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ORIGINAL REPORT

# Databases for pediatric medicine research in Europe—assessment and critical appraisal†

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## SUMMARY

**Purpose** To identify and describe European health care databases that can be used for pediatric pharmacoepidemiological research.

**Methods** A web-based survey was conducted among all European databases that were listed on the website of the International Society of Pharmacoepidemiology (ISPE) and/or known by an expert group. The survey comprised of questions regarding (a) the nature of the database, (b) database size, (c) demographic, clinical and drug related data provided, (d) cost, and (e) accessibility of the database.

**Results** A total of 25 data sources from 12 European countries were identified and invited to participate in the survey. Responses were obtained from 21 (84%) databases located in 10 different European countries. Seventeen databases were included in the assessment comprising a total of at least 9 million children aged 0–18 years. The majority of databases are based on outpatient data and all keep either prescription or drug dispensing data. Ten databases are based on electronic patient records from primary care physicians and five databases are predominantly claims oriented. Three databases do not belong to either of the above mentioned categories. Almost all of the databases can be used for pediatric drug utilization studies. For drug safety studies it is more appropriate to use electronic patient record databases because of the available clinical information and the potential to obtain additional information.

**Conclusions** There are many European healthcare databases providing an enormous potential for pediatric pharmacoepidemiological research. Future research should focus on methods to bring data from different databases together to use the full capacity effectively. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — pediatric; databases; drug utilization; drug safety

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## INTRODUCTION

Computerized health care data has proven to be a valuable resource for pharmacoepidemiological and health services research and the European Medicines

Evaluation Agency (EMEA) now recommends the use of electronic health records when conducting post-authorization drug utilization and safety studies.[1]

Health care databases comprising patient data, drug exposure, outcomes, and confounders are now available in many European countries. A systematic review of abstracts presented at the 16th International Conference on Pharmacoepidemiology in 2005 showed that the majority of European pharmacoepidemiological studies are conducted using automated general practice, pharmacy, or insurance data.[2] However, all studies used only a single datasource.

The International Society of Pharmacoepidemiology (ISPE) has set up a list of existing database resources for pharmacoepidemiological research. As of January 2006 this list contained about 61 databases of which 16 belong to European countries.[3]

Especially in the pediatric population, for which experimental data are scarce, there is a need to build pharmacoepidemiological research capacity and support in the area of drug utilization, safety, and effectiveness.[4,5]

Drug utilization studies aim to describe how drugs are being used in real practice. Simple descriptions of drug use by age, gender, and time require information on the source population and drug prescription or dispensing data. More detailed information is necessary to perform qualitative drug utilization studies which include the concept of appropriateness and are based upon parameters such as indications, daily dose and duration of therapy.

To assess the association between drug use and outcomes (beneficial or adverse effects) analytical pharmacoepidemiological studies need to be conducted. These studies require valid and complete longitudinal assessment of the population under observation, plus information on drug exposure, outcomes and confounders over time. It is important to have the opportunity to check diagnoses against original records or to go back to the medical doctor if necessary.

In order to support the rapidly expanding agenda of pediatric research, research networks will have to be further developed. Rather than conducting many small studies with little power, efforts should be made to organize multi-national or multisource database studies that will have the advantage of size and allow for the full evaluation of drug- and dose-specific risks, and comparisons between countries.[2]

The aim of this survey was to identify and characterize single existing population-based European healthcare databases which could be used for pediatric medicines research and to classify whether they can and have been used for drug utilization and drug safety research in children.

## METHODS

This is a survey study using a web-based data collection application which was developed by I.Ri.D.I.A.-S.r.l. within the Task Force in Europe for Drug Development for the Young (TEDDY) Network of Excellence (NoE). To appraise the different databases, we evaluated both the survey results and published studies that have used the various databases in the area of pediatric pharmacoepidemiology.

### *Targeted databases*

The providers of all population-based European healthcare databases listed on the website of ISPE ($n = 16$)[3] and others known by the members of the TEDDY pharmacoepidemiology expert group ($n = 9$) were invited to participate in the on-line survey. A reminder letter was sent to non-responders. A follow-up letter was sent to all participating databases to confirm whether the information provided in the on-line questionnaire was correct and to obtain information on publications from the database in general and on pediatric studies in particular.

### *Content of the survey*

The content of the survey was defined by the authors and covered the following issues: general information; the nature of the database, general characteristics and size; the availability of drug exposure and clinical data; accessibility; and cost.

Furthermore all databases included in the survey were asked for a list of the most relevant publications in terms of (a) the database itself; (b) pediatric studies; (c) examples for recent drug utilization and/or safety studies in general.

### *Analysis*

Based on the survey information and the literature, databases were categorized with respect to their potential suitability for use in pediatric drug utilization and drug safety studies. Information collected has been categorized as *demographics, drug exposure, outcomes, confounders, and data access*. Details of the framework that has been used are shown in Table 1.



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Table 1. Detailed information of the participating databases

| | IMS DA UK | Pedianet | IPCI | GPRD | THIN Data | QRESEARCH | SPICE | IMS DA AUSTRIA | IMS DA GERMANY | IMS DA FRANCE | PHARMO | ARNO | IADB | The Danish Prescription Database (NPD) | Finland prescription register | PEM | Swedish Medical Birth Register |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | | | | | | | | | | |
| Unique identifier | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Age | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Gender | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Death | yes | yes | yes | yes | yes | yes | yes | no | no | no | yes | no | limited | no | no | yes | limited |
| Prescriptions (drug exposure) | | | | | | | | | | | | | | | | | |
| Prescriptions | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Unique product code | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| ATC code | yes | yes | yes | no* | no* | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | no* | yes |
| Date of prescription | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | no | yes | yes | no |
| Dosage of prescription | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | no | limited | yes | yes |
| Duration of prescription | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | no | yes | no | no | yes | yes |
| Outcomes | | | | | | | | | | | | | | | | | |
| Laboratory values | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | no | no | no | no | yes | no |
| Diagnostic data (e.g., X-ray, MRT, etc.) | yes | yes | yes | yes | yes | limited | no | yes | yes | no | limited | yes | no | no | no | yes | no |
| Treatment outcome | yes | yes | yes | yes | yes | yes | no | no | no | no | limited | no | no | no | no | yes | no |
| Hospital admission | yes | yes | yes | yes | yes | limited | no | yes | yes | no | yes | no | yes | no | no | yes | no |
| Hospital discharge diagnosis | no | yes | yes | yes | yes | limited | no | no | no | no | yes | yes | yes | no | no | yes | no |
| Referral to specialist | yes | yes | yes | yes | yes | limited | no | yes | yes | no | yes | no | no | no | no | yes | no |
| Results of referral visits | yes | yes | yes | yes | no | limited | no | no | no | no | limited | no | no | no | no | yes | no |
| Confounders | | | | | | | | | | | | | | | | | |
| Diagnosis | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | limited | no | no | no | no | yes | yes |
| Medical history (anamnesis) | yes | yes | yes | yes | yes | yes | yes | no | no | no | yes | no | no | no | no | limited | limited |
| Vaccination | yes | yes | yes | yes | yes | yes | yes | no | no | no | yes | no | no | yes | no | limited | no |
| Allergies | yes | yes | yes | yes | yes | yes | yes | no | no | no | yes | no | limited | no | no | limited | no |
| Indication for prescription | yes | no | yes | limited | limited | limited | no | yes | yes | yes | no | no | no | no | limited | yes | no |
| Height | yes | yes | yes | yes | yes | yes | no | no | no | no | limited | no | no | no | no | no | yes |
| Weight | yes | yes | yes | yes | yes | yes | no | no | no | no | limited | no | no | no | no | no | yes |
| Environmental and life-style characteristics | yes | yes | yes | yes | limited | limited | no | yes | yes | no | limited | no | no | no | no | limited | limited |
| Data access | | | | | | | | | | | | | | | | | |
| Access to raw data | yes | no | yes | yes | yes | yes | no | yes | yes | yes | yes | no | no | no | yes | yes | yes |
| Access to original medical charts | no | yes | yes | yes | no | no | no | no | no | no | yes | no | no | yes | no | limited | no |

*British National Formulary (BNF) Code.



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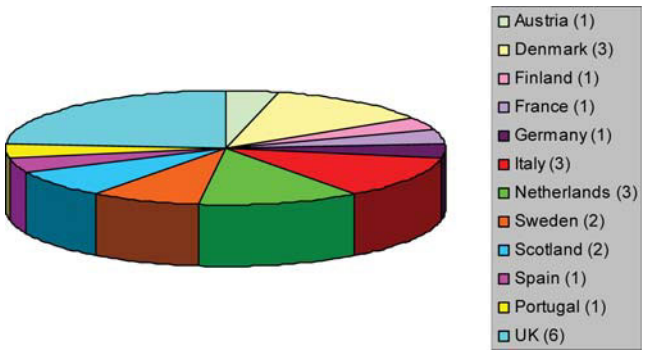


Figure 1. European countries in which databases were identified and included in survey

Databases were classified according to the primary source of data: (a) electronic medical records, (b) prescription claims, or (c) other.

Electronic medical record databases are comprised of electronic patient records from primary care physicians whereas claims databases generally use pharmacy dispensing data or data from reimbursement agencies.

## RESULTS

In total 25 datasources from 12 European countries were identified and invited to participate in the survey (Figure 1). Replies were received from 21 (84%) databases located in 10 different European countries. The Odense Pharmacoepidemiological database and the Pharmacoepidemiological database of North Jutland in Denmark were excluded from further analysis as the Danish prescription database provides comparable data but for 100% of the Danish population. (Table 2)

## NATURE OF THE DATABASES AND GENERAL CHARACTERISTICS

Most of the databases included in this survey were set up between 1991 and 1997 ($n = 7$). Five databases were developed in the 1980s and two within the last 6 years (Table 3). The Swedish Medical Birth Register was established in the 1970s.

The majority of databases included in the survey ($n = 15$) were longitudinal, population-based databases. Ten databases (GPRD, IMS-DA (4 countries), IPCI, Pedianet, QRESEARCH, THIN) use electronic medical record data from GPs and primary care pediatricians and are, therefore categorized as Electronic Medical Record Databases. The GPRD, THIN, QRESEARCH, IMS-DA UK, IPCI, Pedianet are used in countries where primary care physicians are gatekeepers. IMS Germany and France contain electronic medical records but the GP is not a gatekeeper in these countries; patients may see specialists or other doctors without notifying the GP. Therefore, these databases do not necessarily provide a full picture of the longitudinal medical history of a patient.

The Scandinavian databases, the InterAction database, and PHARMO started out as drug dispensing claims databases processing all prescriptions that need to be reimbursed or are prescribed by physicians independently regardless of whether they are reimbursed or not. However, most of these databases are or can be linked with clinical registries related to hospitalizations, laboratories, cancer (e.g., Danish prescription database, PHARMO), death (e.g., Danish prescription database) and sometimes GPs (PHARMO) and have a well defined underlying patient population. The Finnish Prescription Register and the InterAction database are dispensing databases only.

The ARNO observatory is a clinical data warehouse combining data for a single patient collected for administrative use from local and regional programs dedicated to the monitoring of medical prescriptions. As it is a combination of various different databases and registries it has not been allocated to one of the above groups.

The PEM is different from the others as it is an *ad hoc* collection and, therefore does not qualify as an observational health care database. The Swedish Medical Birth register cannot be allocated into one of the above categories as it compiles information on ante- and perinatal factors from different sources.

For the longitudinal medical record databases, the number of registered children aged between 0 and 18 years varied between 30 000 (IMS Disease



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Table 2. List of databases identified and invited to the survey

| Country | Database name | | Included in analysis |
|---|---|---|---|
| UK | General Practice Research Database (GPRD) | www.gprd.com | yes |
| | IMS Disease Analyzer (IMS-DA) | www.imshealth.com | yes |
| | The Health Improvement Network Data (THIN) | www.epic-uk.org | yes |
| | Prescription Event Monitoring (PEM) | www.dsru.org | yes |
| | Prescription Pricing Authority (PPA) | www.dmd.nhs.uk | no† |
| | QRESEARCH | www.qresearch.org | yes |
| Scotland | Scottish Programme for Improving Clinical Effectiveness in Primary Care (SPICE) | http://www.abdn.ac.uk/general_practice/research/special/pcciu-r/index.shtml | yes |
| | Medicines Monitoring Unit (MEMO) | | no† |
| Italy | Pedianet | www.pedianet.it | yes |
| | Sistema Informativo Sanitario Regionale Database-FVG region (FVG) | | no |
| | ARNO Observatory | http://osservatorioarno.cineca.org | yes |
| Denmark | The Danish Prescription Database (NPD) | http://www.dst.dk/TilSalg/Forskningsservice/Fsedatabaser/LMDB.aspx | yes |
| | Odense Pharmacoepidemiological Database (OPED) | | no* |
| | Pharmacoepidemiological Database North Jutland (PDNJ) | | no* |
| Sweden | Swedish Medical Birth Register | www.socialstyrelsen.se | yes |
| | Prescribed Drug Register | | no |
| Netherlands | Integrated Primary Care Information Database (IPCI) | www.ipci.nl | yes |
| | PHARMO-Record-Linkage-System (PHARMO) | www.pharmo.nl | yes |
| | InterAction Database (IADB) | www.iadb.nl | yes |
| Finland | Finland Prescription Register | www.kela.fi | yes |
| Portugal | CEFAR | | no |
| Spain | Base de datos para la Investigacion Farmacoepidemiologica en Atencion Primaria (BIFAP) | | no |
| Germany | IMS Disease Analyzer (IMS DA) | www.imshealth.de | yes |
| Austria | IMS Disease Analyzer (IMS DA) | www.imshealth.at | yes |
| France | IMS Disease Analyzer (IMS DA) | | yes |

*reply received but not included because population already covered by Danish Prescription Database.
†reply received but no information provided.

Analyzer Austria) and 1.15 million (the General Practice Research Database (GPRD). In total, information is available for 4 million children in the medical records databases and at least 1 million children in the three population-based claims databases. (Table 3)

All databases record the age and gender of patients. Death related information is available in 53% ($n = 9$) of the databases. In the Danish prescription database, death related information may be obtained by data linkage. (Table 1)

## CLINICAL AND TREATMENT DATA

Table 1 provides an overview of the information available in each database as they have been provided by the survey.

### *Drug exposure*

All databases that participated in the survey collect information about prescription drugs and the units dispensed or prescribed, most of them also record the dosage regimen which is particularly important for the pediatric population. In the Danish prescription database the dosage regimen is not known, and in the Finland prescription register this information is stored as a text file for 1.5 years only. The prescribed duration of drug use can be obtained in 14 databases but is not known for the Danish and Finish prescription registers.

Information on drugs that need a prescription but are not reimbursed is usually available in electronic patient record databases and in some pharmacy-based dispensing databases (e.g., InterAction, PHARMO) but not in the claims oriented dispensing databases.



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Table 3. Characteristics of participating databases

| Database name | General description of the database | Starting year | Number of children* | % coverage of pediatric population | Children's person years since the beginning | Pediatric drug utilization studies | Pediatric safety studies |
|---|---|---|---|---|---|---|---|
| | Electronic medical record databases | | | | | | |
| The Health Improvement Network (THIN) Data | THIN is a collection of general practice data from GPs' electronic records of their consultations with patients in UK practices[20] | 1985 | 501 936 | Approx. 4 | 5.5 million | — | — |
| General Practice Research Database (GPRD) | The GPRD is a computerized database of anonymized longitudinal medical records from primary care. Currently data are being collected on over 3 million active patients (approx. 9 million in total) from almost 400 primary care practices throughout the UK[6,21,22] | 1987 | 1 146 578 | 6 | 5.1 million | 23–25 | 26–29 |
| IMS Disease Analyzer UK (IMS-DA UK) | IMS DA comprises longitudinal patient data which captures primary care interventions made by the corresponding healthcare professional in the doctor's office. In the UK it comprises information for 3 million patients provided by 570 doctors | 1991 | 460 000 | 5.8 | 2.3 million | 30 | — |
| QRESEARCH | QResearch is a high quality non-profit making general practice derived database for research. It is a large patient level aggregated database of anonymized health records from 520 general practices in the UK over the last 10–15 years[31] | 1988 | 739 977† | 8 | 8.8 million | — | — |
| Scottish Programme for Improving Clinical Effectiveness in Primary Care (SPICE) | The SPICE database consists of electronic patient records collected from over 300 general practices based in Scotland covering approximately 2/5ths of the Scottish population | 2000 | 387 356 | 40 | n.n | — | — |
| Pedianet | The PEDIANET database in Italy is a longitudinal pediatricians general practice database comprising data of children (0–14 years) who are under the care of any of the 105 primary pediatricians that currently provide data to the database | 2000 | 106 554 | n.n. | 315 065 | 32,33 | 32 |
| Integrated Primary Care Information (IPCI) | The IPCI database is a general practice research database, containing information from electronic patient records of 150 GPs covering more than 1 000 000 patients[34] | 1992 | 161 108 | 4 | 550 540 | 35,36 | 37 |

(*Continues*)



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Table 3. (Continued)

| Database name | General description of the database | Starting year | Number of children* | % coverage of pediatric population | Children's person years since the beginning | Pediatric drug utilization studies | Pediatric safety studies |
|---|---|---|---|---|---|---|---|
| | Electronic medical record databases | | | | | | |
| IMS Disease Analyzer France (IMS-DA France) | IMS DA France comprises longitudinal patient data which capture primary care interventions made by the corresponding healthcare professional in the doctor's office. In France it comprises of information for 1.1 million patients provided by 540 doctors. The data are not necessarily complete since other physicians may be consulted without the GP knowing this | 1997 | 190 000 | 2.90 | 1.7 million | — | — |
| IMS Disease Analyzer Austria (IMS-DA Austria) | IMS DA Austria comprises longitudinal patient data which capture primary care interventions made by the corresponding healthcare professional in the doctor's office. In Austria it comprises of information for 0.5 million patients provided by 120 doctors. The data are not necessarily complete since other physicians may be consulted without the GP knowing this | 1995 | 30 000 | 8 | 270 000 | — | — |
| IMS Disease Analyzer Germany (IMS-DA Germany) | IMS DA Germany comprises longitudinal patient data which capture primary care interventions made by the corresponding healthcare professional in the doctor's office[38] The data are not necessarily complete since other physicians may be consulted without the GP knowing this | 1992 | 250 000 | 6 | 2.2 million | — | — |
| | Prescription claims databases | | | | | | |
| PHARMO | The PHARMO database constitutes a well-defined population including 2 million residents in the Netherlands and enables to follow-up drug use and hospitalizations in patients for an average of 10 years.[39] Part of the database (around 200 000 patients) are linked to GP patient records | 1985 | >360 000 | 14 | 2.2 million | 40,41 | — |
| InterAction Database (IADB.nl) | IADB.nl collects drug prescription data from public pharmacies in the Netherlands. IADB.nl is a project of the Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapeutics (SFF), Groningen University Institute for Drug Exploration (GUIDE). The drug prescription database provides longitudinal drug prescription records from more than 50 public pharmacies in Northern and Eastern parts of the Netherlands, covering a population of 500 000 people.[42,43] | 1994 | 111 960 | 3 | 615330 | 44–47 | — |

(*Continues*)


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Table 3. (Continued)

| Database name | General description of the database | Starting year | Number of children* | % coverage of pediatric population | Children's person years since the beginning | Pediatric drug utilization studies | Pediatric safety studies |
|---|---|---|---|---|---|---|---|
| | **Prescription claims databases** | | | | | | |
| The Danish Prescription Database | The Danish Prescription Database aims to provide complete statistics on the use and cost of drugs in the primary health care and the hospital sector in Denmark. It was initiated in January 1994 and covers the entire population of Denmark. Drug prescription and sales data is retrieved from reports submitted by pharmacies, hospital pharmacies, and the Danish Serum Institute to the Register of Medical Product Statistics.[48] | 1995 | n.n | 100 | n.n. | 49 | — |
| Finland Prescription Register | The Finland Prescription Register is maintained by the Social Insurance Institution of Finland (Kela). This register comprises all purchases of medicines which have been reimbursed immediately upon purchase at a pharmacy. In 2004 the register comprised about 97% of all reimbursed prescriptions. The register includes information derived from the prescription, relating to the patient, the medicine, the prescribing doctor, as well as the cost and reimbursement paid for the medicine.[50] | 1994 | 480 000 | 100 | N/A | 51,52 | 53,54 |
| | **Others** | | | | | | |
| ARNO Observatory | ARNO observatory is an on-line multicentric observatory, with an epidemiological approach to a population of almost 10 million people. The distinctive feature of this system is to offer to the Italian Local Health Units (LHU) a Clinical Data Warehouse with homogeneous data deriving from different geographical areas. The system has been conceived to combine and aggregate data collected for administrative use for a single patient and to build comparable epidemiological and economic indicators.[55] | 1987 | 1 500 000 | 17 | 10 million | 56–58 | |
| Prescription-Event Monitoring (PEM) | The Drug Safety Research Unit (DSRU) conducts systematic, pro-active *ad hoc* post-marketing surveillance studies to monitor the safety and utilization of newly marketed medicines prescribed by primary care physicians in England, using the observational cohort technique of PEM. Patients are identified from dispensed NHS prescriptions.[59] | 1984 | 59 490 | N/A | N/A | 60 | — |
| Swedish Medical Birth Register | The Swedish Medical Birth Registry was established in 1973. The purpose of the register is to compile information on ante- and perinatal factors, and their importance for the health of the infant. Even though the basic structure of the register has remained unchanged since 1973. To date the Birth register comprises information on patients' identity, social factors, maternal history, pregnancy, delivery, and the infant particularly at birth.[61] | 1973 | 3 230 794 | 99 of all births | N/A | — | — |

n.n., not named.
N/A, not applicable.
*In 2004.
†In 2006.

Drugs that do not require a prescription (e.g., over the counter (OTC) drugs) will be recorded in some databases such as IMS Disease Analyzer, GPRD, or THIN but only if they have been prescribed by the primary care physician. This is particularly common in the pediatric population because in children these drugs are reimbursed by the National Health Care Systems. The Swedish Medical Birth Registry keeps only information on OTC drugs which have been used by the mother prior to birth.

All databases ($n = 17$) use a coding system for therapy data, such as the Anatomical Therapeutic Chemical Classification (ATC), the British National Formulary (BNF) classification codes, or the Multilex Code. (Table 1)

### *Outcomes*

Clinical data such as symptoms, signs, outpatient diagnoses, laboratory, and diagnostic (e.g., X-Ray, MRI, etc.) results or hospital admissions are usually available in the electronic patient record databases but not completely in the dispensing-based databases. The latter ones need to be linked to other registries such as hospitalizations (e.g., Danish prescription database, PHARMO) death (Danish prescription database) or pathology (e.g., PHARMO) to have clinical outcome data. Whereas inpatient data are frequently linked, the link with outpatient diagnoses is rare.

Validation of outcomes by means of additional data requests from physicians is possible in a few databases, for example, GPRD, IPCI, Pedianet, and PHARMO. These databases would also allow for the collection of patient reported outcomes.

### *Confounders*

Major confounders in pharmacoepidemiological research are indications for prescriptions, severity of the underlying disease, and contraindications (e.g., allergies etc.). Whereas most of this information is available in the electronic medical record databases, particularly diagnosis and indications are not available in dispensing databases. Some electronic medical record databases have indications directly linked to prescriptions (by the physician) (IMS, IPCI, and PEM), in others the indication needs to be deducted from the reason of visit.

### *Accessibility and costs of databases*

The majority of databases ($n = 12$) provide researchers with access to raw data in the database but most do not sell the raw data. On the other hand, the providers of only four databases (GPRD, Pedianet, PHARMO, and IPCI) stated that anonymous copies of original medical charts may be requested by researchers. For all four databases publications exist in which additional data were asked for. None of the databases may be accessed free of charge, although most of them provide special conditions if data are used for academic research purposes.

### *Previous conduct of pediatric research*

All databases have previously been used to conduct pharmacoepidemiological research and numerous scientific publications are available for all of them.

With respect to pediatric pharmacoepidemiological research only 10 out of the 17 assessed databases have studies published which are specifically relevant to the pediatric population. The majority of these studies are qualitative and quantitative drug utilization studies. So far, and to our knowledge only GPRD, Pedianet, and IPCI have published studies that have investigated the safety of specific pediatric drugs. (Table 3)

## DISCUSSION

This survey has shown that pediatric pharmacoepidemiological studies could be conducted based on real life drug utilization and outcome data available for at least 4 million children. A large source population is very important, especially to assess drug safety since drug use is often very short and some events (e.g., cardiovascular) can be quite rare.

The advantages of using automated databases for pediatric medicines research have been well discussed previously.[6] Our survey focused on the European context and indicates that in principle many healthcare databases are available for pediatric pharmacoepidemiological studies. Based on the data needed and the database characteristics multisource studies could be carried out, although most of the databases have not yet been used specifically for pediatric pharmacoepidemiological studies.

The databases identified are particularly useful for studying drug utilization because they record prescriptions or drug dispensing. The results of these utilization studies could generate useful data on age, gender, and country patterns of drug use as well as dosages and duration of use. Off label and unlicensed use of drugs could be studied in all databases providing indications and dosages (electronic medical record databases). Most databases were also suitable for drug safety studies, although the types of outcome



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that can be validly assessed differ considerably between the databases.

Drug safety is a major concern in pediatrics since clinical trials are often not conducted or include a limited number of children. Databases are playing an important role in drug safety research in general since they allow large sample sizes, flexibility in design, are fast and cheap, and are not affected by issues such as selection bias, which can be the case with *ad hoc* studies. As our literature survey showed, only a few databases have been used previously for pediatric drug safety research and there is a need to fill this gap. As shown in the priority list of research needs for off-patent drugs in children which has been published by the EMEA Paediatric Expert Group (PEG), most of the pediatric needs are related to a lack of information on long-term drug safety in children.[7] The majority of databases in our survey are longitudinal databases following up patients for many years. Therefore they are an important data source for obtaining evidence regarding the safety of drugs in children over a longer period of time.

According to the survey, databases containing data from general practices (THIN, GPRD, IMS DA, QResearch, SPICE, and IPCI) and pediatricians (Pedianet) record the most detailed clinical information with respect to outcomes and confounders and are therefore eligible to be used in both utilization and safety studies. THIN, GPRD, IMS UK DA, Pedianet, and IPCI provide the most comprehensive information such as hospital admissions, medical history, treatment outcome, and death.

Combining data from different databases and countries is important in pediatric pharmacoepidemiology to increase sample sizes and to perform long-term follow-up studies. This is exemplified by the need to assess the cardiovascular risk of methylphenidate;[8] the assessment of the risk for stroke or myocardial infarction in children requires sample sizes far exceeding the currently available database experience in Europe.[9]

Combining data from similar sources within one country (UK, NL) is relatively easy since the health care system and the data structure are largely similar. Combination of raw data across countries is not mandatory in order to conduct a multisource study. Rather than looking for a similar raw data format, queries should be tailored for the type of underlying data so an equally structured output across countries can be provided, and the analysis datasets can be combined. This was successfully performed for the IMS-UK, IPCI, and Pedianet databases to describe drug utilization in children.[9a] Similarly data from databases with dispensing linked to hospitalizations could also be combined.

However, before cross-national studies become feasible some barriers need to be removed. Language issues may be one of the most important. This obstacle can be solved by using compatible codes and terminologies. The majority of databases already use codes for therapy data and diagnosis. However, there are different coding systems such as the International Classification of Diseases (ICD), International Classification of Primary Care (ICPC), and Read Code for diagnoses and the ATC-Classification, the Code of the British National Formulary (BNF) or Prescription Pricing Authority (PPA) for prescriptions; different versions among one system(e.g., ICD 9/ICD 10; EPhMRA ATC; WHO-ATC) are being used.

With the exception of the Swedish Medical Birth Register and the PHARMO hospital database, all databases identified in this survey are comprised of outpatient drug data. Therefore medications administered in hospital such as chemotherapy and biologicals and the treatment for rare but severe diseases such as vasculitis or pulmonary hypertension cannot be studied. It has been shown that the incidence of adverse drug reactions in pediatric hospitalized patients is much higher (9.5%) than in pediatric outpatients (1.46%)[10] and the use of unlicensed and off-label drugs is more common in hospitals than in community-based settings.[11] This underlines the importance of pediatric drug utilization and safety research in hospitals.

In recent years, particularly the health care provided to neonates and pre-term neonates has received increasing attention. In the UK the Standardised Electronic Neonatal data system (SEND) has been put in place providing a structured, web-based, and real-time data collection for newborns.[12] Feasibility studies are currently planned to investigate the potential use of SEND in pharmacovigilance. The need to collect information on the most critical group of pediatric patients has also been acknowledged by the European Commission providing funds to develop the European Neonatal Network, a framework to facilitate the development of high-quality outcome epidemiological research as well as academic driven randomized clinical trials; however, they are currently not collecting prescription data.[13]

The further development of these platforms using the rapidly advancing methods in medical informatics will enhance the availability of comprehensive data on neonates although some time will be needed to accumulate sufficient number of patients. One major



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challenge of the neonatal databases will be the ability to follow-up patients after the neonates have been discharged from neonatal care. This limits these databases to study acute adverse drug reactions and outcomes only. Further efforts will have to be made towards the availability of inpatient data that can be used for pharmacoepidemiology.

The importance of studying the teratogenic effects of drugs is well known since the Thalidomide disaster of more than 40 years ago. For most drugs there is no or little evidence regarding their potential impact on the fetus.

Studying teratogenic effects is one of the challenges of pediatric medicines research. Longitudinal databases are potentially suitable to study the impact of maternal use of medicines on child health over time. However, a basic requirement is linkage between data of mothers and babies. Our survey shows that only five databases provide a mother–baby link. One of them is the Swedish Medical Birth Register which was developed for the purpose of analyzing risk during pregnancy and at delivery. However, its most serious data deficiency is probably that information related to infant diagnosis is generally not captured in the database. The same limitation applies to the Danish prescription register and PHARMO database which also provides a mother–baby link but lack more detailed information like outpatient diagnoses and indication. However, both Scandinavian databases have been used to study the effects of drug use during pregnancy previously.[14–19]

## CONCLUSION

In summary this survey provides an overview of the health care databases that are available for pediatric pharmacoepidemiological research in Europe. It shows that there is huge potential for pharmacoepidemiological studies in children. The use of more than one database is essential in pediatric medicines research in order to obtain sufficient sample sizes to study rare but serious adverse drug reactions and to conduct long-term safety studies. In general the majority of the databases identified from this survey may be used to study patterns of drug utilization which can be applied immediately to further prioritize pediatric medicines research. As a result of the new regulation on Medicinal Products for Pediatric use, pharmacoepidemiological studies will become more important, providing evidence on the safety and efficacy of drugs used in children. Future research should focus on establishing methods for bringing existing data from different databases together to maximize their potential.

Databases with information on hospitalized children are scarce. However, the recent developments in electronic prescribing and electronic medical record keeping in hospitals could potentially provide specialist data for pediatric medicines research and should be influenced now to build data sources which can be used in future pharmacoepidemiological research.

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