European Medical Information Framework

Protocol Template for studies in electronic health record data

NOTE: In *red italicised font* is explanatory text and in black straight font is text that must appear.

Once completed, please send this protocol to EMIF.

TITLE PAGE

Title:	*Investigating the relationship in paediatric population between dosing of antibiotics (prescribed, dispensed or administered) and patient's weight.*
Date:	*02/10/2017*
Project number:	*EMIF project ID Number*
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1. Amendments and updates to the protocol

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<20 July 2016>	<All>	< General revision and comment >	<Brainstorming>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

2. Table of Contents

3. List of Acronyms

Acronym	Full meaning
AUH	Aarhus University Hospital
ARS	Agenzia Regionale di Sanità della Toscana
ATC	The Anatomical Therapeutic Chemical classification system for drugs
BMI	Body Mass Index
BSA	Body Surface Area
DB	Database
DC	Data Custodian
DE	Drug Event
EGCUT	Estonian Genome Center of University of Tartu
EHR	Electronic Health Record
EMC	Erasmus University Medical Center
EMIF	European Medical Information Framework
EU	European Union
FP	Family Paediatrician
GP	General Practitioner
HSD	Health Search Database
IPICI	Integrated Primary Care Database
IMASIS	Information System of Parc de Salut Mar
PHARMO	PHARMO Institute for Drug Outcomes Research
PRRE	Private Remote Research Environment
SIDIAP	Information System for the Development of Research in Primary Care
THIN	The Health Improvement Network Database
UNIMAN	University of Manchester

4. Responsible Parties

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5. Abstract

Dosing errors are one of the most common types of medication issues and contribute to the mortality and morbidity within the paediatric population. Paediatric patients are at a higher risk than adults of experiencing such problems because of the need for a dose calculation based on the patient's age, weight (mg/kg), body surface area (mg/m^2), and clinical condition.

Antibiotics are the medications most widely prescribed in the paediatric population and one of the drug classes most commonly reported to be involved in paediatric dosing errors.

Despite a number of studies conducted about antibiotics usage in different European countries, the appropriateness of antibiotic dosing (prescribed by doctors in primary or secondary care, dispensed by community or hospital pharmacies, or administered in hospital settings) according to the child's age, weight and height (and other related parameters, as Body Mass Index - BMI, Body Surface Area - BSA) has not yet been investigated.

In this study, we would like to assess in European Medical Information Framework (EMIF) Electronic Healthcare Records (EHR) databases (DBs) the relationship between dosing of antibiotics prescribed, administered or dispensed (either for outpatients or inpatient settings) to children (age 0-18 yr), and their weight, age and height.

6. Milestones

Milestone	Planned date	Actual date
Protocol sent to all data custodians' review boards	11/12/2017	
Development of Data Extraction and Statistical Analysis Plan	15/01/2018	
Approvals from all data custodians' review boards	15/01/2018	
Data extraction by all data custodians	8/02/2018	
All analytical datasets uploaded in PRRE	15/02/2018	
Quality control analysis	22/02 /2018	
Data analysis	15/03/2018	
Draft report of study results	10/04/2018	
Final report of study results	30/04/2018	
Publication (planned submission date)	30/05/2018	

7. Background

Dosing errors are one of the most common types of medication issues and contribute to the mortality and morbidity of hospitalised patients.[1,2] Paediatric patients are at a higher risk than adults of experiencing such problems because of the need for a dose calculation based on the patient's age, weight (mg/kg), body surface area (mg/m^2), and clinical condition.[3–5] Kaushal et al.[6] found that harmful medication errors were three times more likely in the child than in the adult

population. In a systematic review of 16 studies that investigated the incidence and nature of medication errors, dosing errors were found to be the most common type of issue during the medication use process in the paediatric population.[7] Miscalculation of paediatric dosing can lead to a tenfold or greater rate of dosing errors which can have harmful consequences for patients[26]. Antibiotics are the medications most widely prescribed in the paediatric population and one of the drug classes most commonly reported to be involved in paediatric medication errors.[6,7,9] Subtherapeutic dosing of antibiotics has been identified as a frequent problem in the paediatric population as many clinicians do not consider weight when they calculate the dose, or they simply calculate the paediatric dose as one half of the adult dosing.[6,11,12] Sometimes data on weight is lacking in electronic health records (EHRs) and is not registered by the physician or it is registered in pounds instead of kilograms, which is the reference unit for dosing calculation in children (mg/kg/day). This missing or incorrect information can lead to errors in dosing prescription or dispensation in hospital and pharmacy settings.[10] Optimising antibiotic dosing is essential to avoid treatment failure and minimise the emergence of resistant organisms.[14] Resistance to common antibiotic agents has grown among a majority of bacterial pathogens and is widely acknowledged to be an increasing threat to global public health. [14,15]

Several studies have been published in the last decade either assessing antibiotic use in paediatric populations of single European countries [16,20] or conducting comparisons of paediatric antibiotic use between countries [21,22,23,24]. Findings have shown wide variations across Europe in the prescriptions of systemic antibiotics to children and adolescents. One study found that narrow spectrum penicillins formed the majority of systemic antibiotics in Denmark, whereas prescriptions of broad spectrum penicillins were most frequent in Germany, the Netherlands, the UK and Italy [23]. The highest agent-specific prescription rates were reported for phenoxymethylpenicillin in Denmark, amoxicillin in Germany, the Netherlands and the UK, and amoxicillin plus enzyme inhibitor in Italy, where amoxicillin is also very commonly prescribed. [8,23,24] Macrolides were commonly prescribed in all five countries with the highest use in the age groups 10-14 and 15-18 years. Overall, the prescription rate of cefaclor (a second generation cephalosporin) in German children was the second highest after amoxicillin, and use of second generation cephalosporins was particularly common in very young children. [23] Also in Italy the prescription rate of cefaclor is high. [8]

Despite the abundance of studies investigating antibiotic usage in different European countries, the appropriateness of antibiotics dosing (prescribed by doctors in primary or secondary care, dispensed by community or hospital pharmacies, or administered in hospital settings) according to the child's age, weight and height (and other related parameters, as BMI, BSA), has not yet been investigated.

Using the EMIF platform, this Use Case seeks to evaluate the relationship between dosing of antibiotics prescribed, administered or dispensed (either in outpatient or inpatient settings) to children (age 0-18 yr), and their weight, height, and age. The EMIF platform aims at developing an integrated framework to facilitate harmonisation and re-use of existing pan-European patient-level data to support novel research. The overall vision of EMIF is to be the trusted European hub for healthcare data intelligence, enabling new insights into diseases and treatments. EMIF provides an opportunity to use multiple, large-scale European data sources with access to secondary/inpatient care data to assess different behaviours in antibiotic dosing across different European countries.

8. Research Aims and Objectives

The main aim of this study is to investigate the relationship between antibiotic dosing and the patient's weight in paediatric population (age 0-18 yr).

The study will include the dosing of antibiotics (prescribed by doctors in primary or secondary care, dispensed by community or hospital pharmacies, or administered in hospital settings) either in primary, secondary or inpatient settings.

Specifically, we are including within the "no-hospitalisation care setting" category all the following situations when usually low/medium severe infections occur:

- antibiotics prescribed in primary care by General Practitioners (GPs) / Family Paediatricians (FPs);
- antibiotics dispensed by community pharmacies;
- antibiotics prescribed by specialist doctors for not hospitalised patients;
- antibiotics prescribed or administered during an Emergency Room (ER) access.

We are also including within the "hospitalisation care setting" category the following situations when usually high/severe infections occur:

- antibiotics administered to hospitalised patients;
- antibiotics dispensed by hospital pharmacies in an outpatient or inpatient context.

The distinction between these two categories are related to the severity of disease, type of antibiotics and specific routes of administration.

8.1 Objectives

Primary objective

The study focuses on Drug Events (DEs), a DE being defined as a Prescription/Dispensation/Administration of one of the antibiotics of interest (see §8.5.1) in a 0-18 years old patient, as recorded in one of the different DBs involved in the EMIF project (see §8.4).

It is a descriptive study, with the primary objective to investigate for each DB, the relationship, among the DEs, between the antibiotic dosing and the patient's weight, stratified by:

- type of antibiotic (ATC code),
- care setting (Hospitalisation/No-Hospitalisation).

Whenever the required information is present, the following sub-stratifications will be produced, for each DB:

ATC code + care setting

- age group (Newborns infants/Infants and toddlers/Children/Adolescents);
- calendar year;
- BMI group (Thinness/Normal/Overweight/Obesity);
- type of DE (Prescription/Dispensation/Administration);
- route of administration (Oral/Parenteral/Other).

Further details about sub-stratifications and about how events and measurements are defined, can be found in §9.8.2.

Secondary objectives

Objective 2: To evaluate the frequency distribution of the different types of antibiotics (ATC code) in all DEs, stratified, for each DB, by:

- care setting (Hospitalisation/No-Hospitalisation),
- calendar year,
- age group.

Objective 3: To study the relationships, among the DEs, between the antibiotic dosing and the patient's BSA, stratified, for each DB, by:

- type of antibiotic (ATC code),
- care setting (Hospitalisation/No-Hospitalisation),
- calendar year.

Objective 4: To establish common methods and tools for all different EMIF EHRs to extract and analyse data related to measurements (weight, height, BMI, BSA, age) and drug prescription/dispensation/administration.

9. Research Methods

9.1 Study Design

This study will involve a descriptive analysis of EMIF EHR data to pursue the primary and secondary objectives.

9.2 Setting (Inclusion and exclusion criteria)

All DEs (prescription/dispensation/administration) in a 0-18 years old patient, as recorded in one of the different DBs involved in the EMIF project (see §8.4), will be included in the study as far as they carry the required information for at least one of the study objectives. All DEs available in the DB and collected in every period will be included.

Since the different study objectives require different information, the inclusion/exclusion criteria are defined on a per-objective basis, based on the availability of the required information, as shown in the table reported in §9.8.

9.3 Subjects (Identification of the study population)

Since the statistical units of this study will be the DEs, not the patients, we will use the expression "study population" in a genuine statistical sense: as the set of all statistical units. Thus, the study population will include all the DEs satisfying the inclusion criteria.

Each patient will be accounted for all the DEs recorded in the DBs, possibly contributing to the generation of multiple records per each individual subject, as one patient can potentially generate multiple DEs.

9.4 Data Sources

Ten data sources from six different European countries (Italy, Denmark, The United Kingdom, Estonia, The Netherlands and Spain) will be asked to participate to the study.

9.4.1 UK – THIN data

- Total number of patients: 12 000 000 (last update: 2017-07-27)
- Number of active patients: 3828859 (in January 2013)
- Coding system used: Gemscript codes
- Database start date: 2002
- Type of database: primary care
- Approximate follow-up: Median follow-up of active patients is 9 years

Pseudo-anonymised patient data are collected by THIN in a non-interventional way from the daily record keeping of general practices which use the Vision practice management software and have agreed to contribute to the scheme. As of July 2017, the THIN DB contains primary care medical records from over 12 million patients, of which over 3.8 million are actively registered. IMS Health has a licence to facilitate access to THIN Data for the purposes of medical research. IMS Health and researchers do not have access to practice or patient identifiers. However, the data are pseudo-anonymised in that THIN Additional Information Services (THIN AIS) can contact the GPs so that the GP can provide additional information or contact patients. THIN Data have been used extensively in medical research since 2003 in the UK, Europe and the United States, with over 500 peer review publications utilising the THIN data source. The age and gender profile of the active patient population in THIN has been shown to be comparable to the UK population. Graphs comparing THIN with the Office for National Statistics UK population estimates for 2011 (latest available). Data within THIN are regionally representative as far as is possible within the distribution of the Vision practice software from which they are collected, representing more than 6% of the UK population.

THIN Data have also been shown to be generally representative of the UK in terms of Quality and Outcomes Framework chronic disease parameters. In addition, a study has been performed which compares THIN with data from practices using a different general practice software system (EMIS) and it was shown to match closely with these data, with the main exception that THIN patients are slightly more highly representative of the more affluent social class. As this socioeconomic information is available in THIN, researchers are able to adjust for it in analyses.

All studies using THIN, where the intention is to make public the study results, are subject to obtaining relevant prior ethical approval of the protocol.

9.4.2 Spain – SIDIAP data

- Total number of patients: 6 426 140 (last update: 2017-07-27)
- Number of active patients: 5476072 (in January 2013)
- Coding system used: ATC
- Database start date: 2006
- Type of database: primary care
- Approximate follow-up: 7.4 years from 2006 to 2014

The Information System for the Development of Research in Primary Care (SIDIAP) is a Spanish primary care DB with continuous data collection since 2006 on a total of almost 6.5 million individuals, of which 5.5 million are currently active. The average follow-up for individuals is 7.4

years. SIDIAP uses the International Classification of Diseases, 10th Revision, (ICD-10) coding system.

9.4.3 The Netherlands - IPCI

- Total number of patients: 2.8 million (last update: 2017-07-27)
- Number of active patients: 1800000 (in January 2013)
- Coding system used: ATC
- Database start date: 1995
- Type of database: primary care
- Approximate follow-up: 3 years, but with a wide range

In 1992 the Integrated Primary Care Information Project (IPCI)10 was started by the Department of Medical Informatics of the Erasmus University Medical School. IPCI is a longitudinal observational DB that contains data from computer-based patient records of a selected group of GPs throughout the Netherlands, who voluntarily chose to supply data to the DB. GPs receive a minimal reimbursement for their data and completely control usage of their data, through the Steering Committee and are permitted to withdraw data for specific studies. Collaborating practices are located throughout the Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender.

The DB contains information on about 2.8 million patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have been registered. Turnover occurs as patients move and transfer to new practices. The records of 'transferred out' patients remain in the DB and are available for retrospective studies with the appropriate time periods.

The system complies with European Union guidelines on the use of medical data for medical research and has been validated for pharmaco-epidemiological research. Approval for this study will be obtained from the 'Raad van Toezicht' an IPCI specific ethical review board.

The figure 1 depicts one of the results for this specific DB of the previous BMI use case performed within the EMIF project: it shows the distribution of weight category in the paediatric population (the weight categories were defined from the BMI measurements).

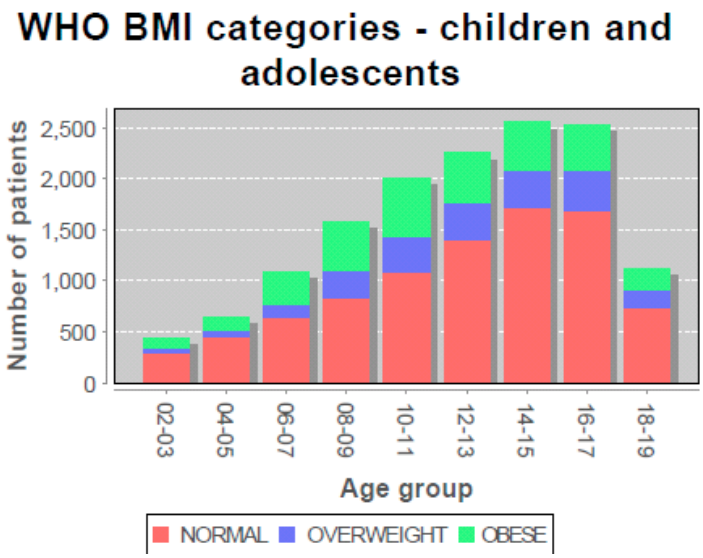


Figure 1 - BMI category distribution (from previous EMIF BMI use case study) for age 2-19 in IPCI

9.4.4 Italy – HSD CSD LPD

- Total number of patients: 1.6 million (last update: 2017-08-30)
- Number of active patients: 950 000 (in January 2013)
- Coding system used: ATC
- Database start date: 1998
- Type of database: primary care
- Approximate follow-up: 10 years

HSD, a longitudinal observational DB that is representative of the general Italian population. It was established in 1998 by the Italian College of General Practitioners. The HSD contains data from computer-based patient records from a select group of GPs (covering a total of 1.6 million patients) located throughout Italy who voluntarily agreed to collect data for the DB and attend specified training courses. The DB includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses, hospital admission, and causes of death.

All diagnoses are coded in ICD9. Drug names are coded according to the ATC classification system. To be included in the study, GPs must have provided data for at least 1 year and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates. At the time in which this study will initiate, 500 GPs homogenously distributed across all Italian areas, covering a patient population of around 800,000 patients, reached the standard quality criteria.

The HSD complies with European Union, guidelines on the use of medical data for research. The HSD has been the data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care. Approval for use of data is obtained from the Italian College of Primary Care Physicians.

The figure 2 depicts one of the results for this specific DB of the previous BMI use case performed within the EMIF project: it shows the distribution of weight category in the paediatric population (the weight categories were defined from the BMI measurements).

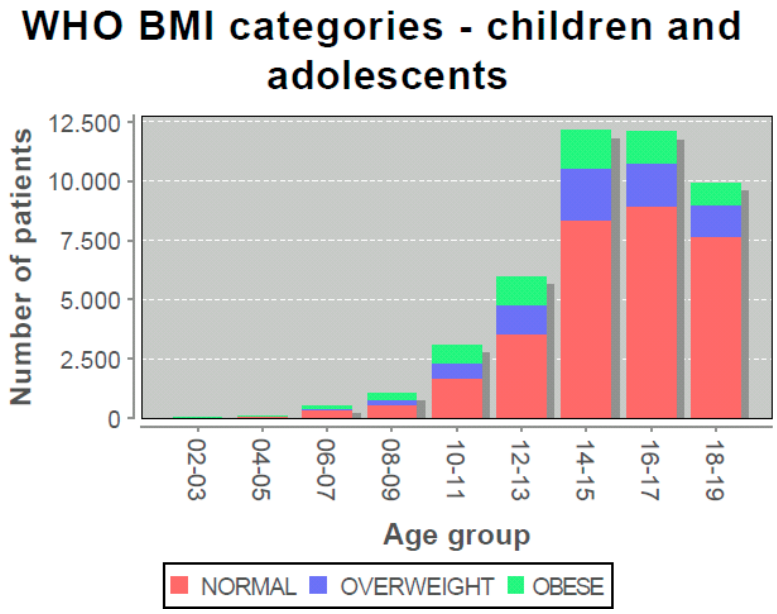


Figure 2 - BMI category distribution (from previous EMIF BMI use case study) for age 2-19 in HSD

9.4.5 Italy – Pedianet

- Total number of patients: 400 000 (last update: 2017-07-27)
- Number of active patients: 150 000 (in January 2013)
- Coding system used: ATC
- Database start date: 2004
- Type of database: primary care
- Approximate follow-up: about 10 years

Pedianet is a longitudinal observational DB that collects epidemiological clinical data for clinical research from family paediatricians involved in the Pedianet network in Italy. This system is based on the transmission of specific data from computerised clinical files, which the paediatricians in the network fill out during their daily professional activities. Informed consent is required from the parents. Such data is collected anonymously by a central server in Padua, where it is validated and elaborated.

Pedianet is an independent network. The coordination of the projects and data analysis is carried out by a scientific committee that include internationally renowned paediatricians, epidemiologists and researchers. Approximately 400 paediatricians throughout the country have taken part in Pedianet projects.

The paediatric population involves infants, toddlers, children and adolescents up to 14 years. The DB contains information on about 400 000 patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have been registered.

The figure 3 depicts one of the results for this specific DB of the previous BMI use case performed within the EMIF project: it shows the distribution of weight category in the paediatric population (the weight categories were defined from the BMI measurements).

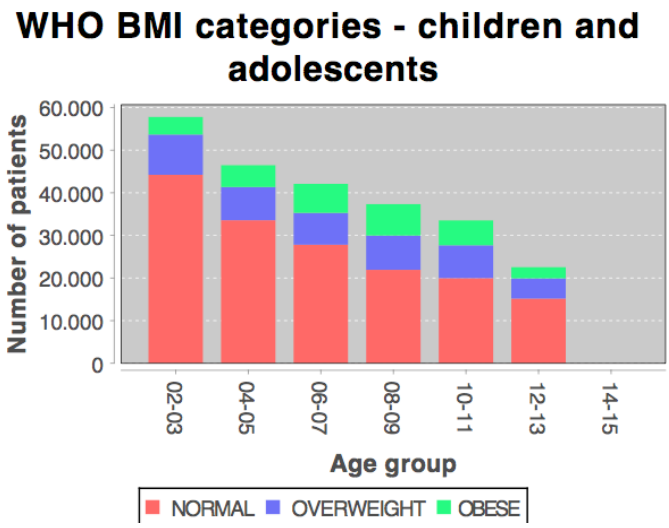


Figure 3 - BMI category distribution (from previous EMIF BMI use case study) for age 2-19 in Pedianet

9.4.6 Italy – ARS

- Total number of patients: 5 million (last update: 2017-07-27)
- Number of active patients: 3 600 000 (in January 2013)
- Coding system used: ATC
- Database start date: 1996
- Type of database: hospital data, administrative data, medication data, outpatient setting data, disease specific registry
- Approximate follow-up: 9 years

The Italian National Healthcare System is organised at regional level: each region is responsible for providing to all their inhabitants a prespecified level of assistance through a national tax-based funding. The ARS (Agenzia regionale di sanità della Toscana data source comprises all the tables that are collected by the Tuscany Region to account for the healthcare services delivered to all the persons that are officially resident in the region. Moreover, ARS collects tables from regional initiatives. A unique anonymised person identifier code allows the linkage of patient-level information from different data tables. ARS data have been extensively used and validated for epidemiologic research purposes. The collection of data into the ARS database started in 1996. Currently the DB contains information from over 5 million subjects with an average follow-up time of 9 years: they are all the subjects who have lived in Tuscany for at least some time from 2003 on, except those who have never requested to be listed in the National Healthcare Service (a negligible part).

The figure 4 depicts one of the results for this specific DB of the previous BMI use case performed within the EMIF project: it shows the distribution of weight category in the paediatric population (the weight categories were defined from the BMI measurements).

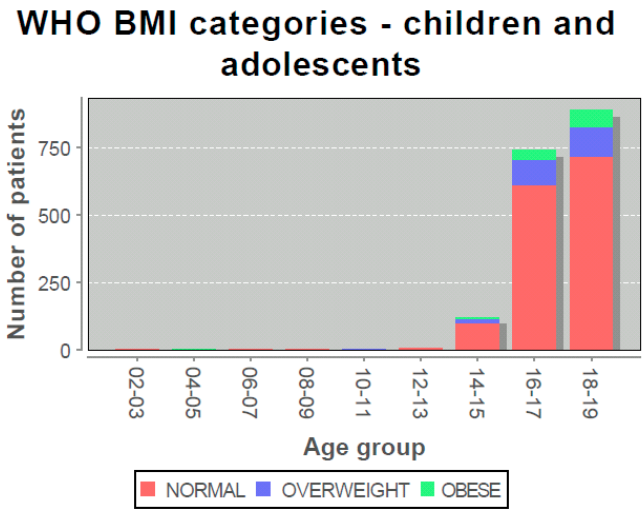


Figure 4 - BMI category distribution (from previous EMIF BMI use case study) for age 2-19 in ARS

9.4.7 Denmark – AUH

- Total number of patients: 2.3 million (last update: 2017-07-27)
- Number of active patients: 1 800 000 (in January 2013)
- Coding system used: ATC
- Database start date: 2000
- Type of database: hospital data, emergency ward data, medication data
- Approximate follow-up: 13 years

The Aarhus University Hospital DB is a system of linkage datasets in the area of the Central Denmark Region and the North Denmark Region. These are the two of five Danish Regions with a combined population of 1.8 million inhabitants and is representative of the population of Denmark. The population is entirely covered by a system of linkable registries and other administrative data sources. Since the healthcare is free and tax-supported in Denmark anyone will be recorded in these DBs regardless of for instance age or income. The Civil Registration System holds key demographic data on all inhabitants in the population and maintains the civil registration code which is assigned to everyone at birth. The AUH system of DBs includes data from in-patient, outpatient and ER visits from all somatic hospital in the two Regions. Surgical procedures and selected in-hospital treatments are available since 1999. In addition, prescriptions dispensed at the pharmacies, laboratory measurement and causes of death are available.

The figure 5 depicts one of the results for this specific DB of the previous BMI use case performed within the EMIF project: it shows the distribution of weight category in the paediatric population (the weight categories were defined from the BMI measurements).

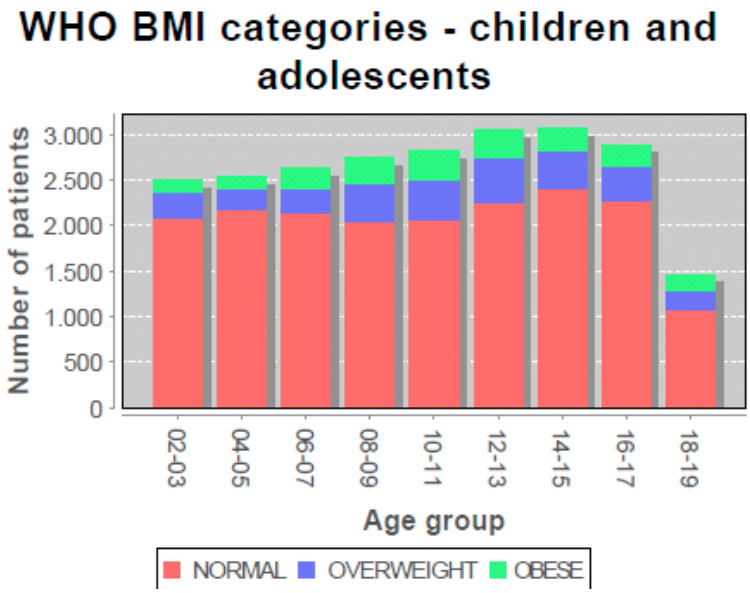


Figure 5 BMI category distribution (from previous EMIF BMI use case study) for age 2-19 in AUH

9.4.8 Netherlands – PHARMO

- Total number of patients: 8.4 million (last update: 2017-07-27)
- Number of active patients: 4 400 000 (in January 2013)
- Coding system use: ATC
- Database start date: 1990
- Type of database: medication data, hospital data, primary care data, disease specific registry
- Approximate follow-up: 10 years

The PHARMO Database Network is a population-based network of healthcare DBs and combines data from different healthcare settings in the Netherlands. These different data sources, including in- and out-patient pharmacy, clinical laboratory, and hospitals are linked on a patient level through validated algorithms. The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years.

9.4.9 Spain - IMASIS

- Total number of patients: > 1 million (last update: 2017-07-27)
- Number of active patients: missing
- Coding system used: Internal codification and national Spanish Drug codification
- Database start date: 1990
- Type of database: emergency ward data, biobank, hospital data,
- Approximate follow-up: 4.75

The IMASIS information system is the Electronic Health Records (EHRs) system of the Parc Salut Mar Barcelona Consortium that is a complete healthcare services organization. Currently, this information system includes the clinical information of two general hospitals, one mental health care centre, one social-healthcare centre and five ER settings in the Barcelona city area in Spain. In the future the system will include information of the EHRs of thirteen primary care teams. The Hospital del Mar is the principal public health facility, while social-public health services are concentrated at the Esperança Hospital and the Forum Centre. It also provides services for mental

health and addiction for adults, children and youths at the Dr Emili Mira Centre. The first version of IMASIS information system was designed in 1984 and afterwards it was completely implemented and extended in several phases. Currently IMASIS includes administrative and clinical information of patients who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, ER and major ambulatory surgery. The DB contains information on over than 1 million patients and half of them have at least one diagnosis coded using “The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)”.

9.4.10 Estonia - EGCUT

- Total number of patients: 52 000 (last update: 2017-07-27)
- Number of active patients: 50 000 (in January 2013)
- Coding system used: ATC
- Database start date: 1990
- Type of database: biobank, disease specific registry
- Approximate follow-up: 4 years

9.5 Variables

9.5.1 Variables definition

Patients input file

- **Patient ID**
- **Gender**
- **Birth-date**
- **StartDate**
- **EndDate**

Drugs input file

- **Patient ID**
- **ATC code**: antibiotic type
- **Date of drug event**
- **Dosing convertible in mg/day or mg/kg/day:** 1=dosing available and convertible, 0=dosing available but not convertible (and not valued if dosing is not available at all)
- **Dosing** (mg/day or mg/kg/day)
- **Dosing unit of measurement**: mg/day or mg/kg/day
- **Care setting**: NO-HOSP=No-Hospitalisation, HOSP=Hospitalisation
- **Drug event type**: P=Prescription, A=Administration, D=Dispensation
- **Route of administration**: Or=Oral, P=Parenteral, Ot=Other

Measurements input file

- **Patient ID**
- **Measurement type:** (H=Length/Height (cm), W= Weight (kg), BMI (kg/m^2), BSA (m^2))
- **Date of measurement**
- **Value**

9.5.2 Drug event definition

All different kinds of healthcare providers (e.g. paediatricians, GPs, doctor specialists, nurses, pharmacists) and healthcare settings (e.g. primary care, hospital care, pharmacy, inpatient and outpatient settings) are of interest for the study. All events of either antibiotics prescription or dispensation or administration will be considered.

Specifically, we are including within the “no-hospitalisation care setting” (code NO_HOSP in Drugs input file, as indicated in §8.5.1.2) all the following situations when usually low/medium severe infections occur:

- antibiotics prescribed in primary care by GPs/FPs;
- antibiotics dispensed by community pharmacies;
- antibiotics prescribed by specialist doctors for patients not hospitalised;
- antibiotics prescribed or administered during an ER access.

We are also including within the “hospitalisation care setting” (code HOSP in Drugs input file) the following situations when usually high severe infections occur:

- antibiotics administered to hospitalised patients;
- antibiotics dispensed by hospital pharmacies in an outpatient or inpatient context.

We will focus on the types of antibiotics most frequently prescribed at the European level. Previous studies have demonstrated that there are wide variations across Europe about the kinds and frequency of prescribed antibiotics [21,22,23,24].

According to these findings, the mostly prescribed/administered antibiotics for systemic use (ATC code J01) around Europe in “no-hospitalisation care setting” are:

- **amoxicillin** (ATC code: J01CA04) (the antibiotic mostly prescribed in Netherlands [22,23,24], UK [23,24], one of the two mostly prescribed in Italy[8,21,22,23,24], and often prescribed also in Denmark [23])
- **amoxicillin and enzyme inhibitor** (ATC code: J01CR02) (one of the two mostly prescribed in Italy[8,21,22,23,24] , and often prescribed also in Netherlands [22,23,24])
- **phenoxymethylpenicillin** (ATC code: J01CE02) (the antibiotic mostly prescribed in Denmark [23], and one of the mostly prescribed also in UK [16, 22, 23, 24])
- **pheneticillin** (ATC code: J01CE05) (quite prescribed in Netherlands [22,24])
- **flucloxacillin** (ATC code: J01CF05) (quite prescribed in UK [22,23,24])
- **cefaclor** (ATC code: J01DC04) (quite prescribed in Italy[8,21,24])
- **erythromycin** (ATC code: J01FA01) (quite prescribed in UK [22,23,24])
- **azithromycin** (ATC code: J01FA10) (quite prescribed in Netherlands [22,23,24] , in Denmark [23] and also in Italy [22,23,24])
- **clarithromycin** (ATC code: J01FA09) (quite prescribed in Netherlands [22,24] , and also in Italy [21,22,23,24])

The mostly administered antibiotics for systemic use (ATC code J01) around Europe in “hospitalisation care setting” are:

- **ampicillin** (ATC code: J01CA01) (usually administered via parenteral route)
- **benzylpenicillin** (ATC code: J01CE01) (usually administered via parenteral route)
- **ampicillin and enzyme inhibitor** (ATC code: J01CR01) (usually administered via parenteral route)
- **cefuroxime** (ATC code: J01DC02) (usually administered via oral route)
- **cefotaxime** (ATC code: J01DD01) (usually administered via parenteral route)
- **ceftriaxone** (ATC code: J01DD04) (usually administered via parenteral route)
- **cefpodoxime** (ATC code: J01DD13) (usually administered via oral route)
- **meropenem** (ATC code: J01DH02) (usually administered via parenteral route)
- **sulfamethoxazole and trimethoprim** (ATC code: J01EE01) (usually administered via oral route)

- **ciprofloxacin** (ATC code: J01MA02) (administered both via parenteral and oral route)
- **metronidazole** (ATC code: J01XD01) (administered both via parenteral and oral route)
- **vancomycin** (ATC code: J01XA01) (usually administered via parenteral route)

For each type of antibiotic, we will consider all the routes of administration. The route of administration is optional information in Drugs input file.

Three different types of administration are considered: Oral, Parenteral and Other (including, as an example, inhalation).

In particular, for the selected antibiotics listed above, we are interested to evaluate the dosing prescribed or dispensed or administered, expressed as mg/day or mg/kg/day (they will be provided in Drugs input file as two separate fields). If dosing is already expressed in the DB as mg/kg/day and a valid weight measurement is available (a valid weight measurement is defined as described in §9.5.3), it will then be converted to mg/day in order to evaluate the relationship between dosing and weight.

About dosing, we must face one of the following situations:

- the dosing is present in the original DB and it's expressed or convertible in mg/day or mg/kg/day; in this case:
  a. **Dosing convertible in mg/day or mg/kg/day:** is to be set to 1 (TRUE),
  b. **Dosing:** must contain the dosing in (mg/day or mg/kg/day),
  c. **Dosing unit of measurement**: must be either mg/day or mg/kg/day;
- the dosing is present in the original DB but is not convertible in mg/day or mg/kg/day; this problem arises when the dosing is expressed, e.g., in drops, or spoons or is free text, and is not possible for the DC to convert this into mg/day or mg/kg/day; in this case:
  a. **Dosing convertible in mg/day or mg/kg/day:** is to be set to 0 (FALSE),
  b. **Dosing:** not valued,
  c. **Dosing unit of measurement**: not valued;
- the dosing is missing; in this case:
  a. **Dosing convertible in mg/day or mg/kg/day:** not valued,
  b. **Dosing:** not valued,
  c. **Dosing unit of measurement**: not valued.

Dosing available in mg/day or mg/kg/day will be evaluated in relation to the patient's weight.

Since some DBs use a coding system different from ATC (as of the EMIF Catalogue), in these cases a terminology mapping between the local coding system and the ATC coding system will be performed.

ATC code will be a required information in Drugs input file (as indicated in §8.2).

9.5.3 Measurement definition

Dosing available in mg/day or mg/kg/day will be evaluated in relation to the patient's weight and, whenever available, to BSA (the age and the BMI measurements are used instead to define stratification categories), as depicted in Figure 8.1 and described below.

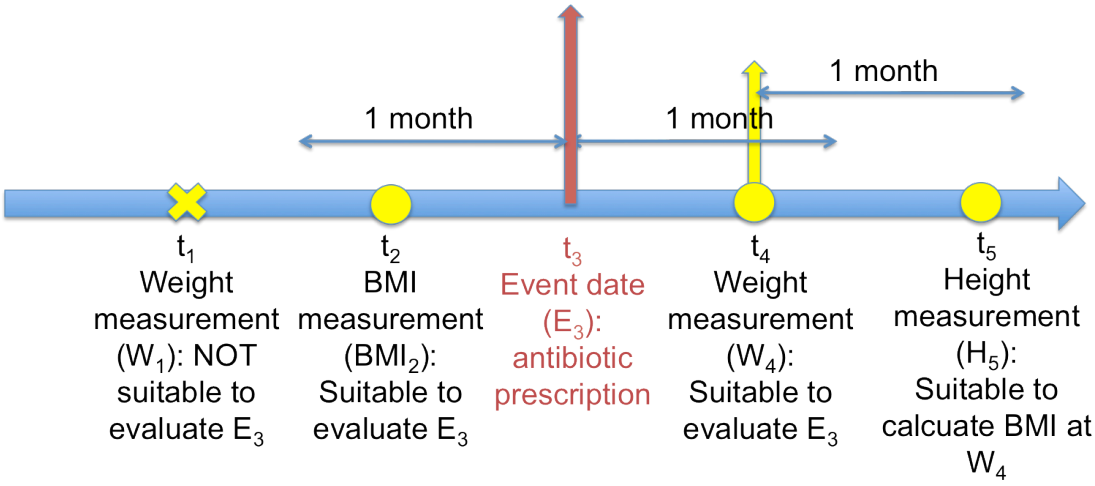


Figure 9.6: Suitable/unsuitable measurements

Weight (kg): A weight measurement will be considered suitable to assess the appropriateness of dosing if the time span between the date of the DE and the date of weight measurement is:

- at most 1 month for children aged 0-2 years,
- at most 2 months for children aged 2-6 years,
- at most 6 months for older children.

If more valid weight measurements are available, the closest in time to the date of the DE will be considered.

Age (expressed in months): in the Drugs input file the date of birth will be provided and age at the date of DE will be calculated.

Age is needed to perform sub-analyses where patients will be stratified according to their age group.

The following age categories will be considered, according to EMEA guidelines[25]:

- Newborn infants: from 0 to 27 days;
- Infants and toddlers: from 28 days to 23 months;
- Children: from 2 to 11 years;
- Adolescents: from 12 to 18 years.

BMI (Body Mass Index) kg/m^2: collected directly as BMI or calculated from height and weight (with a maximum time span between the two measurements of 1 month if the child is less than 2 years old, 2 months if the child is less than 6 years old, or of 6 months if the

child is older). In the latter case the date of BMI calculation is the date of weight measurement and is calculated as follows:

$$\text{BMI} = \frac{Weight\,(kg)}{Height^2\,(m^2)}$$

BMI measurements are needed to perform sub-analyses where patients will be stratified according to their weight categories.

Pediatric growth charts have been widely used globally by researchers, pediatricians, nurses and parents to assess the growth and nutritional status of children. Different growth reference standards exist, among them the mostly used are those defined by WHO (World Health Organization), CDC (United States Centers for Disease Control and prevention), IOTF (International Obesity Task Force). In this study, the WHO growth reference will be used since it is widely used all around the world and it covers all the age range from 0 up to 19 years (so it can be used for all the paediatric population involved in this study).

The following weight categories will be considered, according to the *WHO child growth reference standard*[1] and the *WHO growth reference standard*[2]. Each category is assigned based on a z-score calculated for a given (BMI, age, genre) triple using the tables provided by the two mentioned standards[2,3].

- **Thinness**, defined as:
  - z-score<-2 both for age >= 5years (WHO growth reference standard[3]) and age<5years (WHO child growth reference standard[2]).
- **Normal weight**, defined as:
  - -2<= z-score<1 if age >= 5years (WHO growth reference standard[3]) or -2=<z-score<2 if age<5years (WHO child growth reference standard[2]).
- **Overweight**, defined as:
  - 1<=z-score<2 if age >= 5years (WHO growth reference standard[3]) or 2<=z-score<3 if age<5years (WHO child growth reference standard[2]).
- **Obesity**, defined as:
  - z-score>=2 if age >= 5years (WHO growth reference standard[3]) or z-score>=3 if age<5years (WHO child growth reference standard[2]).

A BMI measurement will be considered suitable to assess the patient's weight category at the time of a DE, if the time span between the date of the BMI measurement and the date of the DE is at most of 1 month if the child is less than 2 years old, 2 months if the child is less than 6 years old, or of 6 months if the child is older. If there are more valid BMI measurements, the closest in time to the date of the DE will be considered.
According to the WHO, for newborn infants and infants and toddlers the BMI has to be calculated from length (height is usually 0.7 cm less than length for patients ages 2 years).

[1] http://www.who.int/childgrowth/standards/technical_report/en/

[2] http://www.who.int/growthref/who2007_bmi_for_age/en/

BSA (Body Surface Area) m^2: collected directly as BSA or calculated from height and weight (with a maximum time span between the two measurements of 1 month if the child is less than 2 years old, 2 months if the child is less than 6 years old, or of 6 months if the child is older). In the latter case the date of BSA calculation is the date of weight measurement and is calculated as follows (Du Bois formula):

$$BSA\ (m^2)=0.007184 \times W(kg)^{0.425} \times H(cm)^{0.725}$$

Please, note that H is in cm.

9.6 Sample Size (Study size)

All available eligible DEs in the DBs will be included.

This study is exploratory and descriptive in nature and therefore sample size calculations are not required.

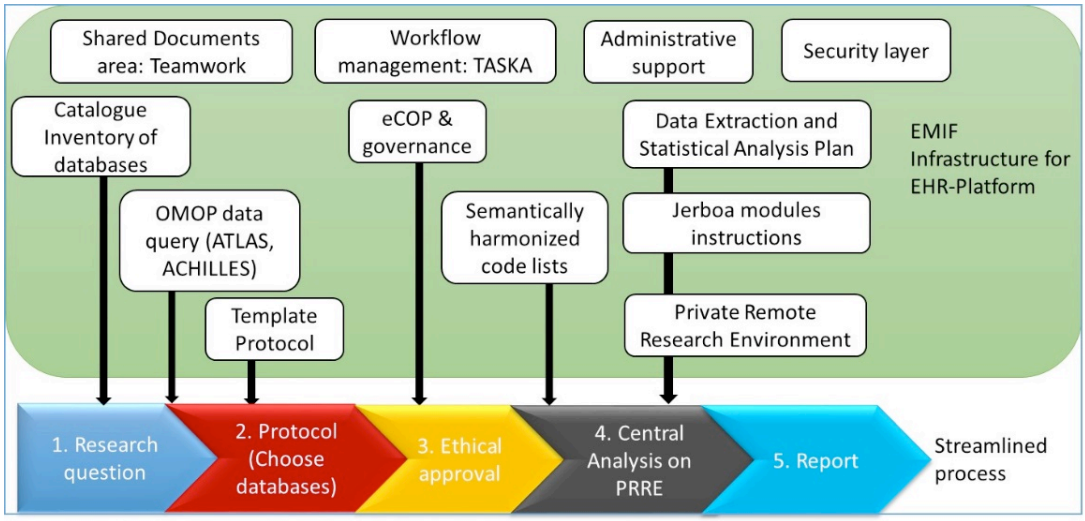
9.7 Data Management and Resourcing Needs

The selection of databases was made using meta-data information available on the EMIF Catalogue (www.emif.eu). We will seek ethical approval from ethical review boards of each data custodian.

A Data Extraction and Statistical Analysis Plan will be prepared once the protocol has been approved by the respective governance boards.

A distributed network approach has been adopted in EMIF to allow partners for maintaining control of their data and to benefit from local DB expert consultation on the appropriate use of data and interpretation of results. Therefore, anonymised row patient-level data will be extracted and managed locally. A custom-built Java based software called Jerboa Reloaded representing an updated version of Jerboa will be used, already used in different previous multi-data source research projects. Jerboa Reloaded will be run by local DB experts allowing the standardisation of the data analysis process. After providing formal written approval, Data Custodians (DCs) will upload the output file with the analytical dataset produced by the software to the Private Remote Research Environment (PRRE) for analysis.

The input files used to run the Jerboa Reloaded, as well as the queries used for extraction, data management and input file creation, will be maintained in each participating institution together with relevant Jerboa Reloaded output files which will be also uploaded and archived in the PRRE together with analysis results.



9.8 Data Analysis

9.8.1 Statistical Analysis Methods

Each of the ten DBs will upload their data in the RRE, in a format specified in the forthcoming Data Extraction and Statistical Analysis Plan (DESAP), suitable for centralised statistical analyses.

9.8.2 Objective Specific Analyses

Objective 1

Since we expect a linear correlation, among the DEs, between the antibiotic dosing (expressed as mg/day) and the patient's weight (expressed in kilos), this relationship will be investigated scatter-plotting the antibiotic dosing against the patient's weight and computing Pearson's correlation coefficient *r*. All the specified stratifications (see paragraph 9.1) will then be carried out to look for differences. To do that, the null hypothesis $r_i=r$ (where *r* is the overall correlation coefficient, and r_i is the correlation coefficient in the *i*-th stratum) will be tested using the following procedure:

- *r* is converted into $z = \frac{1}{2}\, ln\left(\frac{1+r}{1-r}\right)$ (Fischer's formula)
- r_i is converted into $z_i = \frac{1}{2}\, ln\left(\frac{1+r_i}{1-r_i}\right)$
- the standard error $\sigma_{z\text{-}z_i} = \sqrt{\frac{1}{n\text{-}3} + \frac{1}{n_i-3}}$ (where *n* is the overall numerosity and n_i is the numerosity of stratum *i*) is computed;
- $Z_i = \frac{z\text{-}z_i}{\sigma_{z\text{-}z_i}}$ is computed;
- the value α_i is computed, corresponding to the Z-score Z_i;
- only for α_i <0.05 we will conclude that r_i is significantly different from *r*.

A threshold of at least 30 DEs will be considered in each stratification: under this threshold, Pearson's correlation coefficient is not calculated.

Outputs

The following outputs will be provided for each DB and for each type of antibiotic (ATC code) and each care setting (Hospitalisation/No-Hospitalisation):

a. total number of DEs;
b. number and % of DEs for which at least a valid weight indication is provided;
c. number and % of DEs for which at least a valid dosing indication (expressed in the required measure units) is provided;
d. number and % of DEs for which at least a dosing indication would be available in the original DB, but is not provided being in units of measurement not convertible to the required ones;
e. number and % of DEs for which both at least a valid weight and dosing indication are provided;
f. number and % of DEs with at least a valid weight and dosing and BMI indication;
g. number and % of DEs with at least a valid weight and dosing and type of DE indication;
h. number and % of DEs with at least a valid weight and dosing and route of administration indication;
i. the same outputs indicated above (from *a* to *d*) for each of the following sub-stratifications:
    1. type of antibiotic + care setting + age group
    2. type of antibiotic + care setting + calendar year
    3. type of antibiotic + care setting + BMI group
    4. type of antibiotic + care setting + type of DE
    5. type of antibiotic + care setting + route of administration

    The comparison among the different strata will be carried out by means of a Chi-square test.

j. a scatter plot dosing (expressed as mg/day) *vs* weight (expressed in kilos), with its Pearson's rho calculated and visible on the plot (only DEs with at least a valid weight and dosing indication are included);
k. the same output indicated in *f*, with the following sub-stratifications (i.e. one scatter plot for each sub-stratification):
    1. type of antibiotic + care setting + age group
    2. type of antibiotic + care setting + calendar year
    3. type of antibiotic + care setting + BMI group
    4. type of antibiotic + care setting + type of DE
    5. type of antibiotic + care setting + route of administration

Objective 2

The frequency distribution of the different types of antibiotics (ATC code) in all DEs, stratified, for each DB, by

- care setting (Hospitalisation/No-Hospitalisation)
- calendar year
- age group

will be tabulated and graphically presented as histograms.

Outputs

The following outputs will be provided for each DB:

a. frequency distribution (table + histogram) of the different types of antibiotics (ATC code) involved in all DEs, stratified by:
    1. care setting (Hospitalisation/No-Hospitalisation),
    2. calendar year,
    3. age group.

The comparison among the different strata will be carried out by means of a Chi-square test.

Objective 3

The relationship, among the DEs, between the antibiotic dosing (expressed as mg/day) and the patient's BSA (expressed as m^2), for each DB stratified by the type of antibiotic (ATC code) and care setting (Hospitalisation/No-Hospitalisation) will be investigated scatter-plotting the antibiotic dosing against the patient's BSA and computing the Pearson's correlation coefficient *r* to see if there is any linearity.
Moreover, the same analysis will be performed stratifying also by calendar year. To look if any difference exists between the different calendar years, the null hypothesis r_i=*r* (where *r* is the overall correlation coefficient, and r_i is the correlation coefficient in the *i*-th stratum) will be tested using the following procedure:

- *r* is converted into $z = \frac{1}{2}\, ln\left(\frac{1+r}{1-r}\right)$ (Fischer's formula)
- r_i is converted into $z_i = \frac{1}{2}\, ln\left(\frac{1+r_i}{1-r_i}\right)$
- the standard error $\sigma_{z\text{-}z_i} = \sqrt{\frac{1}{n\text{-}3} + \frac{1}{n_i - 3}}$ (where *n* is the overall numerosity and n_i is the numerosity of stratum *i*) is computed;
- $Z_i = \frac{z\text{-}z_i}{\sigma_{z\text{-}z_i}}$ is computed;
- the value α_i is computed, corresponding to the Z-score Z_i;
- only for α_i <0.05 we will conclude that r_i is significantly different from *r*.

Outputs

The following outputs will be provided for each DB:

a. number of DEs with at least a valid dosing and BSA indication is provided;
b. frequency distribution (table + histogram) of the number of DEs for which at least a valid BSA (expressed as m^2) indication is provided, per each type of antibiotic (ATC code) and care setting (Hospitalisation/No-Hospitalisation) and, moreover, sub-stratifying by calendar year;
c. frequency distribution (table + histogram) of the number of DEs for which at least a valid BSA (expressed as m^2) and dosing indication is provided, per each type of

antibiotic (ATC code) and care setting (Hospitalisation/No-Hospitalisation) and, moreover, sub-stratifying by calendar year.

d. for each of the previous stratifications (b.), a scatter plot dosing (expressed as mg/day) *vs* BSA (expressed in m^2), with its Pearson's rho calculated and visible on the plot.

9.9 Quality Control

The analytical datasets are homogeneously produced using Jerboa Reloaded in all DBs locally.

A study-specific PRRE for secure access will be used. Due to data protection and ethical considerations, each partner will work with local data to create output files that will contain only anonymised de-identifiable data that will be shared in the PRRE where only the use case participants (DCs) will have a secure and restricted access and where data will be analysed.

Measurement values outside the range indicated below will be excluded from all the analysis. Anyway, they will be counted in order to understand the general quality of data collected.

Height:
- for newborns (>=0 & <28 gg) -> min: 30 cm, max: 70 cm
- for infants & toddlers (>=28gg & <2 years) -> min: 50 cm, max: 1,20 m
- for children (>=2 years & <6 years) -> min: 70 cm, max: 1,70 m
- for children & adolescents (>=6 years & <18 years) -> min: 70cm, max: 2,5 m

Weight:
- for newborns (>=0 & <28 gg) -> min: 500 g, max: 10 kg
- for infants & toddlers (>=28gg & <2 years) -> min: 500 g, max: 50 kg
- for children (>=2 years & <6 years) -> min: 5 kg, max: 100 kg
- for children & adolescents (>=6 years & <18 years) -> min: 10 kg, max: 300 kg

BMI-> min: 2(kg/m^2), max: 200 (kg/m^2)

BSA-> min: 0,1 (m^2), max: 5 (m^2)

9.10 Limitations of Research Methods

The main limitation may be in some DBs some missing information about, as an example, the dosing of the drug, the code of the drug, or about some patient's measurements (weight, BMI or BSA).

Another limitation may come from the availability of the dosing in units of measurement (e.g. drops or spoons, posology expressed in free text, etc.) not suitable to be converted into the required ones (mg/day or mg/kg/day).

Moreover, not all the medications actually taken by the patient might have been recorded in the DB. One the aim of the study is indeed to evaluate the amount and burden of missing information: as indicated in the specific analysis in 9.8.2, some outputs are aimed to evaluate the % of missing information (e.g. % of DEs for which at least a valid weight indication is provided).

9.11 Future Work

In the future dosing can be evaluated in relation to some specific clinical diagnosis and taking into account also severity of the pathology. Moreover, also the duration of treatment will be analysed.

Finally, other kinds of drugs, different from antibiotics, may be studied.

10. Protection of Human Subjects

10.1 Ethical / Data Utilisation Approval and Subject Consent

Ethical approval will be sought for according to DCs local procedures.

10.2 Subject Confidentiality

Data in the PRRE will be fully anonymised since data will be aggregate; there will be no patient identifiable information.

10.3 Report of Adverse Events

NA

11. Plans for Disseminating Study Results

The findings from these analyses will be circulated within EMIF. It is proposed that these findings will be published in the peer-reviewed literature, subject to approval from the DCs

12. References

1. Kohn LT, Corrigan JM, Donaldson MS. To Err Is Human: Building a Safer Health System. Washington, DC: National Academy Press, 1999. http://www.csen.com/err.pdf. Accessed June 18, 2011.
2. Kozer E, Berkovitch M, Koren G. Medication errors in children. Pediatr Clin North Am. 2006;53(6):1155-1168.
3. Ghaleb MA, Barber N, Franklin BD, et al. Systemic review of medication errors in

pediatric patients. Ann Pharmacother. 2006;40(10):1766-1776.
4. Koren G, Barzilay Z, Greenwald M. Tenfold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. Pediatrics. 1986;77(6):848-849.
5. Koren G, Haslam RH. Pediatric medication errors: predicting and preventing tenfold disasters. J Clin Pharmacol. 1994;34(11):1043- 1045.
6. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric patients. JAMA. 2001;285(16):2114-2120.

7. Wong IC, Ghaleb MA, Franklin BD, Barber N. Incidence and nature of dosing errors in pediatric medications: a systematic review. Drug Saf. 2004;27(9):661-670.

8. Nicolini G., Donà D., Mion T. et al. Use of amoxicillin, amoxicillin/clavulanate and cefaclor in the Italian pediatric population. Journal of Pediatric Infectious Diseases. 2014; 9: 1-9.

9. Aneja S, Bajaj G, Mehandiratta SK. Errors in medication in a pediatric ward. Indian. Pediatr. 1992;29(6):727-730.

10. McPhillips H, Stille C, Smith D, et al. Methodological challenges in describing medication dosing errors in children. In: Henriksen K, Battles J, Marks E, Lewin DI, eds. Advances in patient safety: from research to implementation. Vol 2. Concepts and methodology. Rockville, MD: Agency for Healthcare Research and Quality, 2005:213–23.

11. Naqvi SH, Dunkle LM, Timmerman KJ, et al. Antibiotic usage in a pediatric medical center. JAMA. 1979;242(18):1981-1984.

12. Van Houten MA, Luinge K, Laseur M, et al. Antibiotic utilisation for hospitalised pediatric patients. Int J Antimicrob Agents. 1998;10(2):161-164.

13. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. Nat Med. 2004;10(suppl 12):S122- S129.

14. Bruinsma N, Kristinsson KG, Bronzwaer S, Schrijnemakers P, Degener J, Tiemersma E, Hryniewicz W, Monen J, Grundmann H: Trends of penicillin and erythromycin resistance among invasive Streptococcus pneumoniae in Europe. J Antimicrob Chemother 2004, 54:1045–1050.

15. Jones ME, Karlowsky JA, Draghi DC, Thornsberry C, Sahm DF, Bradley JS: Rates of antimicrobial resistance among common bacterial pathogens causing respiratory, blood, urine, and skin and soft tissue infections in pediatric patients. Eur J Clin Microbiol Infect Dis 2004, 23:445–455.

16. Schneider-Lindner V, Quach C, Hanley JA, Suissa S: Secular trends of antibacterial prescribing in UK pediatric primary care. J Antimicrob Chemother 2011, 66:424–433.

17. Clavenna A, Bonati M: Differences in antibiotic prescribing in pediatric outpatients. Arch Dis Child 2011, 96:590–595.

18. De Jong J, van den Berg PB, de Vries TW, de Jong-van den Berg LT:Antibiotic drug use of children in the Netherlands from 1999 till 2005. Eur J Clin Pharmacol 2008, 64:913–919.

19. Gagliotti C, Morsillo F, Resi D, Milandri M, Moro ML: A three-year population-based study of antibiotic treatments for children.Acta Paediatr 2005, 94:1502–1504.

20. Högberg L, Oke T, Geli P, Lundborg CS, Cars O, Ekdahl K: Reduction in outpatient antibiotic sales for pre-school children: interrupted time series analysis of weekly antibiotic sales data in Sweden 1992-2002. J Antimicrob Chemother 2005, 56:208–215.

21. Lusini G, Lapi F, Sara B, Vannacci A, Mugelli A, Kragstrup J, Bjerrum L:Antibiotic prescribing in pediatric populations: a comparison between Viareggio, Italy and Funen, Denmark. Eur J Public Health 2012, 19:434–438.

22. Sturkenboom MC, Verhamme KM, Nicolosi A, Murray ML, Neubert A, Caudri D, Picelli G, Sen EF, Giaquinto C, Cantarutti L, Baiardi P, Felisi MG, Ceci A, Wong IC: Drug use in children: cohort study in three European countries. BMJ 2008, 337:a2245.

23. Holstiege J, Schink T, Molokhia M, Mazzaglia G, Innocenti F, Oteri A, et al. (2014) Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study. BMC Pediatr 14:174.

24. Bie, Sandra De. Studying Use and Risks of Medicines in Children: a European Approach. Chapter 2. 2013

25. ICH E11 Clinical investigation of drugs in paediatric population.

26. Aseeri, Mohammed A., The Impact of a Pediatric Antibiotic Standard Dosing Table on Dosing Errors. J Pediatr Pharmacol Ther 2013 Vol. 18 No. 3

27. Wang Y., Chen HJ. (2012) Use of Percentiles and Z-Scores in Anthropometry. In: Preedy V. (eds) Handbook of Anthropometry. Springer, New York, NY.