104 statistical safety signals (50.5%). The PRR could identify 94 (90.4%) of these signals and EBGM 37 (35.6%). Based on the literature-based information in the EU-ADR platform literature workflow and the SPCs, 39 signals as identified by ROR (37.5%), 33 signals as identified by PRR (35.1%), and 10 signals (27.0%) as identified by the EBGM are possible new associations.

Table 10.1 Number of signals detected for upper gastrointestinal bleeding

	Without LEOPARD filtering		With LEOPARD filtering	
Data source	Signals identified N	Unknown signals N (%)*	No protopathic bias detected N (%)	Unknown signals N (%)**
EU-ADR (EHR)				
LGPS	55	32 (58.2%)	15 (27.2%)	10 (66.7%)
SCCS	30	15 (50.0%)	5 (16.7%)	2 (40.0%)
VigiBase (SRS)				
ROR	104	39 (37.5%)	-	-
PRR	94	33 (35.1%)	-	-
EGBM	37	10 (27.0%)	-	-

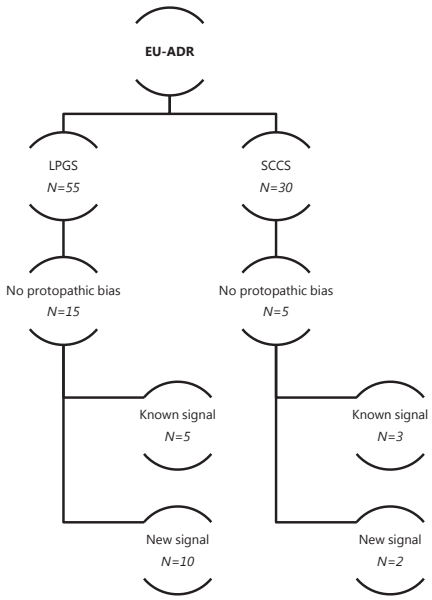
** % of all signals; ** % of signals without protopathic bias. Abbreviations: EGBM=Empiric Bayes Geometric Mean; EHR=electronic healthcare records; LGPS=Longitudinal Gamma Poisson Shrinker; N=number; PRR=proportional reporting ratio; ROR=reporting odds ratio; SCCS=self-controlled case series; SRS=spontaneous reporting system.*

Comparison of the identified signals

The overlap of the number of identified signals between the different methods is illustrated in **figure 10.3**. Using the most liberal approaches (in VigiBase based on ROR and in EU-ADR LGPS without LEOPARD-filtering), 142 different signals were identified, of which 17 (12.0%) were identified in both data sources. Eighty-seven (61.3%) signals were identified in VigiBase only (61.3%), and 38 (26.8%) signals in EU-ADR only. Using the EU-ADR platform literature workflow and the SPCs, 41.2% of the signals identified in both data sources (N=11; 64.7%) are known. Of the 87 signals identified in VigiBase only, 54 (62.1%) are known and of the 38 signals identified only in EU-ADR, 12 (31.6%) are known.

Of the 17 signals identified in both sources, thus with a significant LPGS in EU-ADR and a significant ROR in VigiBase, no indication for protopathic bias was detected using LEOPARD for 6 drugs (35.3%): acetylsalicylic acid, baclofen, diclofenac, enoxaparin, furosemide and ibuprofen. Of these, acetylsalicylic acid, diclofenac, and ibuprofen are known to be associated with UGIB. Furosemide would be considered as a new signal identified in both sources.

Figure 10.2 Number of statistical signals by method within EU-ADR

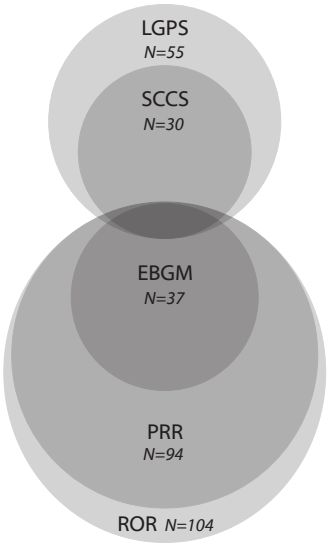


LGPS: RR of LGPS ≥ 1; SCCS: RR of SCCS ≥ 1; no protopathic bias: no indication for protopathic bias based on LEOPARD filtering; Known signal: signal known in literature based on EU-ADR web platform or included in SPC; New signal: signal unknown in literature based on EU-ADR web platform and not included in SPC.

Of the 87 signals identified in VigiBase only based on the ROR, 38 drugs had no exposure in EU-ADR (43.7%) and for 49 drugs there were less than 3 events present during exposure (56.3%). The drugs identified in VigiBase that had no exposure in EU-ADR (N=38), most often belonged to the '*antineoplastic and immunomodulating agents*' (N=15, 39.5%) anatomical main groups of the ATC-classification system (14 antineoplastic drugs). Potential signals that were picked up as signal in VigiBase only and had 1 or 2 events in EU-ADR included terbutaline (N=2), cefixime (N=2), prednisolone (N=2), piroxicam (N=2), warfarin (N=2), naproxen (N=1), azathioprine (N=1), fluconazole (N=1), celecoxib (N=1), sodium chloride (N=1), ketorolac (N=1), darbepoetin alfa (N=1), and cyclophosphamide (N=1). Of these, terbutaline and cefixime could be considered as a new signal.

Of the 38 signals identified in EU-ADR only, using the LGPS, there were no reports in VigiBase for 17 of these (44.7%), 9 had less than 3 reports (7.9%) and 12 (31.6%) did have more than 3 reports, but were not statistically significant using the ROR as reference. The signals identified in EU-ADR only that were not filtered out based on protopathic bias were levothyroxine sodium, fusidic acid,

Figure 10.3 Overlap between different data mining algorithms



	LGPS	SCCS
ROR	17	9
PRR	14	8
EBGM	6	3

An illustration of the overlap between the number of detected signals using the different signal detection methods. SCCS overlaps completely with LGPS. EBGM overlaps completely with PRR. PRR overlaps completely with ROR. In the 2x2-tables the number of overlapping signals between the methods is presented. Abbreviations: EBGM= Empiric Bayes Geometric Mean; LGPS= Longitudinal Gamma Poisson Shrinker; PRR=proportional reporting ratio; ROR=reporting odds ratio; SCCS=self-controlled case series.

xylometazoline, sulfamethoxazole and trimethoprim, oxcarbazepine, phenobarbital, combinations of local anesthetics, trimethoprim and ursodeoxycholic acid.

Discussion

In the current study we compared safety signals for UGIB in children and adolescents identified from electronic health records and spontaneous reporting data. There was very little overlap in the potential signals identified by these two systems; only 12.0% of the statistical significant signals were found in both data sources.

Most of the signals that were identified only within VigiBase did not have exposure data within EU-ADR. These drugs were mainly specialist-prescribed drugs and included chemotherapeutics, biologicals and nervous system drugs. This shows that investigation of these signals with hypothesis testing studies would require linkage of EHR with databases that capture in-hospital drug use and use of biologicals. Some of the identified signals from VigiBase did have exposure and events within EU-ADR, but these signals were not considered statistically significant because of a lack of power. This underlines the need for building larger network with paediatric data to enlarge the sample size in order to increase the number of signals that can be detected or verified. Signals identified in EU-ADR only which had <3 reports in VigiBase were mostly old and widely used drugs. These results might indicate that data mining within EHR and SRS is complementary and may differ in the type of signals that are identified. The highest proportion of known signals was present within those signals identified in both data sources.

In a previous study it was shown that within EU-ADR the best performing method was the sequential use of LPGS and LEOPARD.[303] In the current study we also chose to include SCCS as method for signal detection and listed the results next to the LGPS. SCCS was originally designed as a method for studying vaccine safety and has gained much popularity in this field in recent years.[306,307] This method uses information from the cases (events) only. Because in this method the case serves as its own control, all time-invariant confounding factors are automatically accounted for and with its high efficiency it could be expected to perform well in this population of children and adults where both exposure and events are rare. The application of SCCS may reduce the number of confounded signals and thereby increase the specificity of the signal detection method. We saw that, mainly due to a lack of power, less signals were identified using SCCS. An interesting finding was that in 43.6%, the estimate of the SCCS was not within the 95% CI of the LGPS. In 65.2% of these signals there was an indication for protopathic bias, indicating that SCCS better accounted for the correction for protopathic bias in its estimate, and and gives credence to our hypothesis that SCCS may reduce the number of confounded signals, although the proportion of

statistical signals without an indication of protopathic bias was lower for SCCS. We need to further test how the combination of LGPS, LEOPARD and SCCS may further reduce potential false positive results. We can conclude that the false positive rate is limited when signal detection is done for paediatrics only, mostly because of the lack of power due to limited exposure.

Strengths and limitations

The main strength of this study is the size of the studied cohort, which comprised almost 30 million person-years of follow up. To our knowledge, this is the first study that compares the performance of SRSs and EHR databases for signal detection in children and adolescents. Unfortunately, even if being large in size the power of this cohort is still limited. By using information on ADRs from the EU-ADR web platform we were able to give an estimate on the number of detected known signals as a proxy for specificity. The performance of data mining algorithms on different data sources is ideally tested by calculating sensitivity, specificity, or the area under the receiver operating characteristics curve (ROC curve). A reference standard as developed within the EU-ADR project[308] could not be used in the current study since it was based on data from adults and many of the drugs in the reference standard were not prescribed in the paediatric population. This underlines the need for a reference standard of drug-adverse event associations that can be applicable to the paediatric population. Finally, it was not possible to perform causality assessment on an individual basis since we only used aggregated data. As with all data mining methods it should be emphasized that this is only for hypothesis generation and causality assessment on individual case level remains essential.

Conclusions

The overlap between the number of signals identified within EU-ADR and VigiBase for UGIB in children and adolescents is limited. Signal detection and therefore also verification of signals arising from SRS databases for children in EHR data is currently hampered by a lack of statistical power. VigiBase identified more signals for drugs prescribed by specialists and used in-hospital, like biological and chemotherapeutics. EU-ADR identified more signals for older drugs with a high prevalence of use in outpatients. Enlarging the study population, acquisition of data on in-hospital drug use, and expansion of the study population are essential for improving signal detection or verification opportunities within EHR databases.

Table 10.2 All identified signals for UGIB (ordered by decreasing exposure in EU-ADR)

Drugname	EU-ADR N	Exp. in PY *	Prot. Bias **	Known ? ***	LPGS RR (95% CI)	SCCS RR (95% CI)	VigiBase N	ROR [95% CI]	PRR [χ^2]	EB05
Salbutamol	50	108024	Yes	No	2.9 [2.2-3.8]	2.2 [1.6-3.1]	13	0.8 [0.5-1.3]	0.8 [0.3]	0.5
Amoxicillin and enzyme inhibitor	46	88755	Yes	No	3.7 [2.8-4.9]	3.4 [2.5-4.6]	4	2.6 [1.1-5.9]	2.6 [2.4]	0.8
Amoxicillin	29	64946	Yes	Yes	2.8 [1.9-3.9]	2.2 [1.5-3.3]	73	1.2 [1.0-1.5]	1.2 [2.9]	1.0
Clarithromycin	23	39330	Yes	Yes	4.0 [2.6-5.8]	3.9 [2.5-6.1]	18	1.5 [1.0-2.3]	1.5 [2.8]	1.0
Salmeterol	9	28785	Yes	No	3.0 [1.5-5.3]	2.7 [1.1-6.5]	-	-	-	-
Terbutaline	2	26157	Yes	No	-	-	6	2.2 [1.1-4.4]	2.2 [2.9]	0.9
Ferrous sulfate	13	21964	Yes	SPC	6.4 [3.7-11.0]	5.6 [2.6-11.9]	-	-	-	-
Levocetirizine	12	17563	Yes	No	4.0 [2.2-6.6]	4.2 [1.7-10.5]	1	-	-	-
Azithromycin	7	17012	Yes	No	2.8 [1.3-5.2]	2.3 [1.0-4.9]	24	2.0 [1.4-2.8]	2.0 [11.2]	1.4
Valproic acid	8	14705	Yes	SPC	4.3 [2.1-7.8]	1.1 [0.4-2.8]	31	0.8 [0.6-1.1]	0.8 [0.7]	0.6
Cefixime	2	11937	Yes	No	-	-	11	2.4 [1.5-4.0]	2.4 [7.8]	1.3
Levothyroxine sodium	4	10858	No	No	2.7 [1.1-5.9]	∞	-	-	-	-
Lactulose	7	10274	Yes	No	2.8 [1.3-5.2]	1.1 [0.5-2.6]	-	-	-	-
Phytomenadione	6	9039	Yes	No	4.7 [2.1-9.6]	1.1 [0.3-3.7]	3	3.2 [1.2-8.3]	3.1 [2.5]	0.7
Betamethasone	4	8083	Yes	No	3.0 [1.2-6.5]	2.4 [0.5-11.1]	7	3.3 [1.7-6.1]	3.2 [8.7]	1.4
Phenoxymethylpenicillin	0	7691	-	No	-	-	38	2.3 [1.7-3.0]	2.3 [25.2]	1.7
Ceftibuten	4	7350	Yes	No	2.9 [1.1-6.3]	2.1 [0.8-5.7]	1	-	-	-
Prednisone	8	6932	Yes	SPC	8.9 [3.9-20.3]	2.2 [0.9-5.1]	23	4.2 [3.0-6.0]	4.2 [52.1]	2.7
Fusidic acid	5	6921	No	No	3.0 [1.3-6.0]	2.6 [0.8-8.6]	2	-	-	-
Sertraline	3	6612	Yes	Yes	3.6 [1.2-8.8]	5.5 [0.6-46.8]	7	0.6 [0.3-1.1]	0.6 [1.9]	0.3
Omeprazole	39	6472	Yes	Yes	38.2 [27.6-51.7]	4.0 [2.5-6.3]	10	2.6 [1.5-4.3]	2.6 [7.9]	1.3
Xylometazoline	7	6424	No	No	3.4 [1.6-6.5]	1.5 [0.6-3.7]	-	-	-	-
Hydrocortisone	7	5094	Yes	No	4.0 [1.9-7.5]	3.6 [1.5-8.9]	4	1.3 [0.6-2.9]	1.3 [0.0]	0.4

Drugname	EU-ADR N	Exp. in PY *	Prot. Bias **	Known ? ***	LPGS RR (95% CI)	SCCS RR (95% CI)	VigiBase N	ROR [95% CI]	PRR [χ^2]	EB05
Sulfamethoxazole and trimethoprim	11	5030	No	No	12.4 [5.7-24.5]	4.3 [2.0-9.5]	18	0.4 [0.3-0.6]	0.4 [15.3]	0.3
Ibuprofen	5	4936	No	Yes	5.6 [2.3-13.6]	6.3 [2.4-16.8]	282	8.2 [7.4-9.0]	7.9 [1,573.5]	6.6
Macrogol, combinations	13	4763	Yes	SPC	13.3 [6.5-24.3]	18.8 [8.2-43.3]	-	-	-	-
Lamotrigine	6	4341	Yes	No	9.5 [3.5-25.9]	2.2 [0.6-8.1]	13	0.6 [0.4-1.0]	0.7 [2.1]	0.4
Erythromycin	5	4262	Yes	Yes	6.2 [2.5-16.3]	3.6 [1.1-11.6]	28	1.2 [0.9-1.6]	1.2 [0.6]	0.8
Ranitidine	19	4190	Yes	No	17.7 [10.2-27.9]	2.1 [1.2-3.5]	9	1.3 [0.7-2.2]	1.3 [0.2]	0.6
Clindamycin	0	4027	-	No	-	-	13	2.6 [1.7-4.2]	2.6 [11.4]	1.5
Macrogol	8	3861	Yes	SPC	4.0 [2.0-7.3]	2.8 [1.1-7.5]	1	-	-	-
Naproxen	1	3770	No	Yes	-	-	54	5.8 [4.6-7.3]	5.7 [201.5]	4.3
Oxcarbazepine	3	3713	No	No	5.4 [1.7-19.0]	5.1 [0.5-51.9]	5	0.8 [0.4-1.8]	0.8 [0.0]	0.3
Diclofenac	3	3525	No	Yes	3.7 [1.3-9.1]	1.7 [0.5-6.1]	42	6.4 [4.9-8.2]	6.2 [176.1]	4.4
Domperidone	15	3223	Yes	No	19.8 [10.5-32.8]	4.4 [2.2-8.8]	2	-	-	-
Lactitol	4	2649	Yes	No	4.1 [1.6-9.2]	2.7 [0.7-10.9]	-	-	-	-
Mesalazine	8	2537	Yes	SPC	32.9 [14.1-63.4]	3.7 [1.3-10.2]	11	4.3 [2.6-7.2]	4.3 [24.3]	2.1
Phenobarbital	4	2449	No	No	8.2 [2.5-28.8]	0.7 [0.2-2.2]	5	0.7 [0.4-1.5]	0.7 [0.3]	0.3
Acetylsalicylic acid	6	2335	No	Yes	21.3 [6.0-49.7]	10.2 [2.9-36.0]	206	16.0 [14.2-18.1]	14.9 [2,530.5]	12.3
Combinations, local anest	3	2322	No	No	5.1 [1.6-16.4]	2.4 [0.5-10.8]	-	-	-	-
Prednisolone	2	2214	Yes	SPC	-	-	16	3.1 [2.0-4.7]	3.1 [20.2]	1.8
Trimethoprim	3	2090	No	No	5.2 [1.7-17.2]	2.7 [0.3-23.4]	2	-	-	-
Nystatin	5	1866	Yes	No	5.6 [2.3-13.6]	1.7 [0.6-4.9]	1	-	-	-
Propranolol	3	1761	Yes	SPC	5.3 [1.7-18.6]	5.2 [0.8-33.5]	-	-	-	-
Esomeprazole	9	1704	Yes	Yes	44.2 [21.5-81.2]	9.1 [3.6-23.3]	4	5.0 [2.2-11.5]	4.9 [8.9]	1.3
Furosemide	3	1630	No	No	6.7 [1.9-27.9]	0.8 [0.1-4.7]	5	2.5 [1.2-5.2]	2.5 [3.1]	0.9
Trivalent Ferrous	4	1555	Yes	SPC	6.9 [2.3-23.1]	2.5 [0.8-7.8]	-	-	-	-
Cisapride	4	1524	Yes	No	10.8 [2.9-38.3]	1.0 [0.2-3.9]	10	2.4 [1.4-4.0]	2.3 [6.4]	1.2

Drugname	EU-ADR N	Exp. in PY *	Prot. Bias **	Known ? ***	LPGS RR (95% CI)	SCCS RR (95% CI)	VigiBase N	ROR [95% CI]	PRR [χ^2]	EB05
Ispaghula (psylla seeds)	4	1484	Yes	No	5.8 [2.1-16.8]	1.4 [0.4-5.4]	-	-	-	-
Ketoprofen	0	1461	-	Yes	-	-	22	6.6 [4.6-9.4]	6.4 [95.3]	3.9
Lansoprazole	6	1432	Yes	Yes	37.3 [12.9-79.5]	5.2 [1.9-14.0]	4	3.7 [1.6-8.5]	3.7 [5.3]	1.0
Baclofen	6	1348	No	SPC	55.3 [22.2-115.6]	1.8 [0.4-7.4]	8	2.9 [1.6-5.3]	2.9 [8.2]	1.3
Azathioprine	1	1281	Yes	SPC	-	-	7	2.5 [1.3-4.6]	2.4 [4.6]	1.1
Enoxaparin	3	1198	No	SPC	15.3 [2.7-63.5]	6.3 [1.4-28.7]	5	4.6 [2.2-9.6]	4.5 [10.3]	1.4
Pantoprazole	13	1135	Yes	Yes	89.7 [50.0-149.4]	33.2 [14.1-78.0]	2	-	-	-
Combinations, cough and cold	3	1128	Yes	No	6.4 [1.9-26.3]	17.3 [3.5-86.7]	-	-	-	-
Magaldrate	4	1093	Yes	SPC	34.8 [6.3-92.6]	17.9 [5.1-62.5]	-	-	-	-
Fluconazole	1	1002	No	Yes	-	-	6	2.2 [1.1-4.4]	2.2 [2.9]	0.9
Piroxicam	2	904	No	Yes	-	-	20	11.5 [7.9-16.9]	11.0 [171.1]	6.0
Sucralfate	4	903	Yes	No	38.1 [7.0-99.6]	4.4 [1.4-14.1]	-	-	-	-
Ursodeoxycholic acid	8	703	No	No	82.7 [38.7-157.0]	3.7 [1.4-9.3]	-	-	-	-
Ordinary salt combinations	4	666	Yes	No	33.9 [6.1-90.8]	8.1 [2.7-24.6]	-	-	-	-
Bisacodyl	5	625	Yes	No	47.3 [15.4-107.0]	78.8 [18.3-339.8]	1	-	-	-
Rabeprazole	4	534	Yes	No	61.7 [17.5-152.3]	13.5 [3.0-61.7]	-	-	-	-
Dexamethasone	3	487	Yes	Yes	40.3 [4.9-127.7]	11.6 [0.7-185.5]	16	3.4 [2.2-5.2]	3.4 [24.2]	2.0
Warfarin	2	443	No	Yes	-	-	15	9.9 [6.4-15.4]	9.5 [106.0]	4.7
Meloxicam	0	398	-	Yes	-	-	3	6.2 [2.4-16.3]	6.0 [8.1]	1.1
Celecoxib	1	331	Yes	Yes	-	-	11	8.7 [5.2-14.5]	8.4 [64.4]	3.7
Rofecoxib	0	273	-	SPC	-	-	13	13.0 [8.1-20.8]	12.2 [123.4]	5.3
Theophylline	0	249	-	Yes	-	-	10	2.4 [1.4-4.1]	2.4 [6.8]	1.2
Indometacin	0	249	-	Yes	-	-	32	12.1 [9.0-16.4]	11.5 [295.0]	7.3
Flurbiprofen	0	228	-	SPC	-	-	6	8.1 [4.1-16.1]	7.8 [29.3]	2.4

Drugname	EU-ADR N	Exp. in PY *	Prot. Bias **	Known ? ***	LPGS RR (95% CI)	SCCS RR (95% CI)	VigiBase N	ROR [95% CI]	PRR [χ^2]	EB05
Mycophenolic Acid	0	162	-	Yes	-	-	13	5.0 [3.1-7.9]	4.9 [36.3]	2.6
Acetazolamide	0	126	-	SPC	-	-	4	7.5 [3.2-17.3]	7.2 [15.8]	1.6
Heparin	0	107	-	Yes	-	-	17	5.4 [3.6-8.1]	5.3 [54.8]	3.0
Sodium Chloride	1	106	No	Yes	-	-	4	4.8 [2.1-11.0]	4.7 [8.2]	1.2
Ketorolac	1	98	No	Yes	-	-	16	8.0 [5.2-12.1]	7.7 [86.8]	4.1
Zafirlukast	0	82	-	No	-	-	4	8.3 [3.6-19.2]	8.0 [18.0]	1.7
Etodolac	0	78	-	Yes	-	-	3	12.4 [4.7-33.0]	11.7 [19.8]	1.5
Zidovudine	0	59	-	No	-	-	15	2.6 [1.7-4.0]	2.6 [13.1]	1.5
Darbepoetin Alfa	1	57	Yes	Yes	-	-	3	14.2 [5.3-38.0]	13.3 [23.1]	1.5
Clopidogrel	0	34	-	Yes	-	-	5	12.5 [5.8-26.6]	11.8 [39.3]	2.6
Niflumic Acid	0	33	-	No	-	-	23	13.6 [9.5-19.4]	12.8 [237.3]	7.2
Tenoxicam	0	27	-	SPC	-	-	4	21.0 [8.8-50.0]	19.1 [51.8]	2.5
Cyclophosphamide	1	26	No	No	-	-	20	3.7 [2.5-5.3]	3.6 [35.2]	2.3
Orlistat	0	25	-	No	-	-	6	5.3 [2.7-10.4]	5.1 [16.2]	1.8
Sirolimus	0	23	-	No	-	-	6	6.1 [3.1-12.1]	6.0 [20.1]	2.0
Tolmetin	0	20	-	SPC	-	-	3	8.3 [3.2-22.0]	8.0 [12.1]	1.2
Lincomycin	0	18	-	No	-	-	6	3.4 [1.7-6.6]	3.3 [7.5]	1.3
Octreotide	0	17	-	Yes	-	-	3	7.2 [2.7-18.9]	7.0 [10.0]	1.2
Deferasirox	0	17	-	SPC	-	-	4	4.3 [1.9-9.8]	4.2 [6.8]	1.1
Tiaprofenic Acid	0	12	-	SPC	-	-	9	10.7 [6.1-18.9]	10.2 [66.2]	3.8
Pentoxifylline	0	5	-	SPC	-	-	3	17.1 [6.4-46.2]	15.8 [28.3]	1.6
Ganciclovir	0	4	-	SPC	-	-	8	9.5 [5.2-17.2]	9.1 [50.0]	3.2
Bosentan	0	3	-	No	-	-	5	6.0 [2.8-12.6]	5.8 [15.5]	1.7
Dexketoprofen	0	3	-	SPC	-	-	3	26.5 [9.6-73.0]	23.4 [44.2]	1.8
Etoposide	0	3	-	No	-	-	14	2.9 [1.9-4.6]	2.9 [15.8]	1.7

Drugname	EU-ADR N	Exp. in PY *	Prot. Bias **	Known ? ***	LPGS RR (95% CI)	SCCS RR (95% CI)	VigiBase N	ROR [95% CI]	PRR [χ^2]	EB05
Phenylbutazone	0	2	-	SPC	-	-	3	8.6 [3.3-22.6]	8.3 [12.6]	1.3
Mefenamic Acid	0	1	-	Yes	-	-	6	2.2 [1.1-4.2]	2.1 [2.6]	0.9
Cytarabine	0	0	-	SPC	-	-	14	2.3 [1.5-3.5]	2.3 [8.5]	1.3
Melphalan	0	0	-	Yes	-	-	3	5.8 [2.2-15.3]	5.7 [7.4]	1.0
Flucytosine	0	0	-	No	-	-	3	13.0 [4.9-34.6]	12.2 [20.8]	1.5
Methylprednisolone	0	0	-	SPC	-	-	11	2.5 [1.5-4.2]	2.5 [8.7]	1.3
Sultamicillin	0	0	-	No	-	-	3	3.8 [1.5-9.9]	3.8 [3.6]	0.8
Cefdinir	-	-	-	Yes	-	-	21	14.0 [9.7-20.4]	13.2 [223.9]	7.1
Vincristine	-	-	-	No	-	-	20	2.2 [1.5-3.2]	2.2 [11.3]	1.4
Azidocillin	-	-	-	No	-	-	14	68.2 [40.9-113.8]	50.8 [635.4]	29.1
Doxorubicin	-	-	-	No	-	-	12	3.0 [1.9-4.8]	3.0 [13.7]	1.6
Dactinomycin	-	-	-	No	-	-	10	6.0 [3.5-10.1]	5.8 [35.2]	2.6
Irinotecan	-	-	-	Yes	-	-	9	16.4 [9.2-29.0]	15.2 [105.7]	4.9
Alosetron	-	-	-	No	-	-	8	29.4 [15.7-54.8]	25.6 [166.2]	6.0
Simeticone	-	-	-	No	-	-	8	32.4 [17.3-60.8]	27.9 [182.3]	6.4
Cisplatin	-	-	-	No	-	-	7	2.7 [1.4-5.0]	2.6 [5.5]	1.1
Gefitinib	-	-	-	SPC	-	-	7	38.9 [19.7-76.9]	32.6 [184.5]	6.2
Ifosfamide	-	-	-	SPC	-	-	7	3.0 [1.6-5.7]	3.0 [7.4]	1.3
Pancrelipase	-	-	-	No	-	-	7	26.2 [13.5-50.8]	23.2 [127.7]	5.0
Clofarabine	-	-	-	SPC	-	-	6	10.0 [5.0-19.9]	9.5 [37.8]	2.7
Daunorubicin	-	-	-	No	-	-	6	3.6 [1.8-7.1]	3.6 [8.6]	1.3
Acetylsalicylic Acid And Aluminium Glycinate And Magnesium Carbonate	-	-	-	SPC	-	-	5	23.7 [10.9-51.7]	21.2 [77.6]	3.3
Amino Acids And Xylitol	-	-	-	No	-	-	5	108.0 [43.1-270.5]	69.8 [274.8]	7.4
Carboplatin	-	-	-	Yes	-	-	5	2.4 [1.1-5.0]	2.4 [2.7]	0.9

Drugname	EU-ADR N	Exp. in PY *	Prot. Bias **	Known ? ***	LPGS RR (95% CI)	SCCS RR (95% CI)	VigiBase N	ROR [95% CI]	PRR [χ^2]	EB05
Pegaspargase	-	-	-	No	-	-	5	2.1 [1.0-4.5]	2.1 [1.9]	0.8
Acetylsalicylic Acid And Citric Acid And Sodium Bicarbonate	-	-	-	SPC	-	-	4	51.8 [20.5-130.9]	41.1 [119.6]	3.2
Epoprostenol	-	-	-	SPC	-	-	4	5.8 [2.5-13.4]	5.7 [11.1]	1.4
Gemcitabine	-	-	-	No	-	-	4	9.0 [3.9-21.0]	8.7 [20.1]	1.8
Latamoxef	-	-	-	SPC	-	-	4	9.4 [4.0-21.8]	9.0 [21.0]	1.8
Oxyphenbutazone	-	-	-	No	-	-	4	11.4 [4.9-26.7]	10.9 [26.7]	2.0
Tolazoline	-	-	-	Yes	-	-	4	64.8 [25.1-167.6]	48.8 [143.3]	3.5
Acetylsalicylic Acid And Ascorbic Acid	-	-	-	SPC	-	-	3	7.0 [2.7-18.5]	6.8 [9.7]	1.2
Acetylsalicylic Acid And Caffeine	-	-	-	SPC	-	-	3	16.2 [6.0-43.5]	15.0 [26.6]	1.6
Acetylsalicylic Acid And Caffeine And Paracetamol And Salicylamide	-	-	-	SPC	-	-	3	8.1 [3.1-21.4]	7.8 [11.7]	1.2
Alteplase	-	-	-	SPC	-	-	3	10.8 [4.1-28.7]	10.3 [16.8]	1.4
Anti-D Immunoglobulin	-	-	-	No	-	-	3	9.3 [3.5-24.5]	8.9 [13.9]	1.3
Ascorbic Acid	-	-	-	No	-	-	3	6.1 [2.3-15.9]	5.9 [7.9]	1.1
Carbenicillin	-	-	-	No	-	-	3	24.3 [8.9-66.5]	21.7 [40.5]	1.8
Certolizumab	-	-	-	No	-	-	3	7.0 [2.7-18.5]	6.8 [9.7]	1.2
Corticosteroid	-	-	-	SPC	-	-	3	9.0 [3.4-23.7]	8.6 [13.4]	1.3
Dasatinib	-	-	-	SPC	-	-	3	8.1 [3.1-21.4]	7.8 [11.7]	1.2
Drotrecogin Alfa	-	-	-	SPC	-	-	3	14.2 [5.3-38.0]	13.3 [23.1]	1.5
Gemtuzumab	-	-	-	SPC	-	-	3	11.2 [4.2-29.8]	10.7 [17.6]	1.4
Glycerol And Glycine Max And Lecithin	-	-	-	No	-	-	3	7.7 [2.9-20.2]	7.4 [10.9]	1.2
Hydrocodone	-	-	-	Yes	-	-	3	6.1 [2.3-15.9]	5.9 [7.9]	1.1

Overview of the identified signals within EU-ADR and VigiBase. List is ordered by decreasing exposure in EU-ADR. Estimates in grey are significant signals.

: Exposure in PY within EU-ADR; **: Protopathic bias based on LEOPARD; * Yes: Known ADR according to EU-ADR web platform; SPC: Listed in SPC; No: Not known ADR according to EU-ADR web platform nor listed in the SPC.*

Abbreviations: N=number of events or reports; Exp. in PY= exposure in person years; Prot. Bias=protopathic bias; Subst.=substantiation; LPGS= ; RR=risk ratio; 95% CI=95% confidence interval; SCCS=self controlled case series; ROR=reporting odd ratio; PRR=proportional reporting ratio; χ^2=chi square estimate.

Chapter 11

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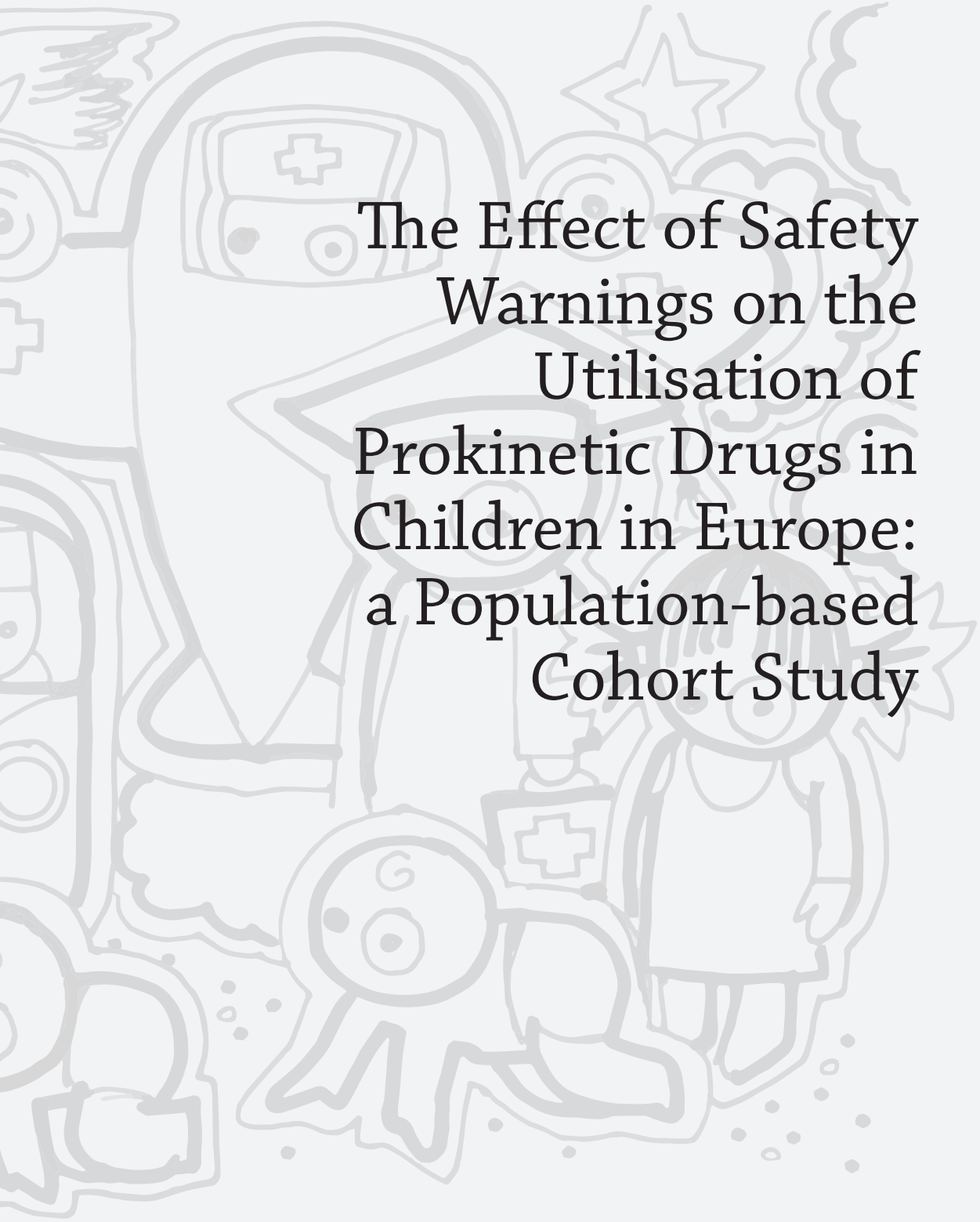


The Effect of Safety Warnings on the Utilisation of Prokinetic Drugs in Children in Europe: a Population-based Cohort Study

Abstract

Background

Several safety warnings have been issued in recent years in Europe concerning potential serious adverse events associated with the use of prokinetic drugs in children, including a recent restriction in the indication of use for metoclopramide. The effect of such warnings is unknown. In this study we aim to describe prescription patterns of prokinetic drugs in children and to assess the effect of safety warnings on these patterns.

Methods

A retrospective population-based study was conducted within 3 primary care electronic healthcare databases in the Netherlands (1997-2008), Italy (2001-2008), and Spain (2001-2008). Annual prevalence and incidence rates of use for prokinetics were calculated (users/1,000 person years (PY)) and stratified by country, calendar-time, age and sex. Interrupted time-series analysis using an ARIMA (autoregressive integrated moving average) model was performed to assess the effect of safety-warnings on the utilisation pattern.

Results

A total of 978,867 children (2,990,373 PY) were included. The incidence of any prokinetic drug was 24.8 users/1,000PY in Spain, 14.4/1,000PY in the Netherlands and 14.0/1,000PY in Italy. An Italian contra-indication for the use of metoclopramide in children had a significant negative effect on prescribing. International warnings for domperidone decreased prescribing in Italy and the Netherlands. For cisapride (Netherlands) the largest reduction was seen after the withdrawal in the United States. Safety warnings for metoclopramide and domperidone did not significantly reduce prescribing in Spain.

Conclusions

Safety warnings, restrictions of use and changes in the product information of prokinetic drugs resulted in a significant decrease of prescription rates in those countries where restriction of use measures were implemented.

Introduction

In 2011, after a formal evaluation of the paediatric use of metoclopramide, it was decided in Europe (EU) to contraindicate this drug in children <1 year of age and to advise against prescribing it to children from 1 year of age and adolescents with the exception of treatment of postoperative nausea and vomiting.[309] These restrictions were applied in all countries of the European Union and were the outcome of an Article 45 procedure, in which all available paediatric studies with metoclopramide were assessed. This procedure is part of the Paediatric regulation, which came into force in 2007.[14] Information on this issue was provided to healthcare professionals in Europe among others by the distribution of DHPCs (Direct Healthcare Professional Communication). Already in 2004, Italy contraindicated the use of metoclopramide in children up to the age of 16,[310] and in February 2007, the Dutch Medicines Evaluation Board restricted paediatric indications of metoclopramide because of the risk of developing extrapyramidal disorders[311] and this was followed by the recent restriction throughout Europe.

The use of metoclopramide and other prokinetic drugs in children has been controversial for several years as their indication of use is often self-limiting, their effectiveness is questionable,[312-315] and finally their use has been associated with serious adverse drug reactions.[316-319] Several safety warnings concerning the other prokinetic drugs were issued in recent years. Cisapride was restricted to specific subgroups from 2000 onwards following reports of sudden cardiac death and ventricular arrhythmias and was finally withdrawn from the market in 2010.[320-328] For domperidone a EU referral procedure to harmonise the summary of product characteristics (SPC) was finalised in 2002,[329] and warnings on an increased risk of EPD in infants were included in all EU SPCs for domperidone at that time.

The effect of these safety warnings and risk communications on the prescription rate of these drugs in children is unknown. We studied the effect of safety warnings on the use of prokinetic drugs in children in three European countries using primary care databases.

Methods

Study design

A retrospective population-based cohort study was conducted to describe the pattern of use of prokinetic drugs in children. Interrupted time-series analyses were applied to assess the effects of safety warnings on the utilisation of these drugs.

Setting

Data were used from three primary care databases in Italy, the Netherlands and Spain according to a common study protocol.

These population-based databases comprise primary care data on children. In the Netherlands, the general practitioner (GP) is responsible for the primary care of children whereas in Spain and Italy, primary care and family paediatricians are the gatekeepers of care for children. These databases contain the complete automated patient files, with detailed information on the population, diagnoses and prescriptions, and use of these databases has been proven valid for pharmacoepidemiological research.[58] Details of the databases have been described elsewhere.[60-63]

In brief, since 2000, the *Pedianet* database contains paediatric electronic medical records from 150 family paediatricians in Italy until the age of 14 years.[62] The *Integrated Primary Care Information database* (IPCI) comprises paediatric and adult electronic medical records from more than 400 Dutch GPs since 1996.[60,61] The *BIFAP database* is a longitudinal observational population-based database kept by the Spanish agency for medicines and medical devices that collates, from 2001 onwards, the computerised medical records of more than 2,000 primary care physicians, including more than 350 primary care paediatricians throughout Spain.[63]

Study period

For the Netherlands the study period ran from January 1st 1997 to December 31st 2008. For Italy and Spain, the study period ran from January 1st 2001 to December 31st 2008 since no data prior to January 2001 were available. The earlier study start for the Netherlands allowed us to evaluate the effect of prescribing restrictions for cisapride.

Study cohort

Children were followed from the start of entry (start of study period, date practice was up to date, date of registration plus 6 months or just born) into the study until their 18th (Netherlands and Spain) or 14th (Italy) birthday, leaving the practice, death, or latest data drawn down, whichever came first.

Different age strata were created within one-year and two-year periods, and broader age categories. These age categories were chosen according to the guidelines of the International Conference on Harmonisation; 0-<2 years, 2-≤11 years and 12-<18 years.[111] For each child the person time of follow-up was cal-

culated, and stratified by calendar year, calendar month, age in years and age categories.

Definition of exposure

Prokinetic drugs are grouped under the chemical subgroup A03FA 'Propulsives' of the Anatomical Therapeutic Chemical (ATC) classification system.[30] We considered A03FA overall and the individual drugs; metoclopramide (A03FA01), cisapride (A03FA02), domperidone (A03FA03), bromopride (A03FA04) (Italy only), clebopride (A03FA06) (Spain only), and cinitapride (A03FA91) (Spain only). Subsequently we focused on the prokinetic drugs for which safety warnings have been issued in the last years: metoclopramide, cisapride, and domperidone.

Statistical analysis

Prevalence and incidence rates

For the annual and monthly prevalence rates, the number of children *being prescribed* a drug in a specific calendar year or month was counted, these children received at least one prescription for the drug in this calendar year or month. For the annual incidence rates the number of children was counted *initiating* that drug in a specific calendar year, without a previous prescription during the study period.

Prevalence and incidence rates for the study drugs were estimated and either expressed per 1,000 person years (PY) or per 1,000 person months (PMs). Because of the dynamic nature of the population we used person time rather than number of individuals for both the prevalence rate and incidence rate.

Prevalence rates should thereby be interpreted as the number of children per 1,000 who used a study drug in one year or one month. Annual incidence rates should be interpreted as the number of children per 1,000 who started using a study drug, without a previous prescription within the study period.

Rates, including the 95% confidence interval (95% CI), were calculated and stratified by age, sex, country and calendar year to account for differences in distributions between populations and to allow for direct comparisons within groups. To compare rates between country, age categories, or sex, the rate ratio (RR) with a 95% CI was calculated. The cohort of incident users was used to describe the characteristics of the users.

Seasonal trends

To study possible seasonal trends, the prevalence of use during the entire study period was stratified by calendar month. All prescriptions in the same month in the different study years (1997, 1998, etc.) were aggregated.

Interrupted time-series analysis

Interrupted time series analysis using an *a*uto-regressive, *i*ntegrated, *m*oving *a*verage model [ARIMA (*p,d,q*)] was applied to assess the effects of safety warnings on the monthly prevalence of use of prokinetic drugs.[330]

The safety warnings were considered as intervention and dummy variables were created with a value of 0 prior to the date of intervention and with a value of 1 after the date of intervention. For *cisapride* multiple interventions were analysed: March 2000 (first warning published in the Netherlands, followed by the withdrawal in the United States (US) in April 2000[326,328]), January 2002 (restriction to prescribing by specialists only (Netherlands)[323]) and September 2002 (Dutch DHPC on further restriction of cisapride[322]). For each intervention for cisapride, the effect was compared to the period preceding the last intervention. Date of intervention for *domperidone* was chosen at June 2002 (EU referral[329]). For *metoclopramide,* March 2004 (contra-indication Italy)[310] was analysed and for the Netherlands additionally February 2007 was analysed to study the restriction in indication in the Netherlands.[311]

ARIMA models were estimated prior to the intervention using the expert modeller function within SPSS, which accounted for possible seasonality within the data. This estimated model was applied on the entire set using the prevalence rate of the study drug as outcome and the intervention (dummy variable) as independent variable. The output is the change in prevalence due to the intervention (β) with a corresponding *p*-value.

Statistical significance was assumed for two-sided *p*-values <0.05. Statistical analyses were performed using SPSS software version 15.0 (SPSS Inc, Chicago, IL, US).

Results

A total of 978,876 children contributing a total of 2,990,373 person-years of follow-up were included. Most included children were Spanish (N=608,998; 59.2%), followed by Italian (N=198,813; 29.1%) and Dutch (N=171,065; 11.6%).

The median age for starting one of the individual study drugs is more of less similar in the Netherlands and Spain and somewhat lower in Italy where only

children <14 years of age were included. Based on the median age, cisapride was prescribed in the youngest children, followed by domperidone and metoclopramide (**table 11.1**).

Incidence and prevalence of use

The incidence of any prokinetic drug, in comparison with the Netherlands (14.4 users/1,000 PY), was higher in Span (24.8 users/1,000 PY) (RR 1.7, 95% CI 1.7-1.8) and similar in Italy (14.0 users/1,000 PY) (RR 1.0, 95% CI 0.9-1.0). The difference

Table 11.1 Characteristics cohorts of incident users

	Netherlands	Spain	Italy
Prokinetics- total			
Number of incident users: N (%)	4,391 (100.0)	36,296 (100.0)	11,323 (100.0)
Boys	2,090 (47.6)	17,407 (48.0)	5,915 (52.2)
Girls	2,301 (52.4)	18,889 (52.0)	5,408 (47.8)
Median age (range)	4.8 (0.0-17)	9.1 (0.0-17)	4.1 (0.0-13)
Boys	4.1 (0.0-17)	8.1 (0.0-17)	4 (0.0-13)
Girls	5 (0.1-17)	9.9 (0.0-17)	4.2 (0.0-13)
Metoclopramide			
Number of incident users: N (%)	246 (100.0)	10712 (100.0)	1877 (100.0)
Boys	92 (37.4)	4881 (45.6)	940 (50.1)
Girls	154 (62.6)	5831 (54.4)	937 (49.9)
Median age (range)	13 (0.7-17)	15 (0.0-17)	4.6 (0.0-13)
Boys	10 (0.7-17)	15 (0.0-17)	4.4 (0.1-13)
Girls	14 (2.4-17)	15 (0.1-17)	4.7 (0.0-13)
Cisapride			
Number of incident users: N (%)	203 (100.0)	159 (100.0)	7 (100.0)
Boys	94 (46.3)	96 (60.4)	5 (71.4)
Girls	109 (53.7)	63 (39.6)	2 (28.6)
Median age (range)	2.4 (0.1-17)	1.5 (0.1-17)	1 (0.1-6.8)
Boys	1.25 (0.1-17)	1.35 (0.2-16)	1 (0.2-6.8)
Girls	3.1 (0.1-17)	2 (0.1-17)	2.75 (0.1-5.4)
Domperidone			
Number of incident users: N (%)	4,103 (100.0)	23,414 (100.0)	9,384 (100.0)
Boys	1,974 (48.1)	11,479 (49.0)	4,945 (52.7)
Girls	2,129 (51.9)	11,935 (51.0)	4,439 (47.3)
Median age (range)	4.4 (0.0-17)	6.3 (0.0-17)	4 (0.0-13)
Boys	4.1 (0.0-17)	5.6 (0.0-17)	3.8 (0.0-13)
Girls	4.8 (0.1-17)	7 (0.0-17)	4.1 (0.0-13)

Table 11.2 Incidence of use of prokinetics stratified by age and country (new users/1,000 PY)

	Prokinetics total			Metoclopramide			Cisapride			Domperidone		
	Incid.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]	Incid.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]	Incid.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]	Incid.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]
Netherlands												
0-<2 years	33.8 [31.9-35.7]	*ref*	*ref*	0.1 [0.0-0.2]	ref	*ref*	2.9 [2.4-3.5]	ref	*ref*	31.1 [29.3-33.0]	*ref*	*ref*
2-<4 years	26.8 [25.1-28.5]	0.8 [0.7-0.9]	*ref*	0.8 [0.5-1.1]	6.4 [2.3-18.4]	*ref*	0.4 [0.2-0.6]	0.1 [0.1-0.2]	*ref*	26.1 [24.4-27.8]	0.8 [0.8-0.9]	*ref*
4-<6 years	16.0 [14.7-17.3]	0.5 [0.4-0.5]	*ref*	0.6 [0.4-0.9]	5.0 [1.7-14.4]	*ref*	0.2 [0.1-0.3]	0.1 [0.0-0.1]	*ref*	15.6 [14.3-16.9]	0.5 [0.5-0.6]	*ref*
6-<8 years	9.8 [8.8-10.8]	0.3 [0.3-0.3]	*ref*	0.3 [0.1-0.5]	2.6 [0.8-8.1]	*ref*	0.3 [0.1-0.5]	0.1 [0.1-0.2]	*ref*	9.4 [8.4-10.4]	0.3 [0.3-0.3]	*ref*
8-<10 years	7.9 [7.0-8.8]	0.2 [0.2-0.3]	*ref*	0.6 [0.4-0.9]	5.3 [1.8-15.2]	*ref*	0.1 [0.0-0.2]	0.0 [0.0-0.1]	*ref*	7.3 [6.4-8.2]	0.2 [0.2-0.3]	*ref*
10-<12 years	7.8 [6.9-8.7]	0.2 [0.2-0.3]	*ref*	0.6 [0.3-0.8]	4.6 [1.6-13.5]	*ref*	0.3 [0.1-0.4]	0.1 [0.0-0.2]	*ref*	7.1 [6.3-8.0]	0.2 [0.2-0.3]	*ref*
12-<14 years	8.2 [7.3-9.1]	0.2 [0.2-0.3]	*ref*	0.9 [0.6-1.2]	7.6 [2.7-21.3]	*ref*	0.3 [0.1-0.5-]	0.1 [0.1-0.2]	*ref*	7.4 [6.5-8.3]	0.2 [0.2-0.3]	*ref*
14-<16 years	8.7 [7.8-9.6]	0.3 [0.2-0.3]	*ref*	1.4 [1.0-1.8]	11.7 [4.2-32.2]	*ref*	0.6 [0.3-0.8]	0.2 [0.1-0.3]	*ref*	7.2 [6.3-8.0]	0.2 [0.2-0.3]	*ref*
16-<18 years	13.1 [11.9-14.2]	0.4 [0.3-0.4]	*ref*	2.6 [2.0-3.1]	21.0 [7.7-57.2]	*ref*	0.9 [0.6-1.2]	0.3 [0.2-0.4]	*ref*	10.6 [9.5-11.6]	0.3 [0.3-0.4]	*ref*
total	14.4 [14.0-14.8]	-	*ref*	0.9 [0.8-1.0]	-	*ref*	0.6 [0.6-0.7]	-	*ref*	13.3 [12.9-13.7]	-	*ref*
Spain												
0-<2 years	34.0 [33.1-34.8]	*ref*	1.0 [0.9-1.1]	2.8 [2.5-3.0]	*ref*	22.7 [8.5-60.7]	0.5 [0.4-0.6]	*ref*	0.2 [0.1-0.2]	27.2 [26.4-27.9]	*ref*	0.9 [0.8-0.9]
2-<4 years	25.2 [24.5-25.9]	0.7 [0.7-0.8]	0.9 [0.9-1.0]	3.3 [3.0-3.5]	1.2 [1.1-1.3]	4.2 [2.8-6.1]	0.1 [0.1-0.1]	0.2 [0.1-0.3]	0.2 [0.1-0.4]	19.2 [18.6-19.8]	0.7 [0.7-0.7]	0.7 [0.7-0.8]
4-<6 years	19.1 [18.5-19.8]	0.6 [0.5-0.6]	1.2 [1.1-1.3]	3.0 [2.7-3.2]	1.1 [1.0-1.2]	4.9 [3.2-7.6]	0.1 [0.0-0.1]	0.1 [0.1-0.2]	0.3 [0.1-0.8]	14.4 [13.9-15.0]	0.5 [0.5-0.6]	0.9 [0.8-1.0]
6-<8 years	17.0 [16.3-17.6]	0.5 [0.5-0.5]	1.7 [1.6-1.9]	3.4 [3.1-3.6]	1.2 [1.1-1.4]	10.7 [6.0-18.9]	0.0 [0.0-0.1]	0.1 [0.0-0.2]	0.1 [0.1-0.3]	12.1 [11.6-12.6]	0.4 [0.4-0.5]	1.3 [1.1-1.4]

8-<10 years	16.2 [15.6-16.8]	0.5 [0.5-0.5]	2.1 [1.8-2.3]	3.6 [3.3-3.9]	1.3 [1.2-1.5]	5.6 [3.8-8.4]	0.0 [0.0-0.1]	0.1 [0.0-0.1]	0.2 [0.1-0.8]	11.4 [10.9-12.0]	0.4 [0.4-0.4]	1.6 [1.4-1.8]
10-<12 years	15.8 [15.2-16.3]	0.5 [0.4-0.5]	2.0 [1.8-2.3]	3.8 [3.5-4.1]	1.4 [1.2-1.5]	6.8 [4.4-10.4]	0.1 [0.0-0.1]	0.1 [0.1-0.2]	0.2 [0.1-0.5]	10.6 [10.1-11.0]	0.4 [0.4-0.4]	1.5 [1.3-1.7]
12-<14 years	14.6 [14.1-15.2]	0.4 [0.4-0.5]	1.8 [1.6-2.0]	4.9 [4.6-5.2]	1.8 [1.6-2.0]	5.3 [3.8-7.4]	0.0 [0.0-0.1]	0.1 [0.0-0.2]	0.1 [0.1-0.3]	8.7 [8.3-9.1]	0.3 [0.3-0.3]	1.2 [1.0-1.3]
14-<16 years	26.4 [25.7-27.1]	0.8 [0.8-0.8]	3.0 [2.7-3.4]	13.6 [13.1-14.1]	4.9 [4.5-5.4]	9.6 [7.3-12.5]	0.0 [0.0-0.0]	0.0 [0.0-0.1]	0.0 [0.0-0.1]	10.1 [9.7-10.6]	0.4 [0.4-0.4]	1.4 [1.2-1.6]
16-<18 years	48.4 [47.5-49.4]	1.4 [1.4-1.5]	3.7 [3.4-4.1]	27.5 [26.8-28.2]	10.0 [9.1-10.9]	10.8 [8.8-13.2]	0.0 [0.0-0.0]	0.0 [0.0-0.1]	0.0 [0.0-0.1]	16.0 [15.4-16.5]	0.6 [0.6-0.6]	1.5 [1.4-1.7]
total	24.8 [24.5-25.0]	-	1.7 [1.7-1.8]	7.8 [7.7-7.9]	-	8.8 [7.9-9.9]	0.1 [0.1-0.1]	-	0.2 [0.1-0.2]	14.5 [14.3-14.7]	-	1.1 [1.1-1.1]
Italy												
0-<2 years	24.1 [23.3-25.0]	*ref*	0.7 [0.7-0.8]	2.8 [2.5-3.1]	*ref*	23.3 [8.7-62.5]	0.0 [0.0-0.1]	*ref*	0.0 [0.0-0.0]	21.1 [20.3-21.9]	*ref*	0.7 [0.6-0.7]
2-<4 years	21.7 [20.9-22.5]	0.9 [0.9-0.9]	0.8 [0.8-0.9]	3.6 [3.2-3.9]	1.3 [1.1-1.4]	4.6 [3.1-6.7]	0.0 [0.0-0.0]	0.2 [0.0-2.0]	0.0 [0.0-0.1]	17.9 [17.2-18.6]	0.8 [0.8-0.9]	0.7 [0.6-0.7]
4-<6 years	16.1 [15.4-16.8]	0.7 [0.6-0.7]	1.0 [0.9-1.1]	2.7 [2.4-2.9]	0.9 [0.8-1.1]	4.4 [2.9-6.8]	0.0 [0.0-0.0]	0.2 [0.0-1.9]	0.0 [0.0-0.3]	13.2 [12.5-13.8]	0.6 [0.6-0.7]	0.8 [0.8-0.9]
6-<8 years	10.9 [10.3-11.5]	0.5 [0.4-0.5]	1.1 [1.0-1.2]	2.1 [1.8-2.3]	0.7 [0.6-0.8]	6.5 [3.6-11.6]	0.0 [0.0-0.0]	0.2 [0.0-1.9]	0.0 [0.0-0.2]	8.5 [8.0-9.0]	0.4 [0.4-0.4]	0.9 [0.8-1.0]
8-<10 years	8.9 [8.4-9.4]	0.4 [0.3-0.4]	1.1 [1.0-1.3]	1.6 [1.4-1.9]	0.6 [0.5-0.7]	2.5 [1.7-3.8]	-	-	-	6.6 [6.2-7.1]	0.3 [0.3-0.3]	0.9 [0.8-1.0]
10-<12 years	7.8 [7.2-8.3]	0.3 [0.3-0.3]	1.0 [0.9-1.1]	1.3 [1.1-1.5]	0.5 [0.4-0.6]	2.3 [1.5-3.6]	-	-	-	5.9 [5.5-6.4]	0.3 [0.3-0.3]	0.8 [0.7-1.0]
12-<14 years	5.3 [4.9-5.8]	0.2 [0.2-0.2]	0.7 [0.6-0.8]	0.8 [0.6-1.0]	0.3 [0.2-0.4]	0.9 [0.6-1.3]	-	-	-	4.5 [4.1-5.0]	0.2 [0.2-0.2]	0.6 [0.5-0.7]
total	14.0 [13.8-14.3]	-	1.0 [0.9-1.0]	2.2 [2.1-2.3]	-	2.5 [2.2-2.8]	0.0 [0.0-0.0]	-	0.0 [0.0-0.0]	11.5 [11.3-11.7]		0.9 [0.8-0.9]

[*] Incidence in number of new users per 1,000 person-years, 95% confidence interval is given between the brackets. [#] Rate ratio for age: age category 0-<2 years serves as reference-category. The 95% confidence interval is given between the brackets. [$] Rate ratio between countries: rates in the Netherlands serve as reference-category. The 95% confidence interval is given between the brackets. Rates given in bold are significant based on the 95% confidence interval

Abbreviations: Incid. = incidence; ref=reference-category; 95% CI=95% confidence interval; RR=rate ratio

Table 11.3 Prevalence of use of prokinetics stratified by age and country (users/1,000 PY)

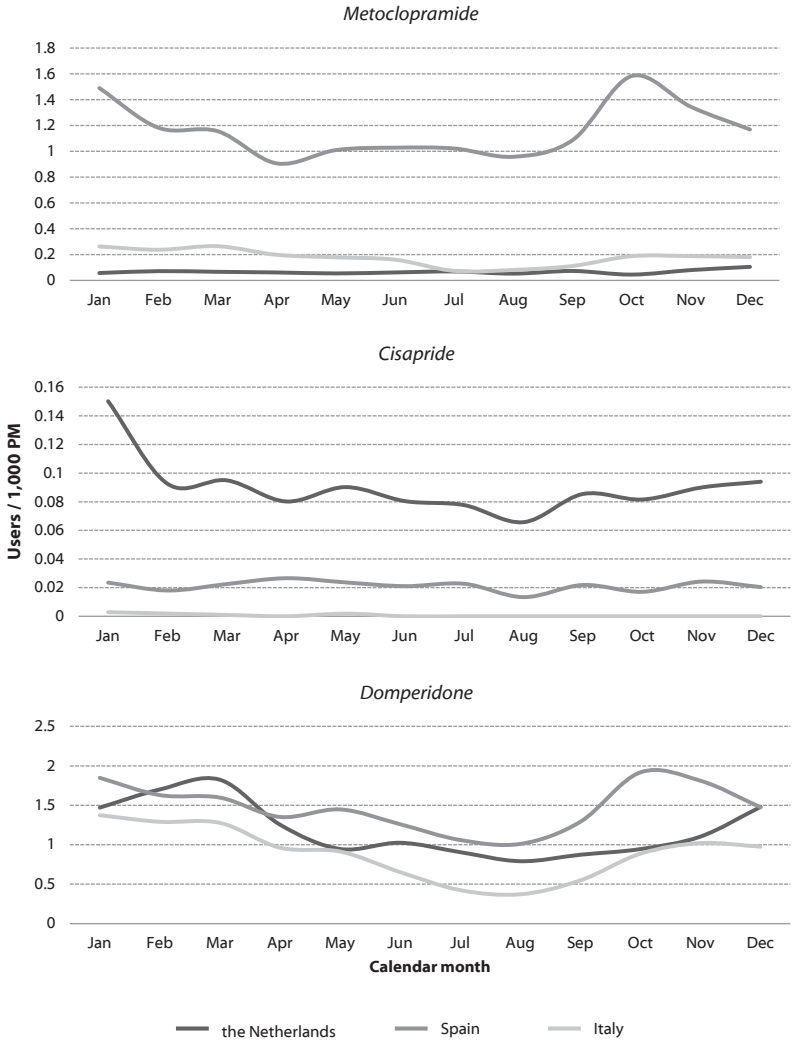
	Prokinetics total			Metoclopramide			Cisapride			Domperidone		
	Preval.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]	Preval.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]	Preval.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]	Preval.* [95% CI]	RR-age # [95% CI]	RR-country $ [95% CI]
Netherlands												
0-<2 years	35.1 [33.1-37.0]	*ref*	*ref*	0.1 [0.0-0.2]	*ref*	*ref*	3.2 [2.6-3.8]	ref	*ref*	32.0 [30.2-33.9]	*ref*	*ref*
2-<4 years	30.1 [28.3-31.8]	0.9 [0.8-0.9]	*ref*	0.7 [0.4-1.0]	8.6 [2.6-28.3]	*ref*	0.7 [0.4-0.9]	0.2 [0.1-0.3]	*ref*	28.9 [27.2-30.6]	0.9 [0.8-1.0]	*ref*
4-<6 years	19.9 [18.5-21.3]	0.6 [0.5-0.6]	*ref*	0.5 [0.3-0.8]	6.4 [1.9-21.5]	*ref*	0.5 [0.3-0.8]	0.2 [0.1-0.3]	*ref*	19.0 [17.6-20.3]	0.6 [0.5-0.6]	*ref*
6-<8 years	12.0 [10.9-13.0]	0.3 [0.3-0.4]	*ref*	0.3 [0.2-0.5]	4.2 [1.2-14.5]	*ref*	0.4 [0.2-0.6]	0.1 [0.1-0.2]	*ref*	11.3 [10.3-12.3]	0.4 [0.3-0.4]	*ref*
8-<10 years	9.7 [8.7-10.6]	0.3 [0.2-0.3]	*ref*	0.6 [0.4-0.9]	7.7 [2.3-25.3]	*ref*	0.2 [0.0-0.3]	0.1 [0.0-0.1]	*ref*	9.0 [8.0-9.9]	0.3 [0.2-0.3]	*ref*
10-<12 years	9.1 [8.2-10.0]	0.3 [0.2-0.3]	*ref*	0.6 [0.4-0.8]	7.1 [2.1-23.6]	*ref*	0.3 [0.1-0.5]	0.1 [0.1-0.2]	*ref*	8.3 [7.4-9.2]	0.3 [0.2-0.3]	*ref*
12-<14 years	9.9 [8.9-10.9]	0.3 [0.3-0.3]	*ref*	0.9 [0.6-1.2]	10.9 [3.4-35.5]	*ref*	0.4 [0.2-0.6]	0.1 [0.1-0.2]	*ref*	8.7 [7.8-9.6]	0.3 [0.2-0.3]	*ref*
14-<16 years	10.8 [9.8-11.8]	0.3 [0.3-0.3]	*ref*	1.5 [1.1-1.9]	18.5 [5.8-58.8]	*ref*	0.6 [0.4-0.9]	0.2 [0.1-0.3]	*ref*	8.9 [7.9-9.8]	0.3 [0.2-0.3]	*ref*
16-<18 years	12.8 [11.7-14.0]	0.4 [0.3-0.4]	*ref*	2.1 [1.7-2.6]	26.0 [8.2-82.2]	*ref*	0.8 [0.5-1.1]	0.2 [0.2-0.4]	*ref*	10.0 [9.0-11.0]	0.3 [0.3-0.4]	*ref*
total	16.3 [15.9-16.7]	-	*ref*	0.8 [0.7-0.9]	-	*ref*	0.8 [0.7-0.9]	-	*ref*	14.8 [14.4-15.2]	-	*ref*
Spain												
0-<2 years	36.2 [35.4-37.0]	*ref*	1.0 [1.0-1.1]	2.8 [2.6-3.1]	*ref*	34.3 [11.0-106.8]	0.7 [0.6-0.8]	*ref*	0.2 [0.2-0.3]	29.6 [28.8-30.3]	*ref*	0.9 [0.9-1.0]
2-<4 years	30.3 [29.5-31.1]	0.8 [0.8-0.9]	1.0 [0.9-1.1]	3.5 [3.2-3.8]	1.2 [1.1-1.4]	4.9 [3.4-7.2]	0.2 [0.1-0.3]	0.3 [0.2-0.4]	0.3 [0.2-0.5]	24.0 [23.3-24.7]	0.8 [0.8-0.8]	0.8 [0.8-0.9]
4-<6 years	24.5 [23.8-25.2]	0.7 [0.7-0.7]	1.2 [1.1-1.3]	3.2 [2.9-3.4]	1.1 [1.0-1.3]	6.0 [3.9-9.2]	0.1 [0.1-0.2]	0.2 [0.1-0.3]	0.2 [0.1-0.4]	19.2 [18.6-19.8]	0.6 [0.6-0.7]	1.0 [0.9-1.1]
6-<8 years	21.4 [20.8-22.1]	0.6 [0.6-0.6]	1.8 [1.6-2.0]	3.6 [3.3-3.9]	1.3 [1.1-1.4]	10.5 [6.2-17.8]	0.1 [0.0-0.1]	0.1 [0.1-0.2]	0.2 [0.1-0.3]	16.1 [15.5-16.7]	0.5 [0.5-0.6]	1.4 [1.3-1.6]

8-<10 years	20.3 [19.6-20.9]	0.6 [0.5-0.6]	2.1 [1.9-2.3]	3.9 [3.6-4.2]	1.4 [1.2-1.5]	6.1 [4.1-9.1]	0.1 [0.0-0.1]	0.1 [0.1-0.2]	0.5 [0.2-1.2]	14.8 [14.2-15.4]	0.5 [0.5-0.5]	1.7 [1.5-1.8]
10-<12 years	18.8 [18.1-19.4]	0.5 [0.5-0.5]	2.1 [1.9-2.3]	4.1 [3.8-4.4]	1.4 [1.3-1.6]	7.0 [4.7-10.5]	0.1 [0.1-0.2]	0.2 [0.1-0.3]	0.4 [0.2-0.8]	13.0 [12.5-13.5]	0.4 [0.4-0.5]	1.6 [1.4-1.8]
12-<14 years	17.2 [16.7-17.8]	0.5 [0.5-0.5]	1.7 [1.6-1.9]	5.3 [5.0-5.6]	1.9 [1.7-2.1]	5.9 [4.2-8.2]	0.1 [0.0-0.1]	0.1 [0.1-0.2]	0.2 [0.1-0.3]	10.5 [10.1-11.0]	0.4 [0.3-0.4]	1.2 [1.1-1.4]
14-<16 years	29.3 [28.6-30.0]	0.8 [0.8-0.8]	2.7 [2.5-3.0]	14.3 [13.8-14.8]	5.0 [4.6-5.5]	9.3 [7.3-12.0]	0.0 [0.0-0.1]	0.1 [0.0-0.1]	0.1 [0.0-0.1]	11.7 [11.2-12.1]	0.4 [0.4-0.4]	1.3 [1.2-1.5]
16-<18 years	41.3 [40.4-42.1]	1.1 [1.1-1.2]	3.2 [2.9-3.5]	21.9 [21.2-22.5]	7.7 [7.1-8.4]	10.2 [8.1-12.7]	0.0 [0.0-0.1]	0.1 [0.0-0.1]	0.1 [0.0-0.1]	14.0 [13.5-14.5]	0.5 [0.5-0.5]	1.4 [1.3-1.6]
total	27.0 [26.7-27.2]	-	1.7 [1.6-1.7]	7.3 [7.2-7.5]	-	8.9 [7.9-10.0]	0.2 [0.1-0.2]		0.2 [0.2-0.2]	16.9 [16.7-17.1]		1.1 [1.1-1.2]
Italy												
0-<2 years	25.1 [24.2-26.0]	*ref*	0.7 [0.7-0.8]	3.0 [2.7-3.3]	*ref*	36.3 [11.7-113.1]	0.0 [0.0-0.1]	*ref*	0.0 [0.0-0.0]	21.8 [20.9-22.6]	*ref*	0.7 [0.6-0.7]
2-<4 years	25.1 [24.3-26.0]	1.0 [1.0-1.1]	0.8 [0.8-0.9]	4.4 [4.0-4.7]	1.5 [1.3-1.7]	6.2 [4.2-9.1]	0.0 [0.0-0.0]	0.2 [0.0-2.0]	0.0 [0.0-0.1]	20.2 [19.5-21.0]	0.9 [0.9-1.0]	0.7 [0.7-0.8]
4-<6 years	19.4 [18.6-20.1]	0.8 [0.7-0.8]	1.0 [0.9-1.1]	3.2 [2.9-3.5]	1.1 [0.9-1.2]	6.0 [3.9-9.2]	0.0 [0.0-0.0]	0.2 [0.0-1.9]	0.0 [0.0-0.1]	15.5 [14.9-16.2]	0.7 [0.7-0.8]	0.8 [0.8-0.9]
6-<8 years	13.1 [12.5-13.7]	0.5 [0.5-0.6]	1.1 [1.0-1.2]	2.3 [2.1-2.6]	0.8 [0.7-0.9]	6.7 [3.9-11.5]	0.0 [0.0-0.0]	0.4 [0.1-2.4]	0.0 [0.0-0.1]	10.2 [9.7-10.8]	0.5 [0.4-0.5]	0.9 [0.8-1.0]
8-<10 years	11.1 [10.5-11.6]	0.4 [0.4-0.5]	1.1 [1.0-1.3]	1.9 [1.6-2.1]	0.6 [0.5-0.7]	3.0 [2.0-4.4]	0.0 [0.0-0.0]	-	-	8.2 [7.7-8.7]	0.4 [0.3-0.4]	0.9 [0.8-1.0]]
10-<12 years	9.2 [8.7-9.8]	0.4 [0.3-0.4]	1.0 [0.9-1.1]	1.4 [1.2-1.6]	0.5 [0.4-0.6]	2.4 [1.6-3.7]	0.0 [0.0-0.0]	-	-	7.0 [6.5-7.5]	0.3 [0.3-0.3]	0.8 [0.7-1.0]
12-<14 years	6.1 [5.6-6.6]	0.2 [0.2-0.3]	0.6 [0.5-0.7]	0.7 [0.6-0.9]	0.2 [0.2-0.3]	0.8 [0.5-1.2]	0.0 [0.0-0.0]	-	-	4.9 [4.4-5.3]	0.2 [0.2-0.2]	0.6 [0.5-0.6]
total	16.1 [15.8-16.3]	-	1.0 [1.0-1.0]	2.5 [2.4-2.6]	-	3.0 [2.7-3.4]	0.0 [0.0-0.0]	-	0.0 [0.0-0.0]	12.9 [12.7-13.2]	-	0.9 [0.8-0.9]

[*] *Prevalence in number of users per 1,000 person-years, 95% confidence interval is given between the brackets.* [#] *Rate ratio for age: age category 0-<2 years serves as reference-category. The 95% confidence interval is given between the brackets.* [$] *Rate ratio between countries: rates in the Netherlands serve as reference-category. The 95% confidence interval is given between the brackets. Rates given in bold are significant based on the 95% confidence interval.*

Abbreviations: preval. = prevalence; ref=reference-category; 95% CI=95% confidence interval; RR= rate ratio

Figure 11.1 Seasonal trends of prevalence of prokinetic drugs



was age-dependent and children aged 16-<18 years were started 3.7 times more frequently on prokinetics drugs in Span than in the Netherlands (RR 3.7, 95% CI 3.4-4.1) **(table 11.2)**.

The annual prevalence of use of any prokinetic drug up to puberty is highest in the youngest (0-<2 years), children; up to 36.2 users/1,000 PY (95% CI 35.4-37.0) in ES, 35.1 users/1,000 PY (95% CI 33.1-37.0) in the Netherlands and 25.1 users/1,000 PY (95% CI 24.2-26.0) in Italy. The prevalence increased again around puberty up to 41.3 users/1,000 PY (95% CI 40.4-42.1) in Spain (16-<18 years) and

12.8 users/1,000 PY (95% CI 11.7-14.0) in the Netherlands (16-<18 years) (*no data available in Italy*) **(table 11.3)**.

When investigating the study drugs of interest (metoclopramide, cisapride and domperidone), it was shown that the incidence was higher for metoclopramide in Spain and Italy than in the Netherlands (**table 11.2**). The incidence and preva-

Figure 11.2 Prevalence of prokinetic drugs stratifed by age

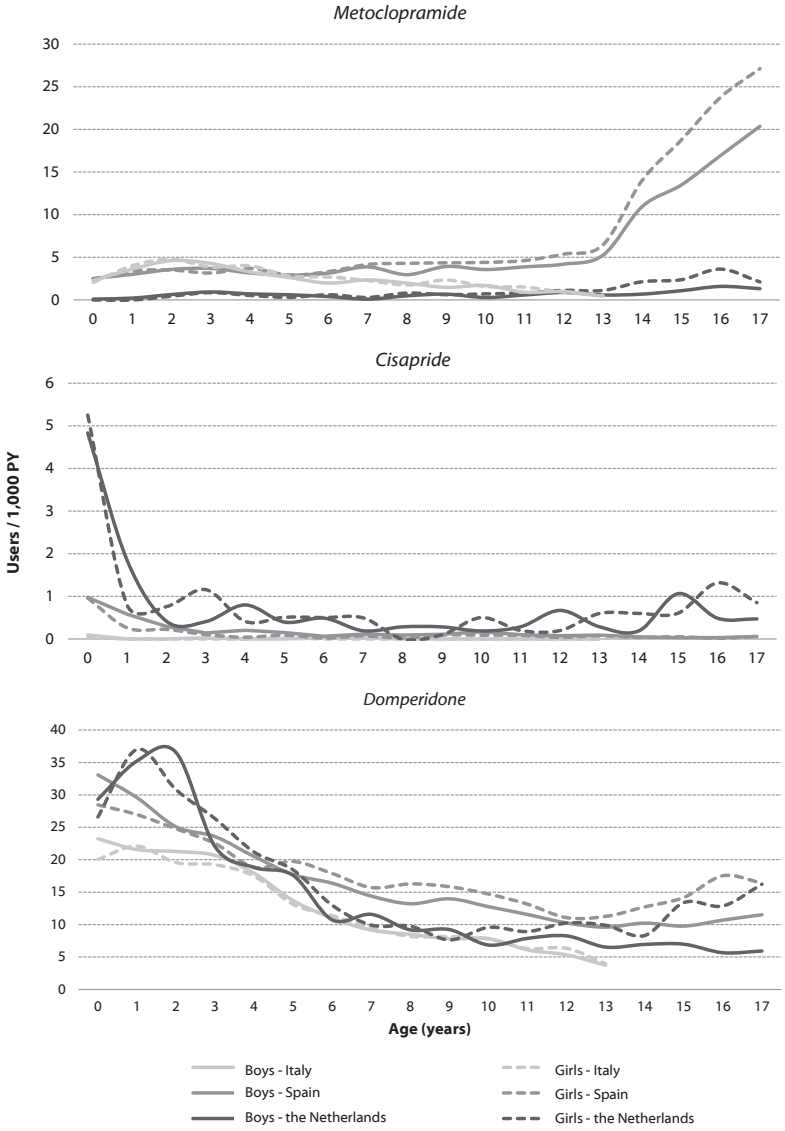
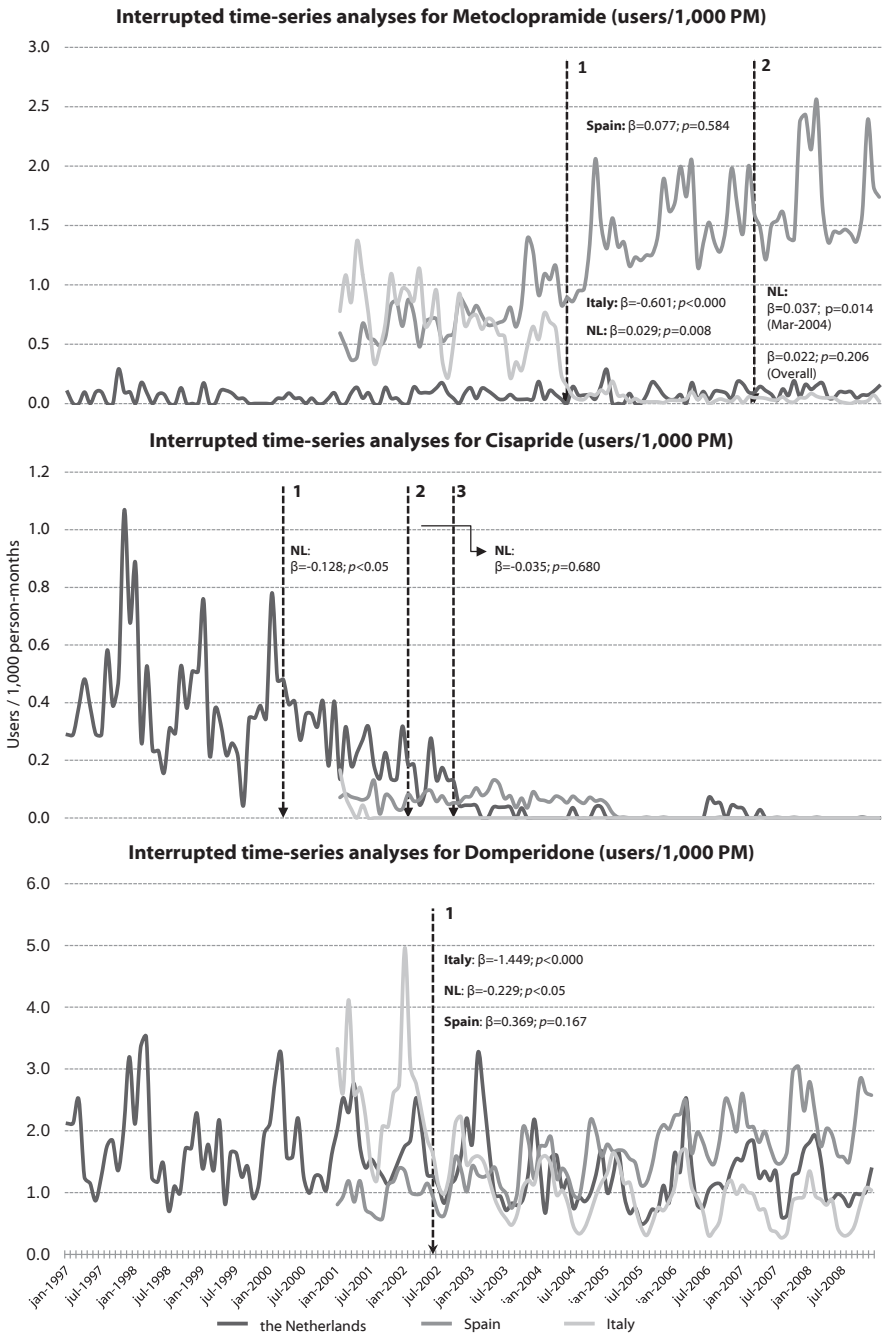


Figure 11.3 Interrupted time-series analyses (users/1,000 PM)



NL=the Netherlands

lence of metoclopramide use increases strongly after puberty in all countries (**tables 11.2 and 11.3**). Prescriptions for metoclopramide in Spain were most prevalent in January and October and were relatively stable in between. No clear seasonal trend was present for the Netherlands and Italy (**figure 11.1**).

The incidence and prevalence of cisapride use was low over the total study period in each country. Due to the earlier start of the study period, cisapride use could mainly be observed in the Netherlands, showing that use was highest in 0-<1 years of age (5.0 users/1,000 PY; 95% CI 4.0-6.0). In the Netherlands, cisapride prevalence rates showed a peak in January but was constant over the other months (**figure 11.1**).

Domperidone was the most common prescribed prokinetic drug in all three countries with roughly similar incidence and prevalence rates in the Netherlands, Italy and Spain (**table 11.2**). In each country, domperidone was mainly prescribed to young children. Prescriptions of domperidone were lowest in the summer; in July for Spain and in August for the Netherlands and Italy. Prescribing was highest in October for Spain, in January for Italy and in February for the Netherlands (**figure 11.1**).

Prevalence of use of all prokinetic drugs combined was significantly higher in girls than in boys in both Spain (RR 1.16, 95% CI 1.14-1.18) and NL (RR 1.15, 95% CI 1.09-1.21), and comparable in Italy (RR 0.98, 95% CI 0.95-1.02). The higher prevalence rates for girls is mainly observed from puberty on. In the Netherlands the higher prevalence in girls is most prominent for domperidone and metoclopramide. No significant sex-differences for the prevalence of cisapride use were present (**figure 11.2**).

Interrupted time-series analysis

The Italian contra-indication for the use of metoclopramide in children has been published in the first quarter of 2004. The monthly prevalence of metoclopramide use followed an ARIMA (1,0,0)(0,0,0) model until March 2004 in Italy and the Netherlands, in Spain it followed an ARIMA (0,1,1)(0,1,0) model. The intervention reduced the prevalence of metoclopramide prescriptions in Italy (β=-0.601; p<0.000). Using the same intervention period, a small increase (β=0.029) was seen in the Netherlands (p=0.008) and in Spain (β=0.077, p=0.584).

In the Netherlands the restriction in February 2007 did not reduce the prescriptions of metoclopramide compared to March 2004 (β=0.037; p=0.014) nor overall (β=0.022; p=0.206).

Only data from the Netherlands was available to study the impact of the safety warnings on use of cisapride. The monthly prevalence of cisapride use in the

Netherlands followed an ARIMA (1,0,0)(0,0,0) model until the withdrawal in the US. Between the withdrawal of cisapride in the US in March 2000 and the restriction of prescriptions by specialists only, the prevalence of cisapride used decreased (β=-0.128; p=<0.05). The subsequent restrictions issued in 2002 further decreased the prevalence to almost zero, however there was no additional significant effect of these interventions (β=-0.035; p=0.680).

The monthly prevalence of domperidone use in the Netherlands followed an ARIMA (0,0,0)(1,1,0) model until the European-wide referral in June 2002. In Italy and Spain it followed an ARIMA (1,0,0)(0,0,0) model. The referral was associated with a significant decrease of domperidone use in both Italy (β=-1.449; p<0.000) and the Netherlands (β=-0.229; p<0.05). The referral procedure an opposite effect in Spain, where the prevalence rate of domperidone prescribing increased (β=0.369; p=0.167).

Discussion

Triggered by the recent European restriction of the indication for use of metoclopramide in children, we showed that, irrespective of the controversy around their use, prokinetic drugs are still prescribed widely in the Netherlands, Italy and Spain. Interestingly there were big differences in the use of the prokinetics between the countries and the effect of the safety warnings differed for the different prokinetic drugs and for the different countries.

Prokinetic drugs were prescribed at remarkable higher rates in Spain than in Italy or the Netherlands. In particular the prevalence of metoclopramide was much higher from puberty on; up to 10 times higher at the age of 16-18 years. The high prevalence and incidence of use in children and adolescents in Spain is worrying especially in view of the questionable effectiveness and the safety profile that has specified risks of extrapyramidal disorders, tardive dyskinesia, QT prolongation, and sudden cardiac death.[316-319]

The debate on the safety of prokinetic drugs started with cisapride. Following reports of sudden cardiac death and ventricular arrhythmias, cisapride was withdrawn from the US market in 2000 and was followed by several warnings and restrictions in the indication of use in Europe during the succeeding years.[320-328] Currently, cisapride is no longer marketed in the studied countries and the effect of the restriction of use could only be studied in the Netherlands. Following the withdrawal in the US, a significant decrease in cisapride prescribing was observed. The restriction that followed in 2002 had no *additional* decreasing effect, the utilisation pattern however decreased further to zero. In an earlier study by Wilkinson *et al*. it was shown that the first safety warning on the use of cisapride mainly had an effect on the number of new prescriptions, while the total number of prescriptions decreased only after further warnings.[331]

After the issues concerning cisapride, the safety and effectiveness of metoclopramide and domperidone were questioned. Both drugs are associated with a higher risk of extrapyramidal disorders and tardive dyskinesia.[318,332,333] This risk of extrapyramidal disorders led to a contra-indication of metoclopramide for children and adolescents under the age of 16 in Italy in 2004 [310] and a restriction of the paediatric indications in the Netherlands in February 2007, which was effective in reducing prescription rates. No restrictions or warnings were issued in Spain and the prevalence of use remained constantly high in Spain. Recently the use of metoclopramide in children has again been questioned after the finalisation of the European article 45 procedure. Further studies should show whether the article 45 procedure on the use of metoclopramide in children will affect metoclopramide prescription rates in all European countries and whether the effect is comparable to the effect of the contra-indication in Italy.

The safety issues related to domperidone concern both extrapyramidal disorders and QT prolongation.[315,334] In 2002 warnings on the risk of extrapyramidal disorders in children were included in all European SPCs, upon which the utilisation in both Italy and the Netherlands decreased. No reduction in prescriptions was seen in Spain, in contrast, prescription rates of domperidone increased in the most recent years.

Overall a decrease in the utilisation of prokinetic drugs over time was seen in both Italy and the Netherlands while an increase was observed in Spain. The decrease in Italy and the Netherlands can be explained by the impact of the safety warnings as demonstrated in the interrupted time-series analysis. The overall decrease also indicates that the safety warnings did not led to a switch in the type of prokinetic drug prescribed but rather to an overall discouragement to prescribe these drugs.

In Spain, the safety warnings did not result in a decreasing prescription rate which shows that mere changes in the SPC are probably not enough and higher public notoriety through informative notes and/or the implementation of restrictive measures are needed. The increase of prescribing rates in adolescents as compared to children, in particular for metoclopramide, may be partly explained by a higher prevalence of diseases for which these drugs are indicated for in such group, but also it may be reflecting the fact that healthcare of adolescents from 14 years onwards are provided by GPs, who may be less concerned with safety issues of prokinetics than family paediatricians. More research is needed to account for these differences.

Strengths and limitations

The main strength of the current study is the use of three large population-based electronic health care databases, altogether containing data on almost 1 mil-

lion children, contributing almost 3 million person years of follow-up. The use of these primary care data allowed us to assess utilisation patterns and to study the effect of European safety warnings in different geographical regions.

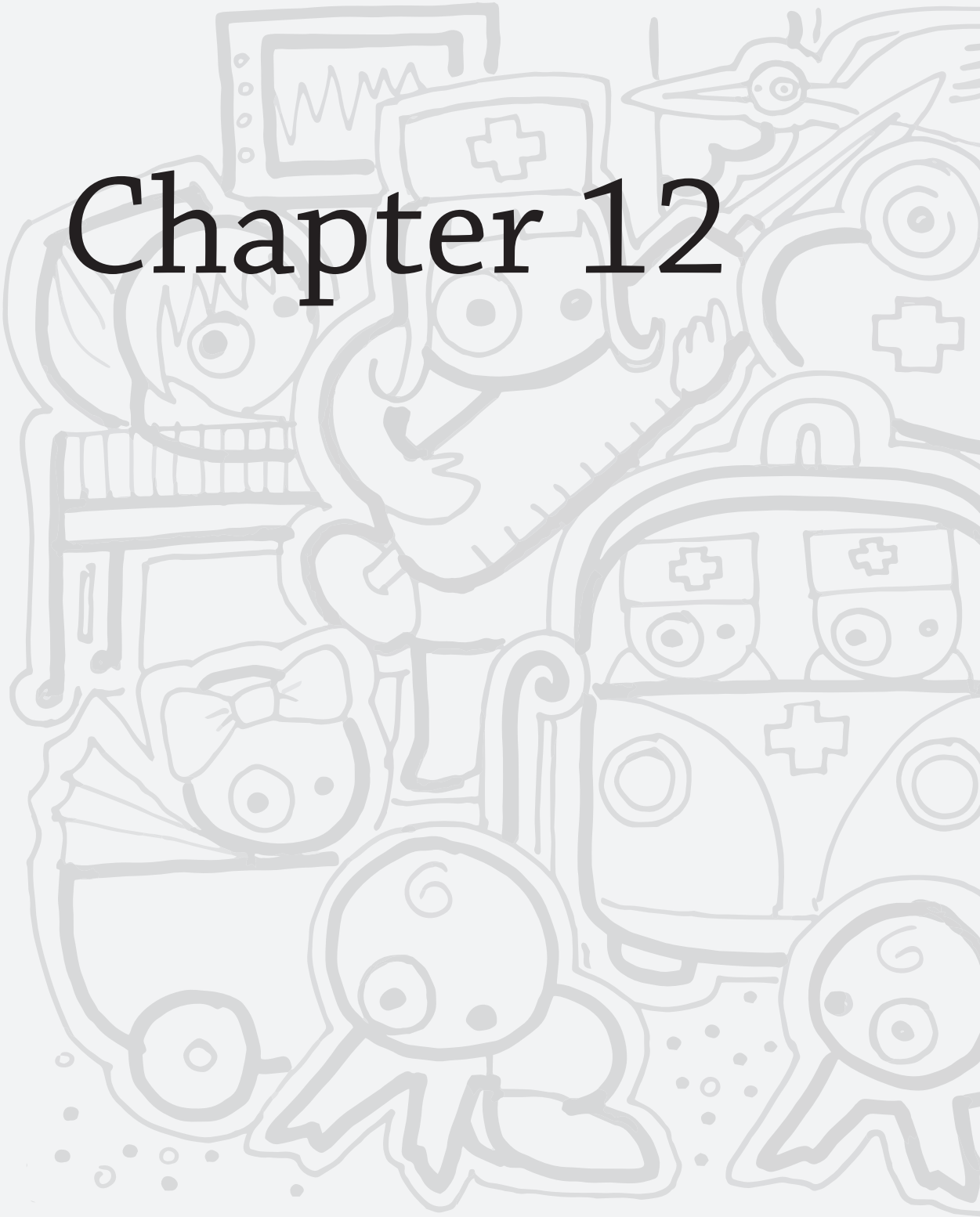
Important limitations are that over-the-counter (OTC) use of prokinetics could not be estimated, probably resulting in underestimation of the actual utilisation, especially for domperidone which is available as OTC drug in most European countries. Furthermore, since we studied drug prescriptions rather than drug intake, the actual drug exposure might be lower than estimated in our study.

Conclusions

Safety warnings and changes in the product information of prokinetic drugs resulted in a significant decrease of prescription rates in those countries where restrictions of use were implemented.

General Discussion and Summary

Chapter 12



General Discussion

Paediatric pharmacoepidemiology and paediatric pharmacovigilance are still in their childhood. The work as described in this thesis aims to add to this area and is based on large observational studies in across Europe as introduced in **Chapter 1** and aimed studying use and risks of medicines in children and adolescents. Many of the chapters dealt with specific methodological issues related to pharmacoepidemiological research within the paediatric population. We have chosen a European approach to study safety and risk of medicines in children since the size of single-country studies is often too limited to draw definitive conclusions. In addition, using data from different countries across Europe allowed us to compare the results amongst the countries and investigate consistency.

In this chapter we discuss the main findings of this thesis and the main methodological considerations of the studies.

Main findings

To which extent are children and adolescents exposed to medicines?

Knowledge on patterns of utilisation of medicines in children is the first step in studying and monitoring paediatric drug effects. Not only can the patterns of use help with respect to prioritisation of research, it can also give information on suboptimal use or undesirable prescribing.[50] Results on the use of different medicines in children and adolescents are an important part of the work described in this thesis.

Overall prescribing of medicines

A broad overview of the exposure to medicines in children and adolescent across Europe is presented in **Chapter 9**. Using data from the EU-ADR (Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge) network on 4.8 million children and adolescents from seven population-based electronic healthcare record databases from Denmark, Italy and the Netherlands, we assessed the number of person years (PY) of exposure. A total of 2,170 medicines were used during the study period with a total exposure of 1,610,631 PY.

Drug use in children in terms of person years was rare in this cohort. Only 18 out of the total 2,170 prescribed or dispensed drugs (<1%) made up half of the total drug exposure time in the paediatric population. A clear trend over age was seen in the prescribing and dispensing of different drug classes. Respiratory and anti-infective medicines were the drug classes with the highest exposure up to 12 years of age. Genitourinary medicines, mainly oral contraceptives in girls, were

increasingly used from age 14 years onwards. For all ages together (0-<18 years), respiratory, anti-infective, dermatological, genitourinary drugs and alimentary medicines had the highest exposure.

Prescribing of anti-infective medicines

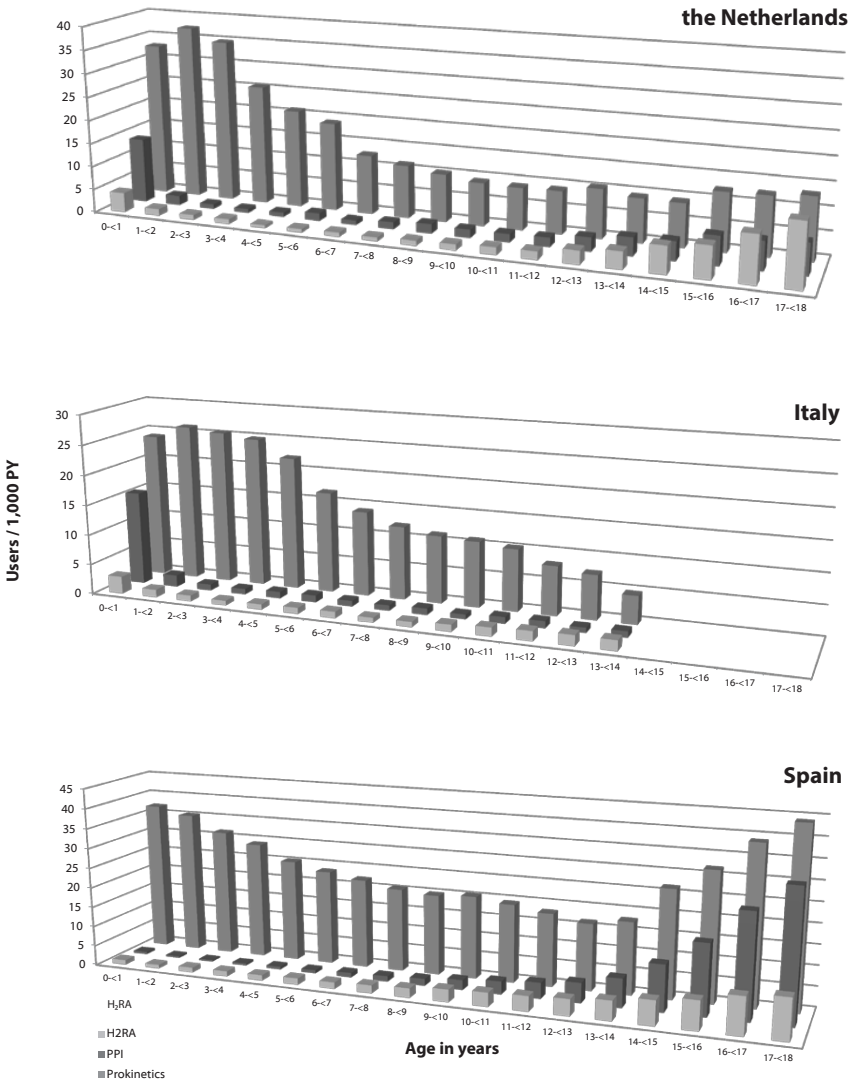
It is known that anti-infective medicines are among the most frequently prescribed medicines in children[50,335] and this was confirmed in our research; indeed anti-infective medicines were the class with the second highest exposure in PY (*chapter 9*). As we used data on prescribing in primary care, the group of anti-infective medicines was mainly represented by antibiotics. Children, and especially young children, are high-volume users of antibiotics, with the majority of antibiotics given for minor upper respiratory tract infections.[50,55] This high rate of paediatric antibiotic prescribing in primary care, often for mild viral infections,[56] warrant monitoring of antibiotic prescribing. Rational and reduced prescribing of antibiotics is important since there is clear evidence that antibiotic-resistance of pathogens is linked to antibiotic prescribing.[51] So far there have been few initiatives aimed at specifically improving the quality of antibiotic prescribing for children.[57] One of these initiatives is the ARPEC (*Antibiotic Resistance and Prescribing in European children*) study. ARPEC is an initiative by the European Society of Paediatric Infectious Diseases (ESPID),[47] and aims to improve antimicrobial prescribing in hospitals and in the community. As part of the ARPEC study we studied in **Chapter 2** the extent of antibiotic prescribing in the Netherlands, the United Kingdom (UK) and Italy during a ≥10 years study period. In our study the antibiotic prevalence rates amongst the studied countries varied with the Netherlands having the lowest prevalence (18.0 users/100 PY) and a two to three-fold higher prevalence rate for the UK (36.2 users/100 PY) and Italy (52.0 users/100 PY), which is in line with previous publications in both children and adults.[50,52,55,67] As expected, amoxicillin with or without clavulanic acid was the most commonly prescribed antibiotic. Notably, in Italy cephalosporins, especially third-generation cephalosporins, were frequently used – a phenomenon not observed in the other countries. This high-volume use of cephalosporins in primary care in children and adults in Italy has been described before.[67,336] Although we did not study the indications for use, it is known from literature that this may partly be explained by differences in treatment guidelines, resistance patterns, availability of medicines but also factors such as physician speciality and region.[73-75,336,337]

ESAC-Net (*European Surveillance of Antimicrobial Consumption Network*) is a Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption. ESAC-Net developed quality indicators, using data on outpatient adult antibiotic use in Europe, to assess the quality of national antibiotic prescribing in Europe.[53,54] These included both drug-specific and disease-specific indicators, but can unfortunately not be directly extrapolated to paediatric antibiotic use in Europe since no age-specific DDDs (defined

daily dose)[30] exist. Since children are an important target group to improve antibiotic prescribing,[77] we would like to make plea for paediatric specific surveillance and data-collection. Both overall prescription rates of antibiotics and specifically of broad spectrum antibiotic prescribing in children may be appropriate quality indicators of good prescribing practice. Since broad spectrum antibiotic prescribing also depends on existing resistance patterns and available medicines, probably more paediatric specific quality indicators are needed. These could include process indicators (adherence to treatment guidelines) such as the proportion of children with acute otitis media who receive antibiotic treatment, or the type of antibiotics prescribed to treat pharyngitis.

While in chapter 2 we investigated the extent of antibiotic during a ≥10 years study period, we studied in **Chapter 3** prescriptions for oseltamivir for a specific period; the influenza A(H1N1)pdm09 pandemic. The occurrence of the 2009 pandemic implied that oseltamivir, an antiviral medicine, was used for the first time on a large scale in infants since its registration in 2002. The pattern of oseltamivir prescriptions over time was in line with the trend in observed influenza like illness (ILI) rates in the studied countries (the Netherlands, UK and Italy) in the same period, a phenomenon also seen in the United States (US).[338] Although Italy reported the highest rates of ILI, the lowest prevalence rate of oseltamivir prescriptions was noted. The differences in prevalence of use in the different countries probably reflect differences in national policy during the pandemic period. Apart from the guidance on use of oseltamivir by the CHMP in May 2009,[81,82] national guidelines were developed rapidly to control the pandemic.[91,94] In the UK the initial response of the public health authorities to the pandemic was very intensive. From the start of the pandemic till July 2009, all contact persons of H1N1 cases in the UK received prophylactic treatment with oseltamivir and schools were closed.[89,95] Also in the Netherlands, oseltamivir treatment was initially recommended (till June 23rd) for all laboratory confirmed cases as for their close contacts, regardless of symptoms.[91,96] In this first summer period of the pandemic, the influenza activity in Italy was limited and no signs of an epidemic were present till the end of October 2009.[97] At that time, oseltamivir prescriptions to children were discouraged and use in children was limited to hospitalised cases because of the risk to develop resistance.[98,99] It is difficult to judge whether there was over- or under prescribing as the efficacy of oseltamivir in the treatment and prevention of influenza, especially in children, is still under debate.[100-102] As advocated by the BMJ (British Medical Journal) open data campaign it is important to obtain transparency considering the efficacy and safety of oseltamivir use. In our view, a European approach on recommendations on the use of antiviral drugs in future pandemics is needed.

Figure 12.1 Prevalence of different gastro-intestinal medicines



In these graphs, the results from chapters 4 and 11 are combined (2001-2008). On the X-axis the age in years is given, on the Y-axis the prevalence of use (users/1,000 PY). Abbreviations: H_2RA=histamine-2-receptor antagonists; PPI=proton pump inhibitors.

Prescribing of gastro-intestinal medicines

The use of gastro-intestinal medicines was studied as these are often prescribed in children. We focussed on three groups of gastro-intestinal medicines: In **Chapter 4** we studied the extent of prescribing proton pump inhibitors (PPIs) and histamine-2-receptor antagonists (H_2RAs), two classes of gastric acid suppressant medicines, in children and adolescents in Spain, the Netherlands and Italy. H_2RAs were mainly prescribed in children up to the age of 1 year in the Netherlands and Italy. PPIs were mainly prescribed in children of 12 years and older in Spain and the Netherlands (*no data available in Italy*). Within these two classes of gastric acid suppressant medicines, the share of PPI prescriptions increased significantly between 2001 and 2008. The off-label use of PPIs in young children has been subject of debate. According to the international guideline on treatment of GERD (Gastro-oesophagal reflux disease), PPIs are the mainstay for the symptomatic treatment of GERD.[108,115-117] However, none of the currently available PPIs have been registered for use in young children.[118] In 2007, the European Medicines Agency (EMA) compiled a list of medicines with 'paediatric needs'. This is a list of drugs for which more data is needed with respect to e.g. pharmacodynamics, pharmacokinetics, efficacy and safety. Gastric acid reducing drugs are part of this list with a need for alcohol-free formulations of ranitidine (H_2RA) and the need of paediatric pharmacokinetics, efficacy, and long term safety data for PPIs.[119] Since the implementation of the new paediatric regulation, stimulating research in children,[14] only two paediatric investigations plans for esomeprazole and rabeprazole (PPIs) have been submitted to and evaluated by the EMA.[120,121] Although it has been speculated by some research groups that there is enough data available on the use of PPIs in young children,[118] we agree with the EMA that data on long-term safety of PPIs and development of age appropriate formulations remains essential, also in the light of the increasing evidence in adults that long term use of PPIs is associated with adverse events such as bone fractures, community-acquired pneumonia and *Clostridium difficile* infections. [104-106]

In **Chapter 11** both the incidence and prevalence of use of prokinetic medicines were studied. Overall a decrease in the utilisation of prokinetic drugs over time was seen in both Italy and the Netherlands while an increase was observed in Spain. In **figure 12.1** the prevalence rates of both gastric acid suppressant medicines and prokinetics (*chapter 4 and 11*) are presented. In the Netherlands and Italy these drugs are mainly prescribed to young children. In Spain, only the use of prokinetics is high in young children and remains high over all ages, even exceeding the prevalence rate of young children form the age of 12 years onwards. The high prevalence and incidence of use of prokinetics is of concern in view of the questionable efficacy and the risk for extrapyramidal disorders, tardive dyskinesia, QT prolongation, and sudden cardiac death.[316-319]

As shown in this thesis, drug utilisation research in children encompasses more than describing off-label use. Drug utilisation research provides insights into the

patterns, quality, determinants, and outcomes of use. The extent of use of medicines in children and adolescents is essential to identify knowledge gaps and to seek where there is room for improvement of prescribing (e.g. in case of inappropriate prescribing). Knowledge on actual use is also important as it defines the denominator in studying adverse drug reactions (ADRs). Information on use of medicines is also part of risk management plans (RMPs) (*see regulatory aspects*) as information on drug use is essential during the entire life-cycle of a drug and information on the extent of drug use is essential to give insight on the potential impact of safety issues.

Reporting of paediatric adverse drug reactions

Post-marketing drug safety surveillance using spontaneously reported ADRs is essential in studying drug risks and is thereby an important source for identifying drug safety signals.[18,19] Analyses of reported ADRs also aids in detecting gaps in the knowledge on drug safety in children and the generation of hypothesis for further (pharmacoepidemiological) research.

ADRs in spontaneous reporting systems

Nationally reported ADRs are internationally gathered in the form of individual case safety reports (ICSRs) in spontaneous reporting systems such as the worldwide VigiBase, the US AERS (Adverse Event Reporting System) and VAERS (Vaccine Adverse Event Reporting System), and the European Eudravigilance.[26,27,31,339]

Figure 12.2 Distribution of the reported medicines in the different spontaneous reporting systems (anatomical main group - ATC)

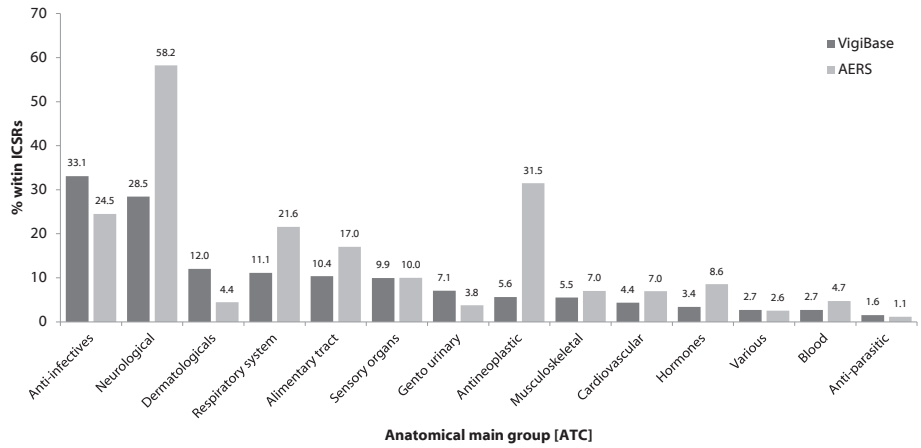
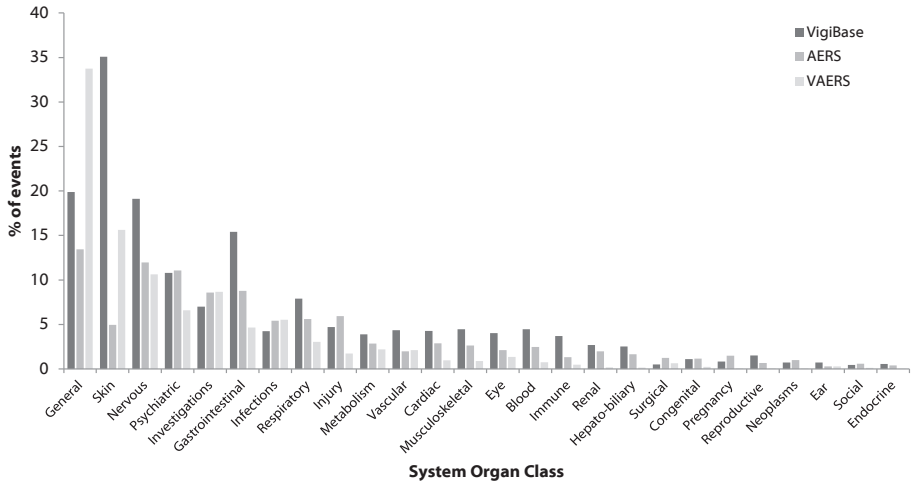


Figure 12.3 Distribution of the reported ADRs in the different spontaneous reporting systems (SOCs)



In **Chapter 7** we described paediatric ICSRs reported to AERS of the FDA (Food and Drug Administration). We compared the results with an overview of the paediatric ICSRs (excluding vaccines) reported to VigiBase as published in 2011 by the World Health Organisation Uppsala Monitoring Center (WHO-UMC) .[263]

Although US reports make up the largest proportion of the ICSRs both within AERS (58%) (*our study*) and within VigiBase (39%) (*study WHO-UMC*), large differences between the results of the two studies were present. The type of reporters differed with more than half of the ICSRs reported by physicians in VigiBase and only a third in AERS. Consumer reports made up 24.9% of the AERS reports while this was only 4.3% within VigiBase. This difference might be due to different time-periods; consumer reporting has indeed increased in recent years.[271] Only a small proportion of the AERS ICSRs concerned reporting by non-manufacturers. The majority was either reported as part of expedited reporting (65%) or as part of periodic reporting. Earlier it was shown that the US reports within VigiBase are mainly reported by manufacturers, while these form only a small proportion of the reports from the other continents.[26] The reported drug groups and events differed. VigiBase reports more often concerned anti-infective and dermatological drugs, while within AERS neurological drugs and antineoplastic drugs were most frequently reported (**figure 12.2**). This finding reflects utilisation differences between the US and Europe, with e.g. high rates of prescriptions of methylphenidate in US adolescents in recent years.[272] Choosing an appropriate time-period to study these drugs is essential since the utilisation of neurological drugs, especially for the treatment of ADHD (attention deficit hyperactivity disorder), has changed tremendously since the start of VigiBase in 1968.[272,273] In **figure**

12.3 the differences in reported ADRs between VigiBase, AERS and VAERS (vaccines only) is presented. An important differences between VAERS and the two non-vaccine based databases is the large number of general disorders and skin disorders within VAERS.

As illustrated in **Chapter 10**, there is a difference in the distribution of the medicines used in the general paediatric population and the medicines reported within spontaneous reporting systems. For safety signals identified in VigiBase only, there was no exposure present or less than 3 events occurring in EU-ADR (see *Paediatric signal detection using electronic healthcare records versus spontaneous reporting systems*). This can partly be explained by study reports within those reporting systems. Pharmaceutical companies are obliged to report all serious adverse events,[22] while reporting by health care professionals and consumers is subject to underreporting.[340] Furthermore, enhanced therapies such as biological and chemotherapeutics are used in only a small proportion of the population, but are associated with more serious but also different adverse events.[341,342] In addition, systems like VigiBase are susceptible for increased reporting due to e.g. the Weber effect or media attention.[24]

An example in which reporting could be driven by media attention in combination with a wide-spread distribution of a new product was seen during the influenza A(H1N1)pdm09 pandemic. The occurrence of the pandemic not only implied large-scale use of oseltamivir (**Chapter 3**), but also several pandemic H1N1 vaccines were licenced using fast track procedures, with relatively limited data on the safety in children and adolescents. In **Chapter 6**, we reviewed safety experience and adverse events from 25 clinical studies and numerous analyses of spontaneous ADR reports for the different pandemic H1N1 vaccines. Much has been published on the safety of these vaccines in children. There have been several trials with different vaccines spanning all age categories, including several trials in children and adolescents with underlying medical conditions. In addition, large monitoring efforts have resulted in much data, with almost 13,000 individual case reports in children and adolescents reported to the WHO-UMC. However, both differences in study methodology and data presentation render meta-analytic safety analyses of the pandemic H1N1 vaccines in the different, relevant, age categories difficult. Especially the diversity in the clinical studies for inactivated non-adjuvanted pandemic H1N1 vaccines re-emphasizes the need for harmonisation of study protocols and homogenous presentation of safety data in clinical study publications.[207,257] Unfortunately, although a large amount of data has been generated, relatively little has been learned on the comparative safety of these pandemic H1N1 vaccines – particularly in children. Adherence to available guidelines for the collection, analysis, and presentation of vaccine safety data in clinical studies will give added value to the enormous work done within the individual studies.[205,258,259]

Hospitalisation due to adverse drug reactions

It is estimated that ADRs occur in more than 10% of the hospitalised children.[12] In **Chapter 5**, we studied ADR-related hospital admissions in children and adolescents in the Netherlands over a six-year period. Adverse drug reactions accounted for 0.75% of all paediatric hospital admissions in our study period, with an incidence of 24/100,000 in the population. Earlier literature reviews showed higher admissions rate due to ADRs up to 1.8-2.1%.[12,131] An earlier study in 2001 in the Netherlands using the same data source showed that 0.8% of the acute hospital admissions were ADR-related.[343] This indicates that the rate is stable over time despite national efforts to reduce this rate. The lower rate as observed in our study compared to literature reviews. is probably an underestimation due to passive coding of ADR relatedness of the admission diagnosis at discharge: notification of the causes of hospitalisation is done on a voluntary basis by the hospitals.[344] We assume that this underreporting is non-differential for the different age categories and different medicines and does not influence the relative risks for hospitalisation. The unique feature of our study is the combination of the admission with national prescription data and population size. However, due to the ecological nature of the study, e.g. no direct link was available between the prescribing data and the hospitalisation data, it was not possible to draw inferences on interactions or causal relationships with other medicines than those registered at discharge. The risk for ADR-related hospital admission was highest in children under the age of 2 years (incidence 169/100,000 children). These young children were mainly admitted for ADRs because of maternal exposure through placenta or breast milk. This underlines that paediatric safety should also consider maternal use of medicines during pregnancy, considering that a recent Canadian study showed that prescriptions were filled in 63.6% of pregnancy.[345]

Paediatric signal detection in spontaneous reporting systems

Signal detection within spontaneous reporting databases is the first step in the detection of a potential safety signal, which may be followed by signal prioritisation and evaluation.[24] Signal detection in spontaneous reporting systems using data mining techniques has proven its value in the past years. It is not only an efficient method for safety surveillance in these large databases, these data mining techniques also allow for earlier detection of safety signals.[25,283,346]

Data mining algorithms rely on the principle of disproportionality and come with underlying assumptions: i. if a certain adverse reaction is caused by a specific medicine, this reaction is reported more often for this medicine than for medicines that do not cause this adverse reaction; ii. the extent of reporting for a certain adverse reaction is equal for different medicines; iii. the overall pattern of reporting is a valid reference to compare a specific combination of a medi-

cine and adverse reaction with.[24] Although spontaneous reporting systems have proven their value for safety surveillance, there are well-recognised limitations and biases such as selective underreporting, stimulated or false positive reporting and the lack of exposure data.[24,42,43] Effort has been put to deal with possible confounding factors such as age, sex and time, all with varying results.[40,276-278]

An important assumption is non-differential reporting,[24,347] but due to the above-mentioned limitations and biases of spontaneous reporting, this assumption is difficult to hold. We studied an important example of non-differential reporting in **Chapter 8**. In this chapter we explored the effect of vaccine-related reports, which made up 54% of all paediatric ICSRs reported to VigiBase, in the period between 2000 and 2006. For ADRs reported less frequently for medicines (non-vaccines) than for vaccines (or the other way around), stratification of the analysis by vaccines and non-vaccines led to an increase of the sensitivity of the signal detection process. We also saw that subgroup analysis led to a decreased sensitivity if the ADR was reported more frequently for medicines than for vaccines. Routine application of subgroup analysis for those types of events can be harmful. However stratification for this group can be informative in specific subgroup analyses for studying the magnitude of class effects for the individual drugs in the class. For example, studying fever convulsions using vaccines only will give an estimate of the disproportionality compared to the other vaccines. In other words for which vaccines are fever convulsions most frequently reported compared to all other vaccines. A similar approach can be used for studying potential ADRs that are frequently occurring in the treated target population. For example, studying cardiovascular effects of diabetic medicines is difficult because of the high background rate of cardiovascular events in diabetes patients. By restriction the signal detection analysis to diabetic medicines only, the individual medicines can be compared with each other while correcting for the increased background risk. This approach can be compared with a nested-case control analysis for cohort studies and therefore might be referred to as '*nested signal detection*'.

Paediatric signal detection using electronic healthcare records

Statistical power of paediatric signal detection in electronic healthcare records

To overcome some of the well-known limitations and biases of signal detection within spontaneous reporting systems and to complement these and other traditional monitoring systems, initiatives in the US and in Europe have set up population-based surveillance systems that make use of longitudinal electronic healthcare data.[44-46,299] In the US these include Mini-Sentinel and the Observational Medical Outcomes Partnership (OMOP).[46,294] In Europe, the EU-ADR Project was initiated in 2008 and is a collaboration of 18 public and private institutions. EU-ADR aims to exploit information from various electronic healthcare record

and other biomedical databases in Europe to produce a computerized integrated system for the early detection of drug safety signals.[44] In principle, the EU-ADR project was not designed for specific paediatric signal detection, but paediatric data were included in the network.

In **Chapter 9** we studied the statistical power of the EU-ADR network to perform paediatric safety signal detection. In this study, we provided estimates of the number of drugs with enough paediatric exposure to be monitored for events currently being investigated within the EU-ADR network. Furthermore, we provided information on the frequency range of events that can be monitored based the on actual drug-exposure in the cohort and we speculated on how large a network should be to monitor drug safety in children. The paediatric population of the EU-ADR network comprised 4.8 million children and adolescents contributing 25.6 million PY of follow-up.

An important first finding of this study was that use of medicines in children was rare and was limited to only a few medicines; only 18 medicines represented 50% and 158 drugs covered 90% of the total drug exposure time (*see overall prescribing of medicines).* Second, the events that were considered to be most relevant for safety monitoring in adults had very low incidence rates (IRs) in the paediatric population. Of the original 13 events present in EU-ADR[293] only 10 events had an annual IR of >1/100,000 PY; acute liver injury, acute renal failure, anaphylactic shock, bullous eruptions, cardiac valve fibrosis, hip fractures, neutropenia, acute pancreatitis, pancytopenia, and upper gastrointestinal bleeding (UGIB). The consequence of this combination of rare events and low-frequent use of medicines was that the number of medicines with enough exposure to allow safety monitoring these events was low. For a rare but serious event such as anaphylactic shock there were no drugs with enough exposure to study a weak association (RR≥2) and only 20 drugs to study a strong association (RR≥6). For a relatively frequent event such as UGIB there were 5 medicines with enough exposure to study a weak association (RR≥2) and 79 drugs for which an association with a RR≥6, if present, can be investigated. The statistical power of a system like the EU-ADR network is much higher for events more frequently occurring in the paediatric population. For example the incidence of febrile seizures in young children has been estimated at 14 / 1,000 PY.[296] Based on this literature-derived incidence a total of 132 medicines within EU-ADR have enough exposure to detect a possible association at RR≥4. Therefore, future initiatives on drug surveillance systems for the paediatric population using electronic healthcare records, should focus on age-appropriate events and definitions. Furthermore, since the majority of the databases are primary care-based, specialist prescriptions (e.g., for antineoplastic drugs) are only captured in the system if continued by the general practitioner. Expansion of the database network to include other populations would be necessary to capture all drugs prescribed in the population not only to increase the size of the studied population, but also to increase the variation in prescribing patterns. Global collaboration will be necessary for further development of

paediatric drug safety monitoring systems using electronic healthcare records, although such collaborations may still be incapable of studying the majority, if not all, drugs used in children and adolescents. Collaboration with other currently ongoing worldwide initiatives using healthcare data for safety surveillance (such as OMOP and Sentinel Initiative[46,294,298]) will also be important for external validation of newly identified safety signals.

Paediatric signal detection using electronic healthcare records versus spontaneous reporting systems

In the study described in chapter 9 we only theoretically explored the power of an electronic healthcare records database for paediatric safety surveillance. Now that these electronic health record-based surveillance systems are being established it is also important to know how the value of mining these longitudinal healthcare database compares to data mining in spontaneous reporting systems.[24] A preliminary study comparing potential signals identified from the EU-ADR network with signals derived from spontaneous reporting systems showed that those adverse events having a low incidence in the general population and commonly regarded as drug-induced were more likely to be identified in spontaneous reporting systems.[297] Therefore in a consecutive study we explored the performance of the EU-ADR network in identifying drug safety signals for UGIB (**Chapter 10**) in children and adolescents (0-20 years) and compared this with the performance of a spontaneous reporting system (VigiBase).

When using the LGPS (Longitudinal Gamma Poisson Shrinker) as data mining algorithm, EU-ADR identified 55 potential signals for and in VigiBase, using the ROR (Reporting Odds Ratio) as method, 104 potential signals for UGIB \were identified. The overlap between the signals identified by EU-ADR and VigiBase was limited. Of the 142 unique potential signals for UGIB, 17 were identified in both sources. Many signals identified by VigiBase were not identified by EU-ADR. Our study showed that these drug-event combinations were missed because of lack of statistical power. The medicines identified within VigiBase had either no paediatric exposure in EU-ADR or less than 3 exposed events.

Signal detection within spontaneous reporting systems or electronic healthcare records gave rise to different results. It has been hypothesised that data mining for safety signal detection within electronic healthcare records and spontaneous reporting systems might be complementary. As supported by the report on "*Practical aspects of signal detection in pharmacovigilance*" of the CIOMS (Council for International Organizations of Medical Sciences) VIII working group, published in 2010, spontaneous reporting systems are especially valuable for events with a low incidence rate in the population, for events with a high drug attributable risk and for drugs prescribed by specialists and used in-hospital.[24] Events with a low background incidence in the population are relatively easy to prove to be

causally related and often clinical observation will suffice (e.g. phocomelia due to thalidomide). Signal detection using electronic healthcare records is better for events with a higher IR and for drugs with a high prevalence of use in primary care (e.g. Angiotensin Converting Enzyme inhibitors and cough). Acquisition of data on in-hospital drug use and expansion of the study population are essential for improving signal detection within electronic healthcare records.

The effect of safety warnings

New information on the risks associated with the use of medicines can lead to changes in the summary of product characteristics (SPCs) of medicines. A newly identified adverse event can be added to the section with adverse events, but can also be included as a safety warning. For some risks specific warnings are issued by the regulatory authorities. **Chapter 11** described the effect of such warnings on the prescriptions of medicines. In the last decade multiple warnings have been issued in Europe on the risks associated with the use of prokinetic medicines (domperidone, metoclopramide and cisapride) in children. Cisapride prescribing was restricted to specific subgroups from 2000 onwards following reports of sudden cardiac death and ventricular arrhythmias and was finally withdrawn from the market in 2010.[320-328] Already in 2004, Italy contra-indicated the use of metoclopramide in children up to the age of 16,[310] and in February 2007, the Dutch Medicines Evaluation Board restricted paediatric indications of metoclopramide because of the risk of developing extrapyramidal disorders (EPD).[311] More recent, in 2011, after a formal evaluation of the paediatric use of metoclopramide, it was decided in Europe to contraindicate this drug in children <1 year of age and to advise against prescribing in children from 1 year of age with the exception of treatment of postoperative nausea and vomiting.[309] Notwithstanding these safety issues, the use of prokinetic drugs in children remained high in the Netherlands, Italy and Spain (*figure 12.1*). In Spain, the safety warnings did not result in a decreasing prescription rate which shows that mere changes in the SPC are probably not enough and higher public awareness through informative notes and/or the implementation of restrictive measures are needed.

Methodological considerations

The two most important data sources for the research described in this thesis were electronic healthcare records and spontaneous reporting databases.

Electronic healthcare records

In **Chapters 9 and 10** we used aggregated data from seven electronic healthcare records in three European countries: Health Search/CSD Longitudinal Patient Da-

tabase (Italy), Integrated Primary Care Information (IPCI, the Netherlands) and Pedianet (Italy) are population-based general practice databases, in which clinical information and medication prescriptions are recorded. Aarhus University Hospital Database (Aarhus, Denmark), PHARMO Network (Netherlands), and the regional Italian databases of Lombardy and Tuscany are all comprehensive record-linkage systems in which drug dispensing data of regional/national catchment area are linked to a registry of hospital discharge diagnoses and other registries. For the studies in **Chapters 2,3,4 and 11** we used data on individual patient level from four different population-based primary care databases; the *IPCI database* from the Netherlands, *The Health Improvement Network (THIN)* from the UK, *Pedianet* from Italy and *BIFAP* from Spain.[60-63]

In the Netherlands and the UK, the general practitioner (GP) is responsible for the primary care of children whereas in Italy and Spain family paediatricians (FPs) are the gatekeepers of primary care for children. The databases contain the complete automated patient files, with detailed information on the population, diagnoses and prescriptions, and use of these databases has been proven valid for pharmacoepidemiological research.[58,59]

The *IPCI database* from the Netherlands comprises paediatric and adult electronic medical records from more than 400 Dutch GPs since 1996.[60,61] The IPCI database contains information on over 1 million patients. *THIN* is a database of primary care medical records from the UK, prospectively collecting data since September 2002 and contains retrospective data since the late 1980's.[59] The *Pedianet* database contains paediatric electronic medical records from 150 FPs in Italy since 2000.[62] Primary care of children in Italy is provided by FPs until the age of 14 years. From 14 years on, health care is taken on by GPs. The *BIFAP database* is a longitudinal observational population-based database kept by the Spanish agency for medicines and medical devices that collates, from 2001 onwards, the computerised medical records of more than 2,000 primary care physicians, including more than 350 primary care paediatricians throughout Spain.[63] The primary care of children in Spain is entrusted to primary care paediatricians until the age of 14 years old. Afterwards, care is taken over by GPs. The BIFAP database combines both the data from primary care paediatricians and GPs.

Data elaboration when combining data from multiple databases

Combining data from multiple databases in multiple countries allowed us to increase the study size and to compare prescribing rates. For these studies, data were elaborated according to a common study protocol. One important aspect when combining data from different databases is the coding dictionaries used for drugs and events. Most of drugs are coded according to the ATC (Anatomical Therapeutic Chemical) classification of the WHO, however this does not hold for all databases e.g. THIN which uses BNF (British National Formulary). Within

electronic healthcare record databases, diseases are coded according to ICPC, ICD9, ICD10 or READ codes. This implies, that code mapping needs to be done before the data-extraction can start. Within the EU-ADR studies pooled data was used. Because of the heterogeneity of the data, processes for the identification of drugs and events were developed to allow harmonised data collection.[301] To ensure harmonised data analyses when using a common study protocol it is of utmost importance that all methods are clearly described in the protocol to ensure uniform data collection and elaboration. Within EU-ADR, this step in the process has been surpassed by the development of a software program; Jerboa ©.[44] Data is collected locally in a common format, after which Jerboa aggregates the data and can calculate prevalence or incidence rates. This ensures that the calculations are equal for all databases.

Exposure outcome data

The results on the overall use of medicines as presented in *Chapter 9* differ somewhat from earlier publications from the TEDDY (Task force in Europe for Drug Development for the Young) network using similar databases.[50] Within the EU-ADR study, the exposure of genitourinary drugs ranks higher, since we used exposure in PY instead of the number of users as used for the TEDDY project. By calculating the exposure in PY, the exposure to medicines used for long periods of time is better represented.

As dosing information was not available in all databases (e.g. Pedianet), we were not able to define the duration of use of the different prescriptions nor were able to compare defined daily dosage (DDDs).[110] In addition, comparing DDDs only makes sense in case medicines are used for similar indications. Unfortunately, indication of use is not present in all databases and our research could not focus on correct prescribing in view of indication of use. Furthermore, DDDs are developed based on adult indication and unfortunately no DDDs specific for children exist. Only for neonatal antibiotic prescribing DDDs have been developed.[348]

Bias and confounding

A limitation of the use of primary databases is that, although prescription records are registered for all individuals, prescriptions initiated by specialists or prescriptions given during hospitalisation can be missed. Also medicines which are available without a prescription, the so-called over-the-counter (OTC) medicines, will be missing in the databases. These factors lead to an underestimation of the prevalence of use of some of the medicines studied, such as OTC-use of analgesics or specialised-prescribing of e.g. neurological drugs and biologicals. This OTC use or specialist prescribing will not have an effect on the age or calendar year stratified analysis of user prevalence, unless the OTC-status changed dur-

ing the study period or is related to age. Finally, since we studied prescriptions only, and not actually refill of the prescriptions or actual use of the medicines, the presented prevalence rates are also an overestimation with respect to actual prevalence of use.

The risk of selection bias within the studies using electronic healthcare records is low as data are collected as part of routine medical care and registration within the databases is not related to any research questions. As explained above, there is the potential of misclassification of exposure when using primary care prescription databases

Spontaneous reporting databases

In **Chapters 8 and 10** we used data from VigiBase of the WHO-UMC, and in **Chapter 7** we used data from the AERS. The details of these systems are presented in **Chapter 1**. In brief, since 1968 VigiBase is maintained on behalf of the WHO-UMC and 97 countries participate in the WHO International Drug Monitoring program. VigiBase currently contains more than 5.0 million ICSRs.[29] AERS is a database that contains information on adverse events and reports on medication errors submitted to the FDA. [31]

Spontaneous reporting systems are a great source for safety information. The advantages include that they i. are large-scaled, inexpensive and simple to operate, ii. cover all medicines during their whole life-cycle, iii. cover the whole population and iv. can be used for hypothesis generating. Weaknesses however include that i. the clinical information to permit thorough case evaluation is often limited, ii. underreporting leads to a decreased sensitivity, iii. the reporting rate is seldom stable over time, and iv. lack of denominator data.[16] Despite of these potential limitations, 36-50% of withdrawals due to safety issues were based on case reports as only evidence.[24,32-34]

As discussed above, there are underlying assumptions for signal detection using these databases which should be kept in mind when interpreting results of signal detection. We discussed the influence of the proportion of vaccines as an example of the violation of the assumption of non-differential reporting. Other factors that might influence the disproportionality estimates include; the number of serious versus non-serious ICSRs, consumer versus health care professional reported ICSRs, company owned databases versus databases of national competent authorities and differences in the distribution of the population characteristics or of the different outcomes within the different databases.[36,279] In **Chapters 5 and 7** we demonstrated that the type of reported ADRs is age-dependent. In **Chapters 2, 3, 4, 9 and 11** the age-dependency of medicines use was shown. The effect of age on either drug use or type of ADRs can also lead to inhomogeneous ADR reporting and jeopardise the assumption that reporting should be

non-differential to guarantee unbiased estimates of measures of disproportionality. This age-dependent frequency of both ADRs and use of medicines favour signal detection in different strata of age. These stratifications are currently not routinely performed within the large spontaneous reporting databases. WHO-UMC acknowledged the concern that child-specific signals may remain hidden due to the superior number of adult reports within VigiBase.[19] Therefore further development is ongoing at WHO-UMC to routinely highlight signals in different paediatric age categories.[349] In its guideline on paediatric pharmacovigilance, the EMA states that statistical methodologies are available to stratify signal detection by age category to the paediatric population as a whole.[350] FDA AERS also recognised the need to strengthen the paediatric drug surveillance systems.[264] However, as far as we aware, paediatric signal detection is not yet routinely done in the signal detection and management process within Eudravigilance of the EMA or AERS of the FDA.

Finally it should be noted that information derived from spontaneous reporting data have hypothesis generation purposes only. Hypothesis should be further tested by means of (observational) safety studies in order to draw firm conclusions.

The performance of data mining algorithms on different data sources is ideally tested by calculating sensitivity, specificity, or the area under the receiver operating characteristics curve (ROC curve).[24] The reference standard as developed within the EU-ADR project[308] could not be used in the current study (**chapter 10**) since it was based on data from adults only and many of the drugs in the reference standard were not prescribed in the paediatric population. This underlines the need for a paediatric specific reference set to serve as gold standard to test the performance of paediatric signal detection within different data sources. Within the *Global Research in Paediatrics Network of Excellence* (GRiP) project, such a reference set is currently under development.[49] Construction of such a set is challenging since such a set is dynamic and classification of an event as positive or negative can change over time.

Regulatory aspects

Pharmacovigilance regulation concerning the use of medicines in children in Europe has strongly changed in the past years. Since 2005, a European RMP is mandatory for the application of a marketing authorisation of a new medicinal product in Europe.[351] In 2007, the paediatric regulation came into place.[1,14,15,352,353] As of September 2009, the SPCs should include information on the use of special populations, including the paediatric population.[354] This included information on indications, posology, special warnings and adverse events. The last change came recently. In 2012 the new pharmacovigilance legislation came into force,[21,22,355,356] which included change in the requirements for a RMP.

The RMP should include information on a paediatric indication and if children are not studied, this should be described as missing information. The RMP included a section '*specific paediatric issues*' which includes issues identified in paediatric investigation plans (PIPs) and thereby links the RMP with the PIPs that were established as part of the 2007 paediatric regulation. Any recommendations for long term follow up of safety or efficacy issues in relation to paediatric use which are mentioned in the paediatric investigation plan should be included in the RMP. If the indication of use is present in children and adolescents and the medicine is not licenced in all paediatric age categories, the potential for off-label paediatric use in the non-authorised age categories should also be discussed.

The 2007 paediatric regulation aims to improve the health of children within Europe. The objectives include: increasing the development of medicines for use in children; ensuring that medicines used to treat children are subject to high quality research and appropriately authorised for use in children; improving the information available on the use of medicines in children; and achieving the above objectives without subjecting children to unnecessary clinical trials or delaying the authorisation of medicines in the adult population. The regulation requires that all applications for marketing authorisation for new medicines, must contain the results of all studies and information required in a previously agreed PIP The PIP will contain a full proposal of all studies (and their timings) necessary to support the paediatric use of an individual product and will cover all paediatric age categories and all necessary age-appropriate formulations. By 2012 1,000 applications were submitted for a PIP or waiver, of which 450 have received a positive opinion by the paediatric committee (PDCO) of the EMA.[1] A guideline for paediatric pharmacovigilance has also been issued in 2007.[350] The aim of the new pharmacovigilance legislation is *better protection of public health through strengthened EU system for medicines safety*. Although no paediatric-specific changes have been made, several changes have been made which have their effect on paediatric signal detection. Signal management and the requirement for continuously monitoring of all available data for the identification of potential safety issues are key features of this new legislation. And for the first time, consumer reporting of suspected adverse events is possible throughout whole Europe. Signals should follow a process of validation, prioritisation and assessment, and an audit trail of activities should be kept as part of the quality management system. In these steps, analyses of the possible impact and extent of utilisation of the medicine or vaccine in special populations, including children, is required. While in its guideline on paediatric pharmacovigilance the EMA states that signal detection can be stratified by age category,[350] unfortunately this is missing in the module on signal management of the guideline on good pharmacovigilance practices (GVP).[357]

The role of pharmacoepidemiology within pharmacovigilance is expanding since continuously monitoring of all available data for the identification of potential safety issues are key in new legislation.

Future perspectives

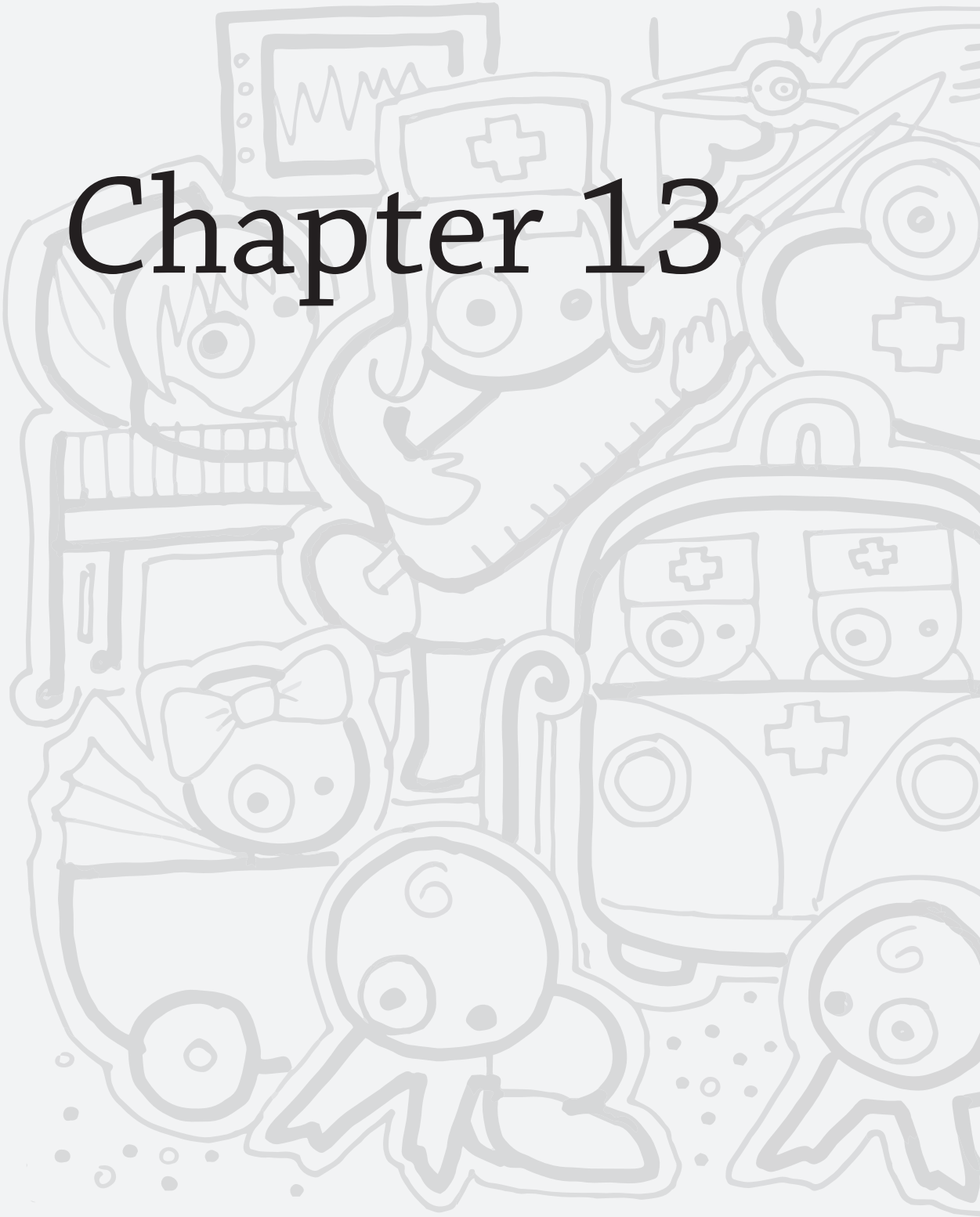
Although the paediatric regulation is a stimulance for studying paediatric drug safety prior to marketing authorisation, post marketing pharmacoepidemiological studies remain essential for studying the real-life use of medicines and for the detection of rare adverse events.

Pharmacovigilance regulation is more and more focussing on signal management and ongoing monitoring of all available data underline the importance of observational studies for studying pharmacovigilance. As pointed out in our studies, in paediatrics single-country studies are most of the time not sufficient to study risks of medicines in children and European-wide or even global collaboration is necessary to build systems capable of studying risks in children on a large scale.

With respect to signal detection within spontaneous reporting databases it is important to further develop methods to stratify the results for specific populations. This is not only of meaning for the identification for paediatric-specific ADRs, but is also of great importance for other special populations like pregnant women and the elderly population. The initiative of the WHO-UMC to further develop methods to routinely highlight signals in different paediatric age categories is of upmost value.

For pharmacoepidemiological studies, an important step in the right direction is the GRiP project. This FP7-funded consortium, aims to implement an infrastructure facilitating the development and safe use of medicines in children on a global level. Currently GRiP is mobilizing 21 partners from Europe, North America and Japan, as well as the WHO. By linking the existing paediatric research networks, GRIP will involve more than 1,000 institutions worldwide. With respect to developing paediatric specific safety signal detection methods GRiP is currently collaboration with the EMA, the FDA and the WHO. Initiatives like the GRiP network are essential to give insight in the use and risks of medicines in children and achieving this goal without subjecting children to unnecessary clinical trials.

Chapter 13



Summary

In recent years there has been increasing awareness on the gap in knowledge on the safety and efficacy of medicines used in children. The work as described in this thesis is based on large observational studies across Europe and aimed to study the use and risks of medicines in children and adolescents. First we studied prescriptions patterns of several classes of medicines in different European countries, second we assessed which adverse drug reactions are commonly reported, third we studied the methodological aspects of performing safety signal detection within paediatrics and last we studied the effect of several safety warning on the prescriptions of prokinetic drugs.

Chapter 1 gives a general introduction to the different topics that were studied in this thesis and provides an overview of the data sources used. The chapter concludes with the outline of the thesis.

Drug utilisation

Chapter 2 describes the extent of primary care antibiotic prescribing in the Netherlands, the United Kingdom (UK) and Italy during a ≥10 years study period. We included almost 3 million children aged 0-<18 years, contributing over 12 million person years (PY) of follow up over a period of 10 to 16 years. The antibiotic prevalence rates amongst the studied countries varied with the Netherlands having the lowest prevalence (18.0 users/100 PY) and a two to three-fold higher prevalence rate for the UK (36.2 users/100 PY) and Italy (52.0 users/100 PY). Amoxicillin with or without clavulanic acid was the most common prescribed antibiotic. Strikingly, in Italy, cephalosporins, especially third-generation cephalosporins were commonly used – a phenomenon which was not observed in the other countries. The high consumption of cephalosporins in primary care in Italy is worrying, since the use of these broad-spectrum antibiotics is associated with higher rates of antimicrobial resistance. The results of this study underline the need for development of internationally agreed paediatric specific quality indicators for primary care prescribing of antibiotics.

Chapter 3 describes the prescription pattern of oseltamivir, an antiviral drug, to children in primary care in the UK, Italy and the Netherlands during the influenza A(H1N1)pdm09 pandemic. Prescription patterns were compared with nationally reported rates for influenza like illness (ILI). The prevalence of oseltamivir prescriptions, stratified by calendar month, showed a biphasic pattern in all countries: A first peak was present in July 2009 and a second peak in October/November 2009. The ILI rates showed a similar pattern, with the highest rates in mid-July (155.3/100,000) in the UK, whereas the influenza A(H1N1) pdm09 epidemic reached its peak in both the Netherlands (189.4/100,000) and Italy (1,253.4/100,000) in the second week of November. Prevalence of oseltamivir prescriptions were highest for children aged 1 to 5 years (Netherlands: 2.6/1,000PM in November; UK: 10.7/1,000PM in July). The prevalence of use in

Italy was limited (max. 0.2 users/1,000PM) while the ILI rates in Italy were highest. The marked variation in prescribing seems to be driven by public health policy. A European or worldwide approach or policy on recommendations on the use of antiviral drugs in future pandemics is warranted.

In **Chapter 4** the extent of prescribing proton pump inhibitors (PPIs) and histamine-2-receptor antagonists (H_2RAs), two classes of gastric acid suppressant medicines, in children and adolescents in Spain, the Netherlands and Italy was studied. H_2RAs were mainly prescribed in children up to age of 1 year in the Netherlands and Italy. PPIs were mainly prescribed in children of 12 years and older in Spain and the Netherlands (no data available in Italy). Within these two classes of gastric acid suppressant medicines, the share of PPI prescriptions increased significantly between 2001 and 2008. There is increasing evidence that long term use of PPIs in adults is associated with adverse events like bone fractures, community-acquired pneumonia and clostridium infections. With the increasing use of PPIs in children and adolescent, studies to the safety of long term use are warranted.

Adverse drug reactions

The results of the study on adverse drug reaction-related hospital admissions in children in the Netherlands are presented in **Chapter 5**. Adverse drug reactions (ADRs) accounted for 0.75% of all paediatric hospital admissions in the Netherlands in the period 2000 to 2005, with an incidence of 24/100,000.children in the population. Risks for ADR-related hospital admission were highest in children under the age of 2 years (incidence 169/100,000 children). These young children were mainly admitted for ADRs due to maternal exposure through placenta or breast milk. This underlines that paediatric safety is also extended to use of medicines in pregnancy.

In **Chapter 6** the safety experience and adverse events from 25 clinical studies and numerous analyses of spontaneous ADR reports for several pandemic H1N1 vaccines in children and adolescents is reviewed. At time of the influenza A(H1N1)pdm09 pandemic, these vaccines were licenced using fast track procedures, with relatively limited data on the safety in children and adolescents. However, the diversity in methods and data presentation in clinical study publications and publications of spontaneous reports hampered the analysis of safety of the different vaccines. As a result, relatively little has been learned on the comparative safety of these pandemic H1N1 vaccines - particularly in children. It should be a collective effort to give added value to the enormous work going into the individual studies by adhering to available guidelines for the collection, analysis, and presentation of vaccine safety data in clinical studies and to guidance for the clinical investigation of medicinal products in the paediatric population. Importantly the pandemic has brought us the beginning of an infrastructure for

collaborative vaccine safety studies in the EU, US and globally.

Chapter 7 described the paediatric individual case safety reports (ICSRs) reported to the Adverse Event Reporting System (AERS), as maintained by the US Food and Drug Administration (FDA). A total of 106,122 paediatric ICSRs (55% boys) (58% US) with a median of 1 medicine [range 0-157] and 3 events [1-94] per ICSR were described. Most commonly reported classes of medicines by decreasing frequency were 'neurological' (58%), 'antineoplastic' (32%) and 'anti-infectives' (25%). Most commonly reported system organ classes were 'general' (13%), 'nervous system' (12%) and 'psychiatric' (11%). We explored of these spontaneous reports are also suitable for studying long term effect of medicines. Unfortunately, duration of use could only be calculated for 19.7% of the reported medicines. Of these 14.5% concerned medicines being used long-term (>6 months). Systemical hormonal preparations, alimentary medicines and antineoplastic/immunomodulating agents were prominently reported after long-term treatment, while anti-infective medicines, musculoskeletal system drugs and sensory organ drugs were reported mostly with short term use. This is in line with what is expected based on indications and from knowledge on use of medicines. Large compilations of paediatric ICSRs might be a suitable additional source to generate signals on delayed events and new onset chronic events. Knowledge on the distribution of the classes of medicines and events within AERS is a key first step in developing paediatric specific methods for drug safety surveillance.

Methods in paediatric safety signal detection

In **Chapter 8** we studied the effect of a large proportion of vaccine-related ICSRs in a spontaneous reporting database on the sensitivity of paediatric safety signal detection methods. We used VigiBase; vaccines made up 54% of all paediatric ICSRs reported in the period between 2000 and 2006. We compared the number of detected signals of disproportional reporting (SDRs) identified using either all paediatric reports available or using subgroups of vaccine-ADR pairs and non-vaccine-ADR. For ADRs reported less frequent for medicines (non-vaccines) than for vaccines, subgroup analysis using non-vaccines only led to an increase of the sensitivity of the signal detection process. If the ADR was reported more frequent for medicines than for vaccines, routine application of subgroup analysis can be harmful since then subgroup analysis led to a decreased sensitivity. Subgroup analysis can in this group be informative in specific subgroup analyses for studying the magnitude of class effects for the individual drugs in the class.

Chapter 9 explored the use of electronic healthcare record database for safety signal detection in paediatrics. To complement safety surveillance in spontaneous reporting systems and other traditional monitoring systems, initiatives in the United States (US) and in Europe have set up population-based surveillance systems that make use of longitudinal electronic healthcare data. Using a paedi-

atric population that comprised 4.8 million children and adolescents contributing 25.6 million PY of follow-up, we studied what the statistical power of the EU-ADR (Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge) network is for performing paediatric safety signal detection. The use of medicines in children was rare and was limited to only a few drugs; only 18 represented 50% and 158 drugs covered 90% of the total drug exposure time. The events that were considered to be most relevant for safety monitoring in adults had very low IRs in the paediatric population. The consequence of this combination of rare events and low use of medicines was that the number of medicines with enough exposure to monitor these events was low. For a rare but serious event like anaphylactic shock there were no drugs with enough exposure to study a weak association (RR≥2) and only 20 drugs to study a strong association (RR≥6). For a relatively frequent event such as upper gastrointestinal bleeding (UGIB) there were 5 medicines with enough exposure to study a weak association (RR≥2) and 79 drugs for which an association with a RR≥6, if present, can be investigated. The statistical power of a system like the EU-ADR network is much higher for events more frequently occurring in the paediatric population. In future initiatives to set up drug surveillance systems for the paediatric population using electronic healthcare records, it is very important to choose age-appropriate events and definitions. Inter-continental collaboration will be necessary to gain enough statistical power for paediatric safety surveillance.

Signal detection and safety warnings

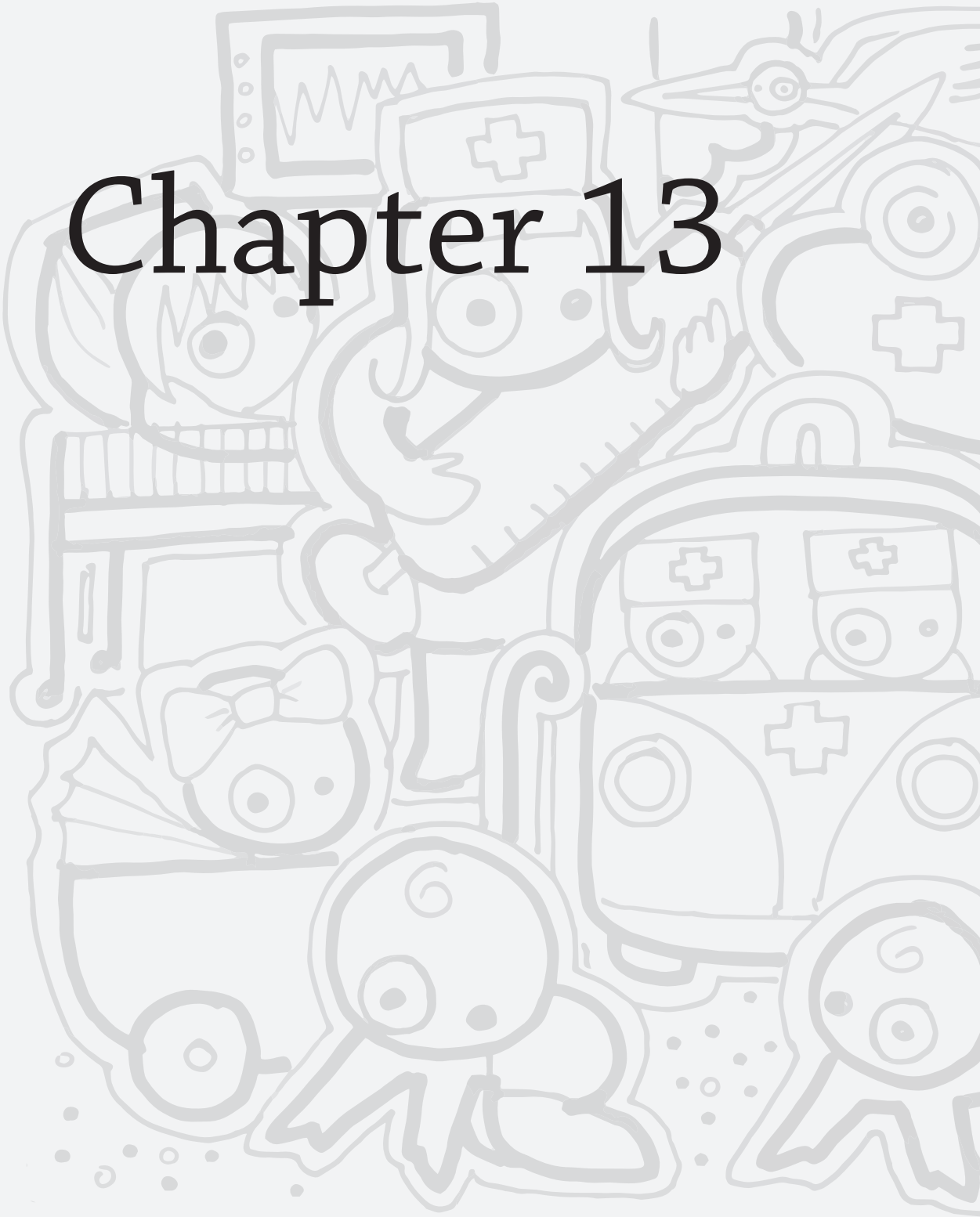
Chapter 10 describes a sequel to the study presented in chapter 9. We compared signal detection for UGIB within a cohort of children and adolescents (aged 0-20 years) from the EU-ADR network with spontaneous reports within VigiBase. Both the number of identified signals and the rate of detected known signals were compared. In total, 142 different signal were identified, of which 17 (12.0%; 41.2% known) in both data sources; 87 in VigiBase only (61.3%; 27.6% known), and 38 in EU-ADR only (26.8%; 13.2% known). VigiBase The signals that were identified only within VigiBase did not have exposure data within EU-ADR or lacked statistical power to detect the event in EU-ADR. Signal detection for children in electronic healthcare record (EHR) data is currently hampered by a lack of statistical power. Enlarging the study population and acquisition of data on in-hospital drug use are essential for improving signal detection within EHR databases.

In **Chapter 11** we studied the effect of safety warnings on the use of prokinetic (domperidone, metoclopramide and cisapride) medicines in Italy, Spain and the Netherlands. In the last decennium multiple warning have been issued for serious adverse events associated with the use of several prokinetic medicines. Overall a decrease in the utilisation of prokinetic drugs over time was seen in both Italy and the Netherlands while an increase was observed in Spain. Safety

warnings had a significant effect on the prescribing in both the Netherlands and Italy. In Spain, the safety warnings did not result in a decreasing prescription rate which shows that mere changes in the Summary of Product Characteristics are probably not enough and higher public notoriety through informative notes and/or the implementation of restrictive measures are needed.

Finally, in **Chapter 12** we discussed the main findings of the research presented in this thesis, made appraisals on the methodological considerations of these studies and made concluding remarks based on the work in this thesis.

Chapter 13



Samenvatting

In de afgelopen jaren is men zich toenemend bewust geworden van het hiaat in de kennis over de veiligheid en werkzaamheid van geneesmiddelen bij kinderen. Het werk beschreven in dit proefschrift was onderdeel van meerdere grote observationele studies in Europa en had als doel om het gebruik en de risico's van geneesmiddelen bij kinderen en adolescenten te bestuderen. Allereerst is het gebruik van verschillende groepen geneesmiddelen in meerdere Europese landen bestudeerd. Daarnaast is in kaart gebracht welke bijwerkingen er vaak worden gerapporteerd en zijn de methodologische aspecten van signaal detectie bij kinderen bestudeerd. Als laatste is het effect van veiligheidswaarschuwingen op de voorschriften van prokinetica bestudeerd.

Hoofdstuk 1 geeft een algemene introductie op de verschillende onderwerpen die in dit proefschrift zijn bestudeerd. Tevens wordt een overzicht van de gebruikte gegevensbronnen gepresenteerd. Het hoofdstuk wordt afgesloten met een overzicht van de hoofdstukken opgenomen in dit proefschrift.

Gebruik van geneesmiddelen

Hoofdstuk 2 beschrijft de omvang van het voorschrijven van antibiotica aan kinderen in Nederland, het Verenigd Koninkrijk (VK) en Italië in de eerste lijn gedurende een studie periode van ≥10 jaar. Bijna 3 miljoen kinderen in de leeftijd van 0-<18 jaar die samen meer dan 12 miljoen persoonsjaren (PJ) aan follow-up vertegenwoordigden werden geïncludeerd in de studie. Het aantal voorschriften voor antibiotica verschilde tussen de onderzochte landen. Antibiotica werden het minst voorgeschreven aan Nederlandse kinderen (18,0 gebruikers/100 PJ) terwijl het twee- tot drievoudige werd voorgeschreven in het VK (36,2 gebruikers/100 PJ) en Italië (52,0 gebruikers/100 PJ). Amoxicilline, met of zonder clavulaanzuur, was het meest voorgeschreven antibioticum. In Italië werden opvallend veel cefalosporines, en dan voornamelijk derde generatie cefalosporines voorgeschreven. Dit hoge voorschrijfgedrag van cefalosporines in de eerste lijn in Italië is zorgwekkend omdat het gebruik van breedspectrum antibiotica is geassocieerd het optreden van antibiotica resistentie. De resultaten van deze studie onderschrijven de noodzaak voor het ontwikkelen van internationale kwaliteitsindicatoren voor monitoring van het voorschrijven van antibiotica aan kinderen in de eerste lijn.

Hoofdstuk 3 beschrijft de voorschriften van oseltamivir, een antiviraal geneesmiddel, aan kinderen in Nederland, het VK en Italië tijdens de influenza A(H1N1) pdm09 pandemie in 2009. Het patroon in het aantal voorschriften per maand werd vergeleken met het landelijk aantal gemelde gevallen van griepverschijnselen. Het voorschrijfpatroon van oseltamivir liet een bifasisch patroon zien in alle landen, met een eerste piek in juli 2009 en een tweede piek in oktober/november 2009. Het aantal gevallen van griepverschijnselen liet een soortgelijk patroon zien. In het VK was de influenza A(H1N1)pdm09 epidemie op zijn hoog-

tepunt halverwege juli 2009 (155,3 gevallen/100.000 inwoners), terwijl zowel in Nederland als Italië het hoogtepunt werd bereikt in november 2009 met 189,4 gevallen/100.000 inwoners in Nederland en 1.253,5 gevallen/100.000 inwoners in Italië. Oseltamivir werd het meest voorgeschreven aan kinderen van 1 tot 5 jaar oud; 2,6 gebruikers/1.000 persoonsmaand (PM) in Nederland (november) en 10,7 gebruikers/1.000 PM in het VK (juli). Ondanks dat in Italië de meeste gevallen van griepverschijnselen werd gerapporteerd werd oseltamivir daar weinig voorgeschreven (max. 0,2 gebruikers/1.000 PM). Het opvallende verschil in gebruik van oseltamivir tussen de landen lijkt voornamelijk te worden veroorzaakt door verschillen in het volksgezondheidsbeleid. Een Europese of wereldwijde aanpak voor het opstellen van aanbevelingen ten aanzien van het voorschrijven van antivirale middelen in toekomstige pandemieën lijkt gerechtvaardigd.

In **Hoofdstuk 4** hebben is de mate van voorschrijven van twee groepen van maagzuurremmers, proton pomp remmers (PPIs) en H_2-receptorantagonisten (H_2RAs), bij kinderen en adolescenten in Spanje, Nederland en Italië bestudeerd. In Nederland en Italië werden H_2RAs voornamelijk voorgeschreven aan kinderen tot één jaar oud. PPIs werden voornamelijk voorgeschreven aan kinderen van 12 jaar en ouder in Nederland en Spanje (*geen gegevens beschikbaar in Italië*). Het aandeel van PPI voorschriften binnen de maagzuurremmers nam significant toe tussen 2001 en 2008. Er is toenemend bewijs dat langdurig gebruik van PPIs bij volwassenen gepaard gaat met een hoger risico op bijwerkingen als fracturen, een pneumonie opgelopen buiten het ziekenhuis en *clostridium difficile* infecties. Het toenemende gebruik van PPIs bij kinderen en adolescenten pleit voor studies naar de risico´s van langdurig PPI gebruik in deze groep.

Geneesmiddelenbijwerkingen

De resultaten van een studie naar Nederlandse ziekenhuisopnames door geneesmiddelenbijwerkingen bij kinderen werden gepresenteerd in **Hoofdstuk 5**. In de periode tussen 2000 en 2005 was 0.75% van alle ziekenhuisopnames bij kinderen gerelateerd aan bijwerkingen. De incidentie van opnames door bijwerkingen was 24 per 100.000 kinderen in algemene bevolking. Kinderen tot de leeftijd van twee jaar liepen het hoogste risico om opgenomen te worden door een geneesmiddelenbijwerking (incidentie 169/100.000). De bijwerkingen in deze jonge kinderen waren vooral gerelateerd aan blootstelling via de placenta of moedermelk aan geneesmiddelen die gebruikt werden door moeders. De resultaten van deze studie onderschrijven dat geneesmiddelenveiligheid bij kinderen, en voornamelijk jonge kinderen, al begint bij het geneesmiddelengebruik van de moeder tijdens de zwangerschap.

In **Hoofdstuk 6** is de veiligheid meerdere pandemische H1N1 vaccins bij kinderen en adolescenten besproken aan de hand van 25 klinische studies en verscheidende gepubliceerde rapportages van bijwerkingen. Ten tijde van de influenza

A(H1N1)pdm09 pandemie in 2009 werden deze vaccins versneld toegelaten op de markt terwijl er beperkte gegevens beschikbaar waren over de veiligheid van deze vaccins in kinderen en adolescenten. De wijze van presenteren van de resultaten en de methodes van de studies verschilden veel van elkaar, wat de analyse van de veiligheid van de verschillende vaccins bemoeilijkte. Hierdoor is er relatief weinig te leren over het verschil in veiligheidsprofiel van de verschillende vaccins voor kinderen. Het enorme werk verricht in de individuele studies zou van grotere waarde zijn als men zich beter houdt aan de beschikbare richtlijnen voor de verzameling, analyse en presentatie van veiligheidsgegevens van vaccins. De pandemie heeft ons wel een belangrijke start voor het opzetten van een infrastructuur voor gemeenschappelijke studies naar de veiligheid van vaccins binnen Europa, de Verenigde Staten en wereldwijd gebracht.

In **Hoofdstuk 7** zijn de bijwerkingsrapporten, zogenaamde 'individual case safety reports' (ICSRs), gemeld voor kinderen aan het *Adverse Event Reporting System* (AERS) van de Amerikaanse *Food and Drug Administration* (FDA) bestudeerd. In deze studie werden 106.122 ICSRs voor kinderen (55% jongens) beschreven. Per rapport werd mediaan één geneesmiddel (0-157) en drie bijwerkingen (1-94) gemeld. Geneesmiddelen uit de volgende groepen werden het meest gemeld: 'zenuwstelsel middelen' (58%), 'chemotherapie en immunotherapie' (32%) en 'anti-infectieuze middelen' (25%). De meest gemelde bijwerkingen waren onder te brengen onder 'algemene aandoeningen' (13%), 'zenuwstelsel aandoeningen' en 'psychische stoornissen' (11%). Ook onderzochten we of ICSRs kunnen worden gebruikt om effecten van geneesmiddelgebruik op de lange termijn te bestuderen. Helaas kon voor slechts 19,7% van de gemelde geneesmiddelen een gebruiksduur worden berekend. Van deze geneesmiddelen werd 14,5% meer dan 6 maanden gebruikt voordat de bijwerking optrad. Deze middelen waren vooral hormonen, gastro-intestinale geneesmiddelen, chemotherapie en immunotherapie. Geneesmiddelen waarbij bijwerkingen juist vaak op korte termijn worden gemeld waren anti-infectieuze geneesmiddelen, geneesmiddelen die de spieren en het skelet aangrijpen en middelen met een KNO of oogheelkundige indicatie. Met behulp van grote verzamelingen ICSRs van kinderen is het wellicht mogelijk om meer kennis over lange termijn effecten van geneesmiddelen te verkrijgen. De kennis uit deze studie over de gemelde bijwerkingen en geneesmiddelen bij kinderen in AERS is een eerste stap in het ontwikkelen van specifieke methodes voor het evalueren van geneesmiddelveiligheid bij kinderen.

Methodes voor signaal detectie bij kinderen

In **Hoofdstuk 8** beschrijft het effect van een groot aantal vaccin-gerelateerde bijwerkingen in een bijwerkingendatabase (VigiBase) op de sensitiviteit van signaal detectie bij kinderen. Van alle bijwerkingen gerapporteerd tussen 2000 en 2006 in VigiBase voor kinderen was 54% gerelateerd aan vaccins. Het aantal statistisch signficante signalen dat werd gedetecteerd indien alle meldingen werden

gebruikt voor de analyse werd vergeleken met het aantal gedetecteerde signalen wanneer óf alleen de meldingen over vaccins óf alleen de meldingen over geneesmiddelen werden gebruikt. Wanneer een bepaalde bijwerking minder vaak werd gemeld voor een geneesmiddel dan voor een vaccin nam de sensitiviteit van de signaal detectie toe als we de analyse alleen binnen de geneesmiddel-gerelateerde meldingen verrichtte. Wanneer alleen die geneesmiddel-gerelateerde meldingen werden gebruikt waarbij de bijwerking vaker werd gerapporteerd voor geneesmiddelen dan voor vaccins werden er signalen gemist. De laatste methode kan echter wel informatief zijn voor het bestuderen van klasse-effecten voor individuele middelen binnen een klasse zoals het bestuderen van koortsconvulsies binnen verschillende vaccins.

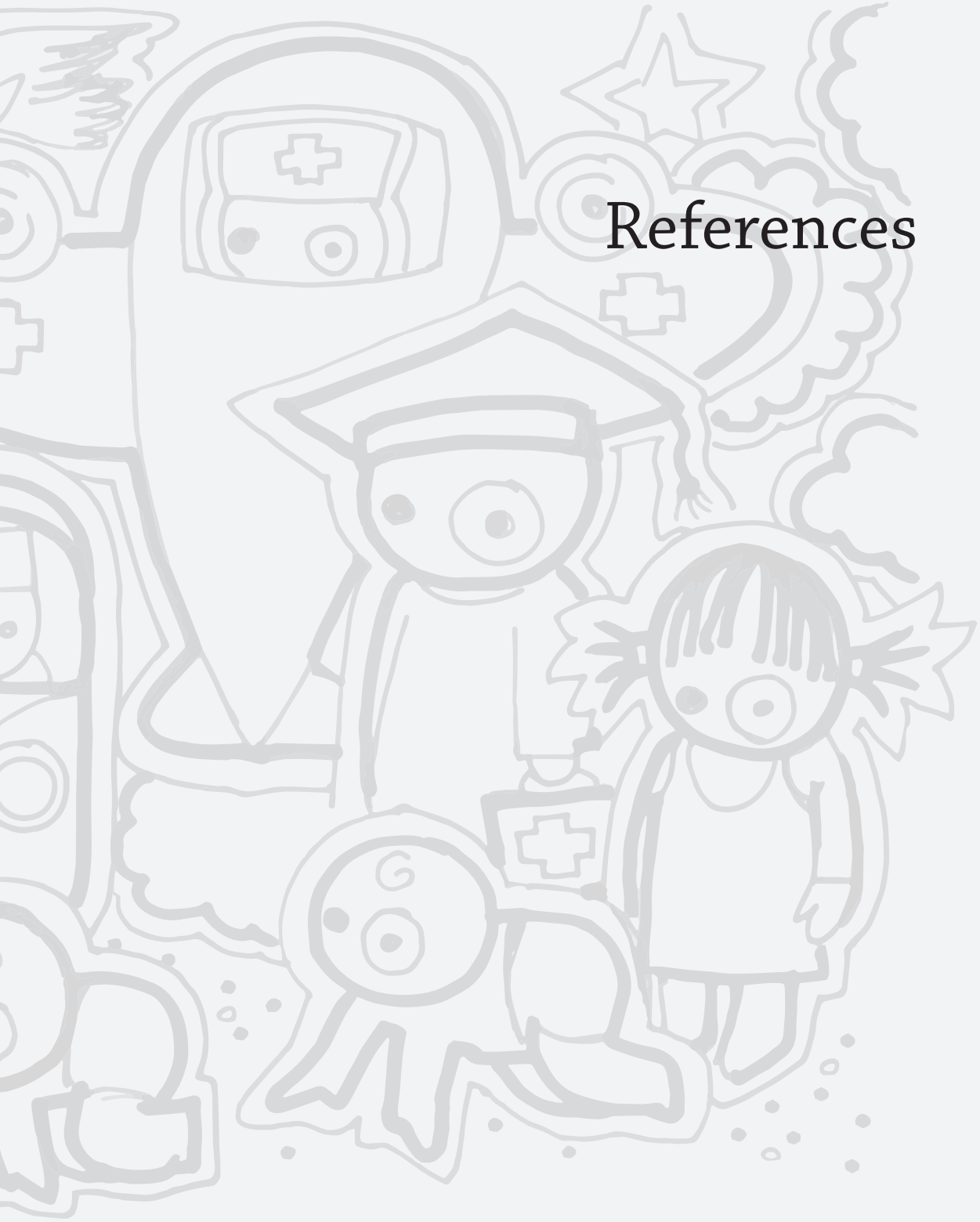
In **Hoofdstuk 9** bestudeerden we signaal detectie voor kinderen binnen elektronische patiëntendossiers. In zowel Europa als in de VS zijn er initiatieven opgezet om de huidige systemen voor geneesmiddelenbewaking voor de evaluatie van gemelde bijwerkingen te ondersteunen. Deze initiatieven maken gebruik van longitudinale elektronische patiëntendossiers om hiermee geneesmiddelbewakingssystemen te creëren. We bestudeerden de power van het EU-ADR netwerk voor het uitvoeren van signaal detectie bij kinderen met behulp van een cohort van 4,8 miljoen kinderen en adolescenten, die samen 25,6 miljoen persoonsjaar aan follow-up vertegenwoordigen. Geneesmiddelgebruik binnen deze populatie was zeldzaam en beperkt zich tot een klein aantal geneesmiddelen; slechts 18 geneesmiddelen vertegenwoordigen 50%, en 158 geneesmiddelen 90% van de totale blootstelling aan geneesmiddelen. Bijwerkingen die als meest relevant worden beschouwd voor monitoring bij volwassenen bleken een lage incidentie bij kinderen te hebben. De combinatie van zeldzame bijwerkingen en weinig voorgeschreven geneesmiddelen zorgden er voor dat het aantal geneesmiddelen met voldoende blootstelling om deze bijwerkingen te bestuderen laag was. Voor een zeldzame, maar ernstige bijwerking als anafylactische shock waren er geen geneesmiddelen die genoeg blootstelling hadden om een zwakke associatie (RR≥2) te bestuderen en slechts 20 geneesmiddelen met genoeg blootstelling om een sterkte associatie (RR≥6) te bestuderen. Voor een meer voorkomende bijwerking als bovenste tractus digestivus bloedingen (UGIB) waren er vijf geneesmiddelen met genoeg blootstelling om een zwakke associatie (RR≥2) en 79 om een sterke associatie (RR≥6) te bestuderen. De power van een systeem als EU-ADR is groter voor bijwerkingen die frequent voorkomen in de algemene populatie. In toekomstige initiatieven voor het opzetten van geneesmiddelbewakingssystemen met behulp van elektronische patiëntendossiers voor kinderen is het van groot belang om bijwerkingen te kiezen passend bij de leeftijd. Intercontinentale samenwerking is noodzakelijk om genoeg statische power te verkrijgen.

Signaal detectie en waarschuwingen voor risico's van geneesmiddelen

De studie beschreven in **Hoofdstuk 10** is een vervolg op de studie in hoofdstuk 9. In deze studie zijn de resultaten van signaal detectie binnen elektronische medische dossiers (EU-ADR) vergeleken met signaal detectie binnen spontane meldingen (VigiBase) voor het optreden van bovenste tractus digestivus bloedingen (UGIB) bij kinderen en adolescenten (0-20 jaar). Zowel het aantal gevonden signalen als het aandeel bekende signalen hierin werd vergeleken. Er werden in totaal 142 signalen gevonden, waarvan er 17 door beide systemen werden geïdentificeerd (12,0%, 41,2% bekend), 87 werden alleen in VigiBase gevonden (61,3%; 27,6% bekend), en 38 alleen in EU-ADR (26,8%; 13,2% bekend). Voor de signalen die alleen in VigiBase werden gevonden was er te weinig blootstelling of een gebrek aan power binnen EU-ADR. Signaal detectie voor kinderen en adolescenten binnen elektronische patiëntendossiers wordt momenteel vooral beperkt door een gebrek aan power. Het uitbreiden van de studie populatie en het toevoegen van gegevens over geneesmiddelgebruik in ziekenhuizen is essentieel om dit te verbeteren.

In **Hoofdstuk 11** hebben we het effect van veiligheidswaarschuwingen op het voorschrijven van prokinetica (domperidon, metoclopramide en cisapride) in Italië, Spanje en Nederland bestudeerd. In het laatste decennium zijn er meerdere waarschuwingen uitgegeven voor ernstige bijwerkingen bij het gebruik van deze groep medicijnen. We zagen een afname van het gebruik van prokinetica bij kinderen over de tijd in Nederland en Italië, terwijl het gebruik in Spanje toenam. De waarschuwingen hadden een significant effect op het voorschrijven in Italië en Nederland. In Spanje werd deze trend niet gezien, dit illustreert dat wijzingen in de SPC waarschijnlijk niet genoeg zijn en dat zwaardere maatregelen zoals beperkingen van gebruik noodzakelijk zijn.

Tot slot zijn in **Hoofdstuk 12** de belangrijkste bevindingen uit het proefschrift bediscussieerd en de methodologische aspecten besproken.



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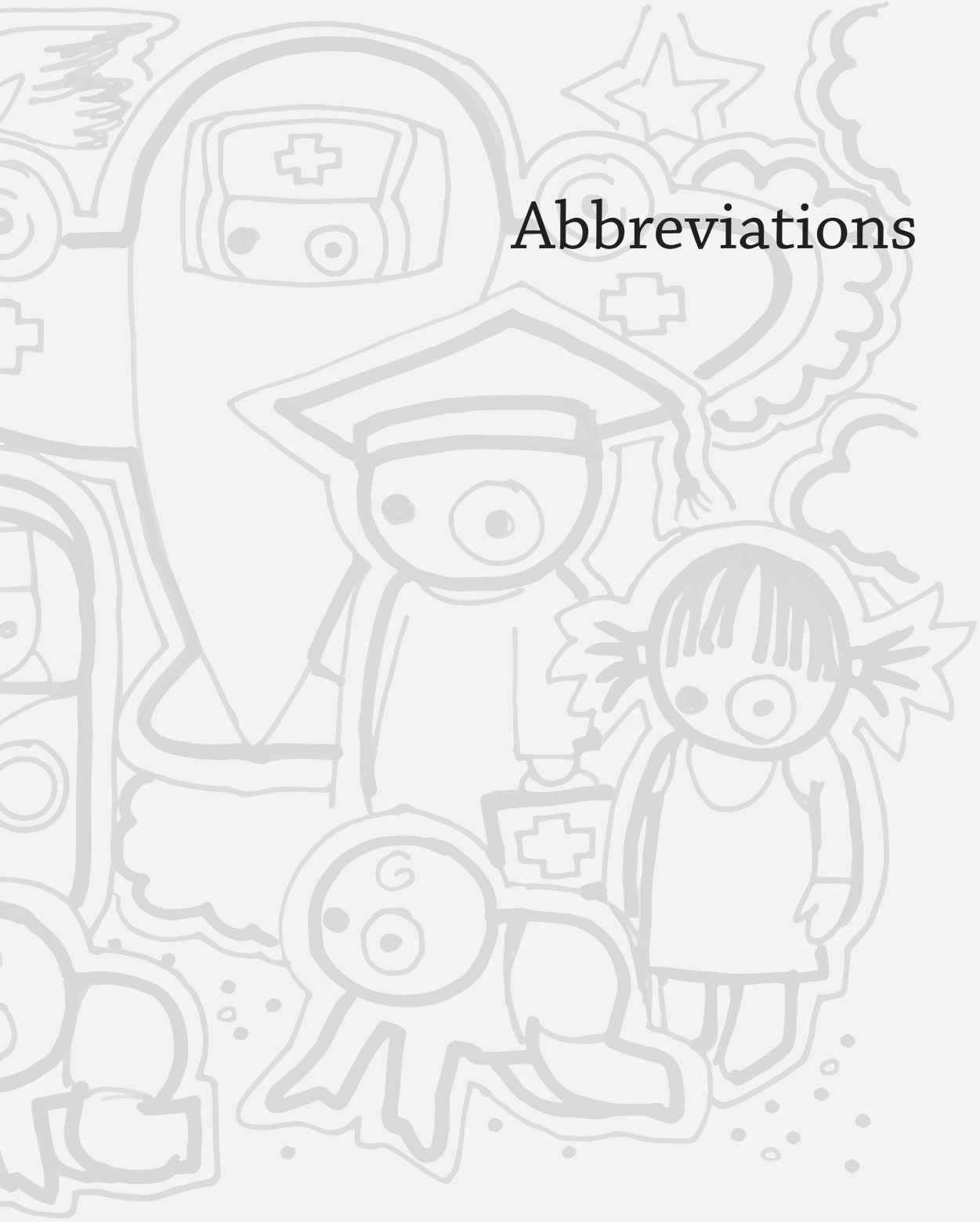

Abbreviations

95% CI	95% Confidence Interval
ADEM	Acute disseminated encephalomyelitis
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse drug reaction
ADRS	Australian Adverse Drug Reactions System
AEFI	Adverse event following immunisation
AERS	Adverse Event Reporting System
AESI	Adverse event of special interest
ARI	Acute respiratory infection
ARIMA model	Auto-regressive, integrated, moving average model
ARPEC	Antibiotic Resistance and Prescribing in European Children
ATC	Anatomical Therapeutic Chemical
BMJ	British Medical Journal
BNF	British National Formulary
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Human Medicinal Products
CIOMS	Council for International Organizations of Medical Sciences
CIRI	Inter-University Centre of Research on Influenza
DDD	Defined Daily Dose
DHPC	Direct Healthcare Professional Communication
DU90%	Drug Utilization 90%
EAHC	Executive Agency for Health and Consumers
EB05	5% of the EBGM quantile of the empirical Bayesian posterior distribution
EBGM	Empirical Bayes Geometric Mean
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EHR	Electronic Healthcare Records
EISN	European Influenza Surveillance Network
EMA	European Medicines Agency
ES	Spain
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESPID	European Society of Paediatric Infectious Diseases
EU / the EU	Europe / the European Union

EU-ADR	Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge
FDA	Food and Drug Administration
FP	Family Paediatrician
GBS	Guillain-Barré syndrome
GERD	Gastro-oesophageal reflux disease
GP	General practicioner
GRiP	Global Research in Paediatrics Network of Excellence
GVP	Good Pharmacovigilance Practices
H_2RA	Histamine-2-receptor antagonists
IC	Information Component
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
ICPC	International Classification of Primary Care
ICSR	Individual Case Safety Report
ILI	Influenza like illness
IMPACT	Immunization Monitoring Program ACTive
IPCI	Integrated Primary Care Information
IR	Incidence rate
ISS	Superior Institute of Health
IT	Italy
LEOPARD	Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs
LGPS	Longitudinal Gamma Poisson Shrinker
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NL	the Netherlands
OMOP	Observational Medical Outcomes Partnership
OR	Odd ratio
ORS	Oculo-respiratory syndrome
OTC	Over-the-counter
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PM	Person months
PPI	Proton pump inhibitors
PPP	Pregnancy prevention program
PRISM	Post-Licensure Rapid Immunization Safety Monitoring

PRR	Proportional reporting ratio
PT	Preferred term
PUMA	Paediatric Use Marketing Authorisation
PY	Person years
RMP	Risk management plan
ROC	Receiver operating characteristics
ROR	Reporting odds ratio
RR	Rate ratio / relative risk
SCCS	Self-controlled case series
SDR	Signal of disproportional reporting
SFK	Stichting Farmaceutische Kerngetallen
SOC	System Organ Class
SPC	Summary of product characteristics
SRS	Spontaneous reporting system
TAFTAR	Transatlantic Task Force on Antimicrobial Resistance
TEDDY	Task force in Europe for Drug Development for the Young
TESSy	The European Surveilance System
THIN	The Health Improvement Network
UGIB	Upper Gastro-intestinal bleeding
UK	United Kingdom
UMLS1	Unified Medical Language System1
US	United States
VAERS	Vaccine Adverse Events Reporting System
VAESCO	Vaccine Adverse Event Surveillance & Communication
VSD	Vaccine Safety Datalink
WHO	World Health Organisation
WHO-ART	WHO-Adverse Reaction Terminology
WHO-UMC	WHO-Uppsala Monitoring Center

PhD Portfolio Publications

PhD Portfolio

Name	Sandra de Bie
Erasmus MC Department	Medical Informatics
Research School	Netherlands Institute for Health Sciences
PhD period	May 2008 – September 2012
Promotores	Prof.dr. M.C.J.M. Sturkenboom; Prof.dr. B.H. Stricker
Co-promotores	Dr. S.M.J.M. Straus; Dr. K.M.C. Verhamme

PhD Training

Research Skills

2008-2010	Master of Science in Health Science, specialisation Clinical Epidemiology, Netherlands Institute for Health Sciences, Rotterdam, the Netherlands, 30 ECTS.

Presentations

Oral presentations

2009	Prokinetic drugs in children; drug utilisation and safety. 25th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Providence, United States.
2010	Paediatric Signal Detection within the WHO-UMC database. TEDDY Final Open Conference, Brussels, Belgium.
2010	Applying Data-Mining Techniques to Paediatric Data within the WHO-UMC Database; the Impact of Vaccines. 10th Annual Meeting of the International Society of Pharmacovigilance, Accra, Ghana.
2011	Signal Detection in Paediatrics and Use of Observational Data to Assess Safety. 23th Annual Euromeeting of the Drug Information Association, Genève, Switzerland.

2011 Paediatric Antibiotic Prescriptions in the Netherlands between 1996 and 2010: an ARPEC study.
29th Annual Meeting of the European Society for Pediatric Infectious Diseases, The Hague, The Netherlands.

2011 Effect of Vaccine-Related Reports on Paediatric Safety Signal Detection.
27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, United States.

2012 The Power of Electronic Healthcare Databases for Active Drug Safety Surveillance in Children and Adolescents: An EU–ADR Study.
28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spain.

2012 Multi-country electronic healthcare databases as a source to study drug safety in children and adolescents.
28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spain.

Poster presentations

2009 Utilisation of anti-infective drugs in Children: a Cohort Study in the Netherlands, Italy and United Kingdom.
Matchmaking event Priomedchild, ERA-Net Priority Medicines for Children, Talinn, Estland.

2010 Characteristics of Paediatric Individual Case Safety Reports within the WHO-UMC Database.
26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, United Kingdom.

2010 Detection of Late Effects of Paediatric Drugs Using Spontaneous Reporting.
26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, United Kingdom.

2010 Applying Data-Mining Techniques to Paediatric Data within the WHO-UMC Database; the Impact of Vaccines.
26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, United Kingdom.

2010	Spontaneous Reports as a Source for Risk Assessment of Long-Term Drug Use in Children. 26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, United Kingdom. 10th Annual Meeting of the International Society of Pharmacovigilance, Accra, Ghana.
2011	Effect of Vaccine-related Spontaneous Reports on Paediatric Safety Signal Detection. 23th Annual Euromeeting of the Drug Information Association, Genève, Switzerland.
2011	Time Series Analysis of the Effect of Safety Warnings on Prokinetic Drug Prescriptions in Children. 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, United States.
2011	Utilisation of Gastro-Intestinal Drugs in Children: Cohort Study in Three European Countries. 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, United States.
2012	Paediatric Antibiotic Prescriptions in three European countries between 1995 and 2010: an ARPEC study. 30th Annual Meeting of the European Society for Pediatric Infectious Diseases, Thessaloniki, Greece (*presented by M. Sturkenboom*).
2012	Paediatric Oseltamivir Prescriptions in Primary Care in the United Kingdom, Italy and the Netherlands during the 2009 Influenza A(H1N1)pdm09 Pandemic: an ARPEC study. 30th Annual Meeting of the European Society for Pediatric Infectious Diseases, Thessaloniki, Greece (*presented by M. Sturkenboom*). 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spain.

International Conferences

2008	11th Biannual Congress of the European Society for Developmental, Perinatal and Paediatric Pharmacology, Rotterdam, The Netherlands.
2009	25th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Providence, United States.

2010	26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, United Kingdom.
2010	10th Annual Meeting of the International Society of Pharmacovigilance, Accra, Ghana.
2011	23th Annual Euromeeting of the Drug Information Association, Genève, Switzerland.
2011	29th Annual Meeting of the European Society for Pediatric Infectious Diseases, The Hague, The Netherlands.
2011	27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, United States.
2012	28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spain.

Courses, Seminars and Workshops

2008-2012	Research Seminars, department of Medical Informatics, Erasmus University Medical Center, the Netherlands.
2008	Training 'EudraVigilance Support Programme' during Pharmacovigilance Working Party; European Medicines Agency, London.
2009-2012	Preconference courses on pharmacoepidemiology; Annual International Conferences on Pharmacoepidemiology & Therapeutic Risk Management.
2009	EudraVigilance Data WareHouse Course; European Medicines Agency, London.
2010	Biomedical English Writing and Communication, Erasmus University, Rotterdam, the Netherlands.
2010	Training on the European PSUR-Worksharing project, European Medicines Agency, London.

Other

Peer-reviewing of papers

2012	Drug Safety
2012	British Medical Journal
2012	Expert Review of Anti-Infective Therapy

Teaching Activities

2010	Supervising practicals Pharmacoepidemiology and Drug Safety, 4th year medical students, Erasmus University, Rotterdam, the Netherlands.
2011-2012	Lecturer 'Datamining in Spontaneous reporting databases', Module on 'Medicines risk identification and quantification - Principles of identifying and recognizing adverse events and safety signals' EU2P, European Programme in Pharmacovigilance and Pharmacoepidemiology.

List of publications

Manuscripts within this thesis

Chapter 2
Sandra de Bie, Katia MC Verhamme, Gino Picelli, Sabine MJM Straus, Giangiacomo Nicolini, Carlo Giaquinto, Bruno H Stricker, Mike Sharland, Miriam CJM Sturkenboom. Developing a Standard Method for Comparing Paediatric Antibiotic Prescribing in Primary Care from a Population-Based Cohort Study in the United Kingdom, Italy and the Netherlands: 1995-2010. *Submitted*.

Chapter 3
Sandra de Bie, Katia MC Verhamme, Gino Picelli, Sabine MJM Straus, Carlo Giaquinto, Bruno H Stricker, Mike Sharland, Miriam CJM Sturkenboom. Marked Variation in Paediatric Oseltamivir Prescriptions in Primary Care During The 2009 Influenza A(H1N1)pdm09 Pandemic: a Population-Based Cohort Study in the United Kingdom, Italy and the Netherlands. *Submitted*.

Chapter 4
Sandra de Bie, Katia MC Verhamme, Sabine MJM Straus, Miguel Gil García, Gino Picelli, Maria de Ridder, Belen Oliva, Mariagrazia Felisi, Bruno H Stricker, Francisco J de Abajo, Miriam CJM Sturkenboom. Increasing Use of Proton Pump Inhibitors in Children: a Cohort Study in 3 European Countries. *Submitted*.

Chapter 5
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Chapter 6
Leonoor Wijnans, **Sandra de Bie**, Jeanne Dieleman, Jan Bonhoeffer, Miriam Sturkenboom. Safety of Pandemic H1N1 Vaccines in Children and Adolescents. *Vaccine. 2011 Oct 6;29(43):7559-71*

Chapter 7
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Chapter 8
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Chapter 9
Sandra de Bie, Preciosa M Coloma, Carmen Ferrajolo, Katia MC Verhamme, Gianluca Trifirò, Martijn J Schuemie, Sabine MJM Straus, Rosa Gini, Ron Herings, Giampiero Mazzaglia, Gino Picelli, Arianna Ghirardi, Lars Pedersen, Bruno H Stricker, Johan van der Lei, Miriam CJM Sturkenboom. The Role of Electronic Healthcare Record Databases in Paediatric Drug Safety Surveillance: a Retrospective Cohort Study. *Submitted*.

Chapter 10
Sandra de Bie, Preciosa M Coloma, Vaishali K Patadia, Katia MC Verhamme, Martijn J Schuemie, Gianluca Trifirò, Sabine MJM Straus, Rosa Gini, Ron Herings, Giampiero Mazzaglia, Gino Picelli, Arianna Ghirardi, Lars Pedersen, Bruno H Stricker,, Johan van der Lei, Miriam CJM Sturkenboom. Signal Detection for Upper Gastro-Intestinal Bleeding in Children: a Comparison Between a Spontaneous Reporting System and Electronic Healthcare Records. *Submitted*.

Chapter 11
Sandra de Bie, Katia MC Verhamme, Miguel Gil García, Gino Picelli, Sabine MJM Straus, Belen Oliva, Bruno H Stricker, Adriana Ceci, Francisco J de Abajo, Miriam CJM Sturkenboom. The Effect of Safety Warnings on the Utilisation of Prokinetic Drugs in Children in Europe: a population-based cohort study. *Submitted*.

Other publications

Carmen Ferrajolo, Katia M.C. Verhamme, Gianluca Trifiró, Geert W. 't Jong, Carlo Giaquinto, Gino Picelli, Emine Sen, Alessandro Oteri, **Sandra de Bie**, Vera E. Valkhoff, Giampiero Mazzaglia, Francesco Rossi, Annalisa Capuano, and Miriam CJM Sturkenboom. Incidence of potential drug-induced liver injury in children: a retrospective cohort study in two European countries. *Accepted for publication in Drug Safety*.

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About the Author

Sandra de Bie was born on 16 December 1980 in the Navy Hospital in Hellevoetsluis, the Netherlands. In 1999, she finished the "VWO" at the "Jacob van Liesveldt College" and started to study Medicine in Rotterdam.

In 2004 she first got acquinted with medical research as she participated in a research project on exercise-associated ECG changes in children operated on tetralogy of Fallot at the department of paediatric cardiology of the Erasmus University Medical Center under supervision of Dr. Jochem van den Berg and Prof.dr. Wim Helbing.

After obtaining her Medical Degree in 2005, she started working as a resident in Paediatrics at the Erasmus MC - Sophia's Childrens Hospital. From 2007, on she worked as a researcher in vaccine trials in both children and adults at Vaxinostics, Rotterdam together with dr. Hans Rümke.

In May 2008, she started the work as described in this thesis. The studies on the use and risks of medicines in children were conducted at the Interdisciplinary Processing of Clinical Information (IPCI) group of the department of Medical Informatics of the Erasmus University Medical Center, Rotterdam, the Netherlands. She was supervised by dr. Katia Verhamme, dr. Sabine Straus, prof.dr. Bruno Stricker and prof.dr. Miriam Sturkenboom. She combined her work as PhD-student with working as an assessor of pharmacovigilance at the Dutch Medicines Evalution Board in the Hague and later in Utrecht.

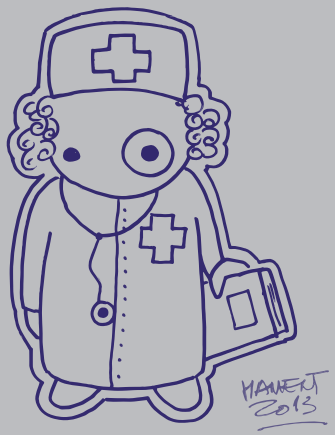
In August 2010, she obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES). From August 2011 on she was a member of the Paediatric Special Interest Group (Paediatric SIG) of the International Society of Pharmacoepidemiolgy (ISPE).

In October 2012 she started working as a resident in Internal Medicine at the Havenziekenhuis in Rotterdam and in January 2013 she started her specialist training in Internal Medicine under supervision of dr. Pieter Wismans and prof.dr. Jan van Saase.

She lives together with Jelmer Alsma in Rotterdam and together they love travelling around the world and discovering new cuisines.

...het is zoals het is en het wordt zoals het wordt...

De 100-jarige man die uit het raam klom en verdween
Jonas Jonasson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