

Medication Errors and Adverse Drug Events

Enhancing detection through spontaneous reporting systems and electronic health records

Victor Pera

Propositions belonging to the thesis

Medication Errors and Adverse Drug Events:
Enhancing detection through spontaneous reporting systems and electronic health records

1. The standardization of healthcare data and the use of standardized analytical tools advance pharmacovigilance by enabling systematic investigation of medication errors and adverse drug events. *(This thesis)*

2. The application of natural language processing methods to extract and normalize drug names from unstructured data is essential for facilitating drug safety research. *(This thesis: Chapters 3, 4, and 6)*

3. Optimizing the detection of new signals related to medication errors and adverse drug events requires enhanced signal validation, which in turn necessitates additional regulatory resources. *(This Thesis: Chapter 3 and 4)*

4. Stratified analyses can reveal safety signals in subgroups, but missing key data elements reduce their effectiveness. *(This thesis: Chapter 4)*

5. A concerning trend is observed in which long-term macrolide prescribing has increased over time, while electrocardiogram assessment prior to treatment initiation remains infrequent. *(This thesis: Chapter 5)*

6. Achieving less spontaneity and more reporting would be beneficial to create a more accurate epidemiological overview of the drug safety landscape. *(Berniker et al., 2001)*

7. Rather than faulting individual healthcare providers, optimizing healthcare processes and systems is key to improve patient safety. *(Kohn et al., 1999)*

8. Patients are the primary victims of medication errors and healthcare providers the secondary. *(Mahat et al., 2024)*

9. To err is human, but an opportunity is lost when no lessons are learned in the absence of awareness. *(Mera et al., 2022)*

10. Evolutionary speaking, our human vision gives us an advantageous edge on analysing graphically displayed data, rather than the data itself.

11. "ἀσκεῖν περὶ δύο τὰ νοσήματα· ὠφελέειν | ἢ μὴ βλάπτειν." In English terms: "As to diseases, make a habit of two things—to help, or at least to do no harm." *(EPIDEMICS I, Hippocrates, ca. 410 BC)*

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Enhancing detection through spontaneous reporting systems and electronic health records

Medicatiefouten en geneesmiddelbijwerkingen:

Detectie verbeteren door middel van spontane meldsystemen en elektronische patiëntendossiers

Thesis

to obtain the degree of Doctor from
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by command of the
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by

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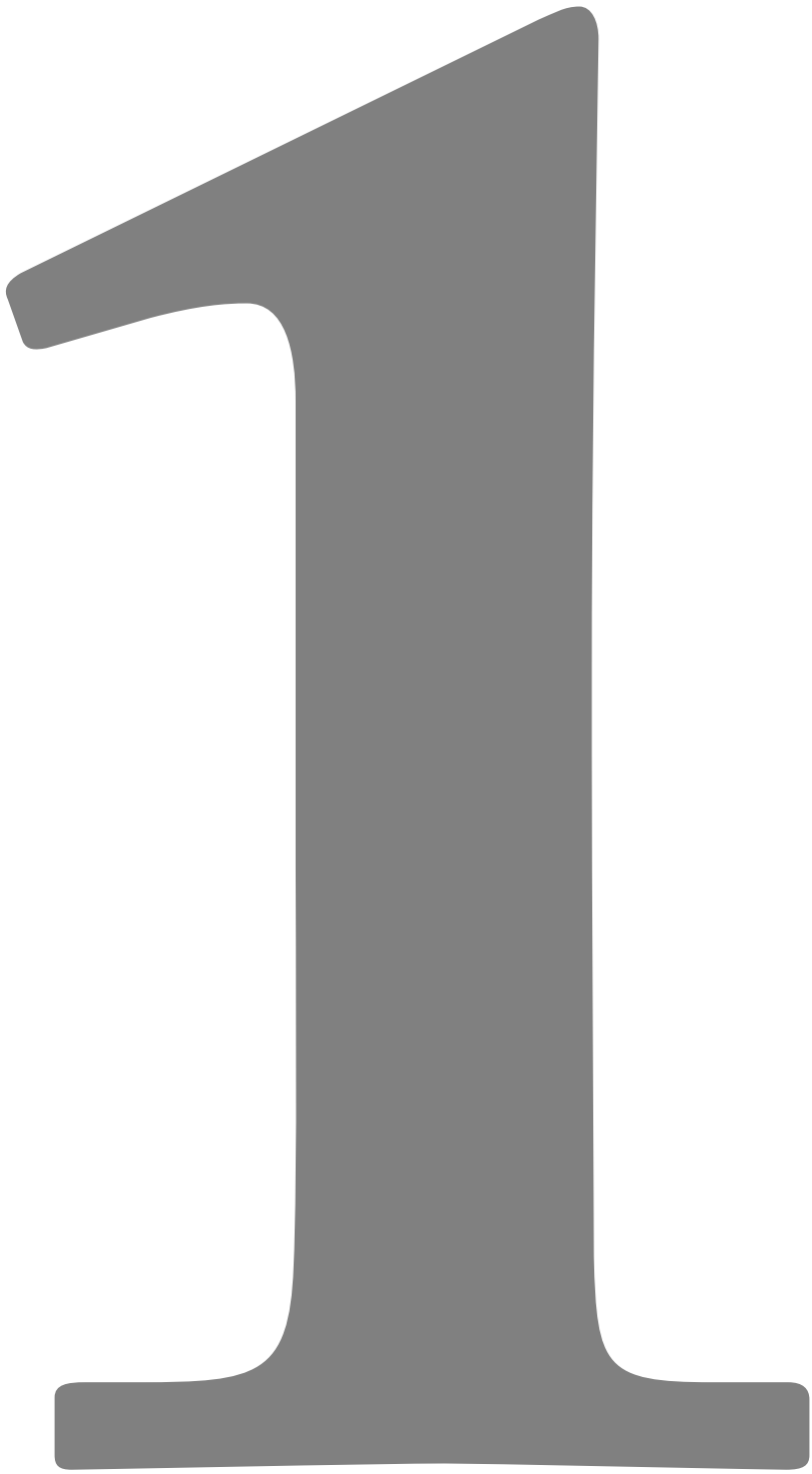

Chapter 1

General Introduction

DEFINITION(S) OF A MEDICATION ERROR

The term medication error (ME) seems at first glance like a simple concept that might be considered self-explanatory to the eye of a layman, but in fact several definitions are used by the scientific research community and regulatory healthcare authorities. For example, the European Medicines Agency (EMA) uses the following definition of ME: "*an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient*", emphasizing that "*mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine are the most common preventable cause of undesired adverse events in medication practice and present a major public health burden*" [1]. The United States of America's (USA) Food and Drug Administration (FDA) follows the National Coordinating Council for Medication Error Prevention and Analysis (NCCMERP) for their definition of MEs namely "*any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare provider, patient, or consumer*" [2]. In addition, the NCCMERP states that "*such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use*" [3]. Despite these definitions from the regulators, various other (sub)definitions for MEs are used within the scientific community up to this day. Often specific classes of MEs are investigated by the scientific research community which partly attributes to heterogenous statements on the occurrence of MEs [4,5]. MEs may occur in a wide variety of ways, such as forgetting to take a dose, not finishing an antibiotic treatment prescribed, getting a wrongfully prescribed drug, receiving a drug prescribed to somebody else, and receiving a dose wrongfully calculated based on body weight, amongst many examples. For classifying and coding purposes, before a report on MEs or adverse drug reactions (ADRs) is submitted, regulatory healthcare authorities such as the EMA and the FDA require the use of a standardised medical terminology called Medical Dictionary for Regulatory Activities® (MedDRA®), which nowadays lists 134 unique Preferred Terms (PTs) at version 28.0 describing various types of MEs.

MEDICATION ERRORS IN RELATION TO ADVERSE EVENTS AND DRUG REACTIONS

When studying a pharmacovigilance topic such as MEs, one has to take into account not to interchangeably use this term with other related, but differently defined terms, such as adverse drug event (ADE) and ADR, which are all considered under the umbrella of medication harm [6]. While numerous variations of these definitions exist [6], the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use defines an ADE as "*an unexpected medical event in an individual receiving drug treatment, in which the event is not necessarily causal to the treatment*" and an ADR as a

"*noxious and unintended event occurring at any dose*" [7]. Of important note, major distinctions between ADRs and MEs is that by definition ADRs are not preventable like MEs and ADRs are always associated with a certain degree of harm, while MEs may not cause any harm (Figure 1). Observed MEs that in hindsight did not cause harm may be considered as trivial MEs (e.g. non-significantly delayed dose or a non-impactful missed dose) or may have held an inherent risk for a potential ADE (e.g. a delayed dose could have caused harm, but it did not due to situational circumstances). On top of that, ADRs are attributed to the pharmacokinetic and pharmacodynamic properties of a drug (i.e. the inherent risk of the drug), while MEs occur due to a certain failure in the drug treatment process. Besides that, a ME is also strongly dependent on the given context which should be taken into account before an event is classified as a ME. For example, a drug overdose in which the user aimed to perform a drug-induced suicide is not considered a ME (as this was an intentional action to cause self-harm), while a drug overdose due to an individual taking a harmful double dose for compensating a missed dose would be considered a ME (as the patient was unaware that it was best to not compensate for the missed dose). Furthermore, ADEs and MEs have a certain overlap when considering their potential outcomes (Figure 1), as both ADEs and MEs may share an event that is both preventable and harmful. Only by analyzing the context in which said event occurred may clarify if it was due to a ME or a collection of circumstances that could not be prevented. To improve our understanding of MEs and to prevent them, continuous research is necessary. Hereby I introduce my thesis focusing on MEs and ADEs, emphasizing the need to further explore these topics as presented in the thesis chapters.

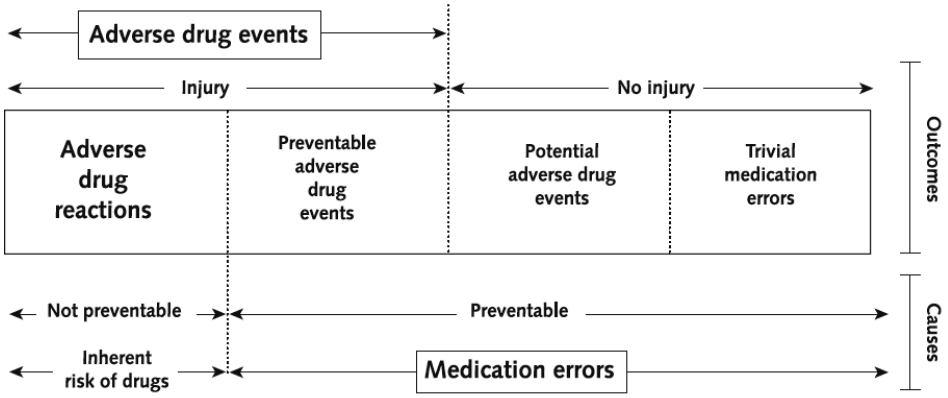

Figure 1. Graphical presentation of the relationship between medication errors, harm, adverse drug reactions, and adverse drug events. From *Annals of Internal Medicine*, Otero M-J, Schmitt E. Clarifying Terminology for Adverse Drug Events, Vol. 142, No. 1, p. 77. Copyright © 2005 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc. [8]

A BRIEF HISTORY ON MEDICATION ERROR RESEARCH

While the concept of MEs has been around for many years, one of the earliest scientific publications that highlighted MEs in the English language was in 1953, by A.K. Byrne who described how students and graduate nurses were at fault of MEs, but also how the study contributed to improvement of hospital procedures [9]. The earliest research on nationwide trends in MEs was published in 1998 by Phillips *et al.* [10]. Death certificates from citizens of the USA were analyzed for cause of death over time. The researchers found that 2,876 people died from MEs in 1983, while 7,391 people died from MEs in 1993, which was an unsettling trend.

A research that followed in 1999, and is considered a landmark publication up to this day, is *To Err Is Human: Building a Safer Health System* by Kohn *et al.* from the Institute of Medicine (IOM) [11]. This 300+ page report sheds light on the topic of errors within the USA healthcare system. These errors are often referred to as medical errors, which also encompasses MEs. This research shocked the USA nation and prompted President Bill Clinton on 7th of December 1999 to meet with consumers and healthcare providers, signing a memorandum for a federal task force, and directing federal agencies to improve safety and healthcare quality [12]. The Quality Interagency Coordination Task Force (QuIC) was directed to evaluate the recommendations of *To Err Is Human,* and an action plan was published in February 2000 by the QuIC as a response to President Bill Clinton's request [13]. The Agency for Healthcare Research and Quality (AHRQ) recognized that up to 2001, scientific research on patient safety practices were limited due to perceptions that considered the ME topic as a weak business case, lack of pressure from the USA public, no allocated research funding, and strong believes that medical errors represented human slips rather than an unsafe healthcare system [14]. It was argued that all of these obstacles needed to be addressed before any progress could be made to make healthcare systems safer throughout time. Many stakeholders of the healthcare sector acknowledged the importance of IOM's publication, and much progress was made on a worldwide scale with regards to patient safety and MEs [15–21]. Since the 21st of July 2012, all Member States of the European Union (EU) are required to adopt the provisions as stated in the pharmacovigilance directive 2010/84/EU, and one of those provisions is reporting suspected adverse reactions, including those forthcoming from MEs [22]. The EMA additionally published their good practice guide on reporting, coding, reporting, and assessing MEs in 2015 [23]. By 2013, more than 3,000 publications were listed on AHRQ's Patient Safety Network, showing how much research, implementations, and improvements have been facilitated in the decade before [24]. The World Health Organization (WHO) launched in 2017 their third Global Patient Safety Challenge titled *Medication Without Harm* with the goal to reduce ME-related harm by 50% in a time span of 5 years [25]. The AHRQ published their 4th report in 2023 from the *Making Healthcare Safer* series [14], of which the second report focused on MEs among other topics [24].

Severity and cost of medication errors

As previously discussed, the outcome of a ME can be anywhere between being harmless and the occurrence of death. In a meta-analysis aiming to quantify the prevalence, severity and type of preventable medication harm across medical care settings, it was estimated that the prevalence of medication harm (following pooling) was on average 3% among patients in a broad range of healthcare settings, and that 26% of this harm is severe or life-threatening, 40% moderate, and 39% mild [26]. Another meta-analysis utilizing research data until June 2023 highlighted that 36% of patients, after admission in emergency departments, experience a ME of which 43% were considered harmful, but not life-threatening [27]. In England alone, MEs occur at a rate of 237 million per year, leading to an annual consumption of 181,626 hospital-bed-days, and contributing to 1,708 deaths [28]. In the USA, for in-hospital patients with a life-expectancy of more than 3 months, medical errors (including MEs) were considered to have contributed to 7,150 deaths annually [29]. Besides the physical harm MEs may inflict, MEs also contribute to decreased trust in healthcare [30], affect the emotional wellbeing and functioning of healthcare providers [31–33], and bring additional costs to the healthcare system. Costs of MEs can range broadly, depending on the type of ME, the (in)direct harm forthcoming from it, and how calculations are made as there is no validated methodology established for it [34]. Research has shown that a ME can be as costly as up to €6,927,078.96 for an error in an anesthetic procedure, considering additional litigation costs [35]. Nationwide USA hospital costs for preventable ADE forthcoming from MEs were estimated to be annually 2 billion United States dollars (US$) [11], and the WHO has estimated that global ME-associated costs are US$ 42 billion annually [36].

A never-ending challenge

In 2025 alone, there were more than 281 publications[1] indexed on PubMed® on the topic of MEs. MEs remain frequently researched as they still persist up to this day, and (cost-) effectiveness of interventions to mitigate MEs are continuously being evaluated [37,38]. The sustained need for understanding and reducing MEs is unsurprising considering (I) that healthcare systems are becoming increasingly more complex, (II) vast amount of new drugs enter the market every single year, (III) a looming shortage of healthcare providers, (IV) available technology for healthcare is being inefficiently used, (V) many healthcare providers experience a high workload and stress, and (VI) a growing healthcare demand as the population is increasingly aging [39,40].

While the need for research on the topic of MEs is still high, it can be a costly and lengthy endeavor to collect data prospectively, while not all healthcare settings may be suitable to collect data retrospectively, and a considerable amount of MEs occur outside the healthcare settings. As somewhat of a solace, spontaneous reporting systems (SRSs) have shown an

1 Using the search term *"Medication Errors"[Majr:NoExp]*, indicating to only search publications that have the MeSH-term *"Medication Errors"* as major topic, and excluding other terms below in the MeSH hierarchy.

important utility since their inception in the field of pharmacovigilance, including for the monitoring of MEs.

Spontaneous reporting systems and the lack of standardization

The purpose of SRSs is to collect reports on ADEs, aiming to identify signals on new, rare, and severe ADRs usually not identified during clinical trials, as part of the post-marketing surveillance of drugs [41]. A few examples of existing SRSs are the UK's Yellow Card scheme [since 1964], the Canada Vigilance Program [1965], the FDA Adverse Event Reporting System (FAERS) [1969], WHO's VigiBase [1978], and the EMA's EudraVigilance [2001]. All of these data-sources are used to identify (new) safety signals based on quantitative or qualitative methods. Quantitative methods used are the disproportionality analysis (e.g. calculation of reporting odds ratio, proportional reporting ratio, information component) or Bayesian data mining methods, with the aim to identify whether the occurrence of a drug-event combination (DEC) is higher than any other DEC within a given SRS. Qualitative methods include case narrative review and regulatory assessment.

Besides ADEs, also MEs can be reported to these databases, thus, SRSs provide a plethora of data and insights on MEs, facilitating pharmacovigilance practices. Despite the data richness and the well-established database structure of SRSs, they also have several shortcomings such as several types of reporting bias, incomplete reports, questionable quality of information, and data-input in a non-standard way [41-43].

Monitoring safety signals (including for MEs) should happen in a uniform, fast, and efficient way. For these reasons, standardization of data is of high essence. Standardization is in particular important for reported drugs which are suspected to be (part of) a root cause of an unfavorable outcome. While FAERS datafiles and the public dashboard are freely available [44], which promote external research, the fact that there are many entries of drug names in a non-standard format (i.e. manual input of free text) makes it difficult to aggregate and analyze data. EMA's EudraVigilance has the benefit of the availability of more standardized drug names, but often enough the name of the active substance and the corresponding Anatomical Therapeutic Chemical (ATC) code for a given drug is missing, while the ATC coding system facilitates consistent and valid drug comparisons in pharmaco-epidemiological studies [45]. All these gaps provide research opportunities as presented in this thesis.

THESIS AIMS AND OUTLINE

The aim of this thesis was to expand our understanding on MEs and ADEs by utilizing a range of observational databases accompanied by in-house developed software tools which facilitated standardization of data sets and analyses. In **Chapter 2**, we describe the validation and development of software that aimed at standardizing drug names for the purpose of improved data aggregation within SRSs which serves as an important input for future analyses on SRSs in Chapter 3, 4, and 6. **Chapter 3** portrays characteristics of spontaneously reported MEs in the FAERS database and focuses on disproportionately reported ME-drug combinations. **Chapter 4** brings a broader overview of frequently and disproportionately reported MEs in EMA's EudraVigilance database with emphasis on stratification of results by sexes and age-groups with improved data visualization. In **Chapter 5**, two observational databases were used to assess the incidence of new macrolide-users among individuals with chronic respiratory diseases. Also, the rate of pre-emptive electrocardiogram (ECG) procedures was assessed for the period before initiation of long-term macrolide therapy. **Chapter 6** utilizes the FAERS database to investigate whether there is a signal of parasitic infections in relation to type 2-immunity monoclonal antibodies. Lastly, in our discussion in **Chapter 7** we summarize our main findings, put them into perspective, and touch upon potentials for future work in the field of MEs and ADEs.

2

Chapter 2

Aioli: Standardising Drugs in the FDA Adverse Event Reporting System (FAERS) to RxNorm and Anatomical Therapeutic Chemical (ATC) Codes

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ABSTRACT

Purpose

The Food and Drug Administration Adverse Event Reporting System (FAERS) is an important source of information on suspected adverse drug reactions, but does not standardise drugs. The Adverse Event Open Learning Through Universal Standardization (AEOLUS) System Provides Standardisation of drugs in FAERS to RxNorm, but its coverage leaves room for improvement and mapping accuracy has not been established. Furthermore, drugs are not mapped to the Anatomical Therapeutic Chemical (ATC) Classification System, which is frequently used in pharmacovigilance studies. Here we develop and evaluate the Aioli system, an extension of AEOLUS, to increase the mapping of drugs in FAERS to RxNorm, and to provide mappings to the ATC coding system.

Methods

Several changes and extensions were made to the AEOLUS mapping process to increase the number of drugs standardized to RxNorm. Information in FAERS fields about ingredient, route, dose amount, dose form, and dose unit was used to map to the most appropriate ATC code. Mapping accuracy was assessed on an evaluation set of 122 FAERS records.

Results

Aioli mapped 94.1% of drug names in FAERS to RxNorm, compared to 90.4% by AEOLUS. In addition, Aioli mapped 80.4% of drug names to ATC codes. Evaluation showed high accuracies, with 92.2% correct mappings to RxNorm and 94.0% to ATC.

Conclusion

We have developed and evaluated the Aioli system that maps drugs in the FAERS database to RxNorm and ATC codes. With increased coverage of drugs and the mapping to ATC, Aioli further improves the usability of FAERS data in pharmacovigilance studies.

INTRODUCTION

Spontaneous reporting systems are important sources of information on suspected adverse drug reactions (ADRs) [1–5]. These systems are used for signal detection and refinement in post-marketing drug safety research and regulatory contexts [51–53]. One of the largest spontaneous reporting systems is the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) [46] FAER. is made publicly available and has been used in numerous post-marketing surveillance studies.

Use of the data in FAERS has several issues, most importantly the presence of duplicate case reports and the lack of standardized drugs. Multiple data dashboards and tools have been developed to improve FAERS data access and quality, but often it is unclear if and how deduplication and standardization is done, or the software is not made available [54]. One of the few open-source systems that does deduplication of data and standardization of drugs in FAERS is the Adverse Event Open Learning through Universal Standardization (AEOLUS) system [55]. AEOLUS standardizes drug names to the RxNorm coding system. Since RxNorm only covers drugs marketed in the United States (US), AEOLUS also uses an RxNorm Extension that includes drugs that are available in non-US markets and was developed as part of the Observational Health Data Sciences and Informatics (OHDSI) project [56]. It was reported that AEOLUS is able to map 93% of the drugs mentioned in FAERS case reports [55], which leaves room for improvement. Also, the accuracy of the mappings was not yet investigated. Furthermore, no mappings are provided to the Anatomical Therapeutic Chemical (ATC) classification system, maintained by the World Health Organization (WHO) [57]. ATC is a frequently used coding system for drugs in observational health data studies, especially in Europe, and is commonly used in drug utilization and pharmacovigilance studies [58,59].

In this study, we develop and evaluate an AEOLUS extension, called Aioli, to increase the mapping of drugs in FAERS to RxNorm, and to provide mappings to the ATC coding system.

METHODS

The Aioli system has been implemented as an extension of the AEOLUS system, replacing the AEOLUS mapping of drugs. The loading of FAERS data files, removal of duplicate reports, mapping of outcomes to Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) concepts, and generation of summary statistics about drug-outcome relationships are still done in AEOLUS and have not been changed. Figure 1 shows the different processing steps in Aioli. In the following, we describe these steps, indicating the changes and extensions that were made to AEOLUS.

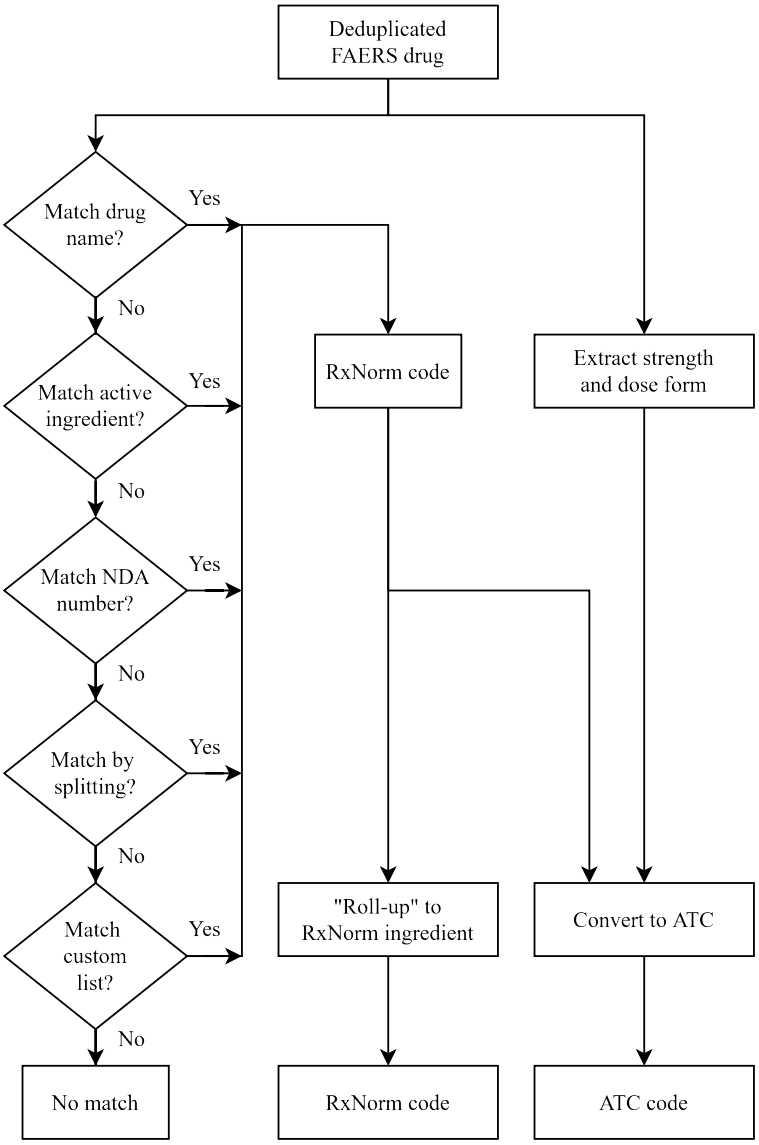

Figure 1. Flowchart of the mapping of drug records in FAERS by the Aioli system. ATC - Anatomical Therapeutic Chemical (Classification System); FAERS - Food and Drug Administration Adverse Event Reporting System; NDA - New Drug Application.

MAPPING TO RXNORM

The drug records in the FAERS reports are mapped to concept unique identifiers (CUIs) of standard code ingredients and clinical drug forms (for multi-ingredient drugs) using the OHDSI Standardized Vocabularies version 5.3, which includes RxNorm and RxNorm Extension as the standard vocabularies for drugs [56]. For brevity, in the following, RxNorm

will also imply RxNorm Extension. Aioli includes the mapping process that was defined in AEOLUS and consisted of a series of consecutive steps [55]. If a step resulted in a successful mapping, the mapping process for the given record was stopped; else, the next step was executed. The following steps were defined:

1. Using regular expressions, drug names (in field drugname in the FAERS data files) are matched against RxNorm preferred terms. The matching is performed iteratively, after subsequent removal of trailing spaces and dots, special characters (e.g., symbols, punctuation, parentheses), dosages, and routes of administration.
2. Active ingredients (in field prod_ai) are mapped to RxNorm CUIs.
3. Drug names are matched with brand names in the European Union Register of Medicinal Products. If a match is found, the corresponding active ingredient is mapped to an RxNorm CUI.
4. New Drug Application (NDA) numbers (in field nda_num) are linked to the active ingredient in the NDA Orange Book [60] and then mapped to RxNorm CUIs.
5. Drug names are split into separate words, and each word is matched with a multi-ingredient, single-ingredient, or brand name, and subsequently mapped to RxNorm.
6. Drug names are matched against a custom list of drug-to-RxNorm CUI mappings manually created with the OHDSI Usagi vocabulary mapping tool [61].
7. Matches in one of the previous steps may result in CUIs from a variety of RxNorm term types, such as ingredients, brand names, and dose forms. Using the relation table in the OHDSI vocabulary, each term type and CUI is converted ("rolled up") to one of two final term types: single ingredient or multiple ingredients.

In Aioli, the AEOLUS mapping process described above was modified in several ways to increase the number of mapped drug names:

- The cleaning step was slightly expanded with additional characters to be removed.
- Matching was not only done against the preferred term for each RxNorm CUI, but also against all synonyms provided in the RxNorm rxnconso table.
- The European Union (EU) Register of Medicinal Products was replaced by the more comprehensive Article 57 database on all medicinal products authorized in the European Economic Area [62].
- The normalization function provided by the RxNorm Application Programming Interface (findRxcuiByString) was integrated to eliminate sources of discrepancies due to differences in word order, use of abbreviations, and American-British spelling differences.
- A manually created custom list of 422 mappings from drug names to RxNorm CUIs was included.
- Minor fixes were made in the final roll-up code to avoid incorrect mappings of brand names to clinical drug forms and of dose forms to drugs.
- A user option was provided to replace the final RxNorm code of a multi-ingredient drug by the RxNorm codes of the single ingredients of that drug.

MAPPING TO ATC

ATC is a classification system in which active ingredients are hierarchically grouped by therapeutic use [57]. This means that a single active ingredient can have more than one code, depending on its therapeutic use, often related to drug strength or route of administration. For example, the drug finasteride in a low dose is used for treating male-pattern baldness (D11AX10) and in a high dose for treating benign prostatic hypertrophy (G04CB01). As another example, the beta-blocker timolol can be administered orally to treat cardiovascular conditions (C07AA06), while it is used in eye drops to treat glaucoma (S01ED01). For accurate mapping of FAERS drug records to ATC codes, it is therefore also necessary to consider the strength and route of administration of a drug.

The current approach to map drug names to RxNorm CUIs uses information from FAERS data fields about drug names, active ingredients, and NDA numbers. Mappings were made to any matching RxNorm term type. To map drugs to ATC codes, information in FAERS fields about route, dose amount, dose form, and dose unit is also used to derive four RxNorm components: ingredients, strength, dose form, and brand name. This information is then used to map to the most detailed RxNorm CUI possible, which is then converted to the most appropriate ATC code by means of an RxNorm-ATC conversion table developed at Erasmus University Medical Center. If a drug has multiple ATC codes but the drug record contains insufficient information to determine a single ATC code, no ATC code is assigned.

EVALUATION

Coverage is defined as the percentage of drug records for which a mapping was available. A unique drug record was defined by the unique combination of the following FAERS fields: drug name, active ingredient, route, dose amount, dose form, dose unit, NDA number. Missing values in these fields were treated as a separate, unique value. For example, if two drug records have the same values for all fields except for one field where one record has some specific value and the other record has a missing value, then the records are considered different. If these records would both have a missing value in that field, the records would be considered the same.

To assess the accuracy of the mapping process, we randomly selected 122 FAERS records. Two researchers (VP and KV) with a background in pharmacy, medicine, and drug safety research independently scored whether the Aioli mappings from FAERS to RxNorm and ATC were correct. Discrepancies between the observers were discussed and resolved in a consensus meeting. Accuracy is defined as the percentage of mappings that were correct according to the human observer. Interobserver agreement was determined by overall

agreement, defined as the percentage of mappings on which the observers agreed, and by kappa, indicating the overall agreement corrected for chance agreement.

RESULTS

We processed a download of the FAERS source data up to June 2023. After deduplication, there were 59,662,138 drug records across 16,485,294 case reports. Of these, 56,153,519 (94.1%) could be mapped to RxNorm by Aioli, whereas 53,909,090 (90.4%) were mapped by the original AEOLUS system. Aioli mapped 47,942,080 (80.4%) drug records to a single ATC code.

There were 4,227,336 unique drug records. Aioli mapped 3,394,928 (80.3%) of these unique drug records to RxNorm, and 2,776,885 (65.7%) to ATC.

Of the 122 drug records in the evaluation set, Aioli mapped 115 (94.3%) to RxNorm and 100 (82.0%) to ATC. There were various reasons why seven drug names could not be mapped to RxNorm, including a spelling mistake (cardiazem instead of cardizem), an orphan drug not marketed in the US and Europe (nimotuzumab), and several of the drug names with multiple ingredients where the mapping procedure was unable to find a matching multi-ingredient RxNorm concept. Since RxNorm served as the basis for the consecutive mapping to ATC, these seven drug names were also not mapped to ATC. An additional 15 drug names could not be mapped to ATC, for example because the terms were too unspecific to assign an ATC code (e.g., calcium, potassium, triamcinolone), contained multiple ingredients in an unknown combination, or the ATC code was missing in the RxNorm–ATC conversion table.

The agreement between the two observers who evaluated the Aioli mappings to RxNorm and ATC was very good: 96.5% agreement and 0.73 kappa for RxNorm mappings, 95.0% agreement and 0.42 kappa for ATC mappings. After establishing a consensus reference standard, the mapping accuracy of Aioli was 92.2% (106/115) for RxNorm and 94.0% (94/100) for ATC. Of the nine RxNorm mapping errors, in five cases the mapped RxNorm string contained the correct ingredient but included dosage information that was not present in the original case record, in two cases the mapping was incomplete (e.g., isosorbide instead of isosorbide mononitrate), one case mapped to insulin regular whereas it should be insulin isophane, and one case contained conflicting brand name and ingredient information in the case record and was mapped to the wrong ingredient (omeprazole instead of pantoprazole). Of the six ATC mapping errors, three were due to an incorrect mapping to RxNorm. For the other three cases, an incorrect or related but less precise ATC code was assigned.

DISCUSSION

The Aioli system described and evaluated in this study shows increased coverage of drug names in FAERS and provides accurate mapping of drug names to RxNorm and ATC codes. Aioli mapped 94.1% of drug names to RxNorm, compared to 90.4% by AEOLUS. In addition, Aioli mapped 80.4% of drug names to ATC codes, a capability that is absent in AEOLUS. The ability to map to ATC codes is particularly beneficial for pharmacovigilance studies in Europe, where ATC is a commonly used coding system. We have used this Aioli feature in several previous studies that analyzed FAERS data [63,64].

Our evaluation of Aioli on a small subset of the mappings demonstrated high accuracies, with 92.2% correct mappings to RxNorm and 94.0% to ATC. These values can be compared with the interobserver agreement scores for RxNorm (96.5%) and ATC (95.0%), suggesting that there is still some room for improvement, in particular, for mapping drug names to RxNorm. Since ATC mapping is based on RxNorm, any improvement in RxNorm mapping will likely also benefit the mapping to ATC.

Our results for mapping drug names to RxNorm are difficult to compare with previous reports of tools for standardizing drug names in FAERS [54]. This is partly due to the steep increase in FAERS data over the years, which resulted in different FAERS data sets being analyzed in different studies. The effect of this can be illustrated by the coverage of drug names by AEOLUS, which was reported to be 93% in the original study (on about 5 million drug records) [55] [10] but dropping to 90.4% in the current study (with almost 60 million drug records). Moreover, only very few studies have reported mapping accuracies. In an older study using the medication extraction tool MedEx on legacy data from the FAERS database [65], the mapping accuracy was 93.5% on a set of 200 drug names. In another study that used AEOLUS tooling [66], two annotators independently assessed 500 mappings and found accuracies of 96.6% and 96.8% for mapping to the correct active ingredient. In our study, we used a stricter annotation rule that penalized the inclusion of additional information not present in the case report. If only ingredient correctness were scored, 5 of the 9 RxNorm mapping errors of Aioli would be considered correct and the mapping accuracy would rise from 92.2% to 96.5%.

Our study has a number of strengths and limitations. A strength is that all of the code of the Aioli system is publicly available and can readily be applied by other investigators. Also, our evaluation of the mappings to RxNorm and ATC provides valuable information on the mapping accuracy and mistakes, while the interobserver agreement scores provide an indication of the maximum feasible accuracy that can be obtained by humans or the system. Finally, the mapping of FAERS data to ATC is new and facilitates the inclusion and analysis of FAERS data in pharmacovigilance studies that utilize the ATC coding system.

A limitation of our study is the relatively small evaluation set. A larger set would yield more reliable accuracy estimates and possibly offer more insight into the errors made by Aioli. Another limitation is that the RxNorm to ATC conversion table used in Aioli is only maintained by a single party (Erasmus University Medical Center). A more robust maintenance solution would be feasible if accurate RxNorm to ATC mappings were incorporated and maintained as part of the OHDSI vocabulary resources. Steps to accomplish this have recently been reported [67]. Such maintenance would include the mapping of new ATC codes, which are published annually, and adaptation to possible alterations in the ATC classification system, although the WHO is keeping these latter changes to a minimum [68]. Our mapping to RxNorm ingredients may also benefit from a large, manually curated drug name-to-ingredient dictionary that has recently been made available as a dynamic resource to foster knowledge sharing and collaboration among researchers developing drug name standardization tools [69].

In conclusion, we have developed and evaluated the Aioli system that maps drug records in the FAERS database to RxNorm and ATC codes. With increased coverage of drugs and the mapping to ATC, Aioli further improves the usability of FAERS data in pharmacovigilance studies.

DECLARATIONS

Conflict of Interest

The authors declare no conflicts of interest.

Funding

The authors received no specific funding for this work.

Data Availability Statement

All code of the Aioli system is publicly available with an Apache License 2.0 on https://github.com/mi-erasmusmc/aioli.



Chapter 3

Descriptive analysis on disproportionate medication errors and associated patient characteristics in the Food and Drug Administration's Adverse Event Reporting System

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ABSTRACT

Background

Medication errors (MEs) are a major public health concern which can cause harm and financial burden within the healthcare system. Characterizing MEs is crucial to develop strategies to mitigate MEs in the future.

Objectives

To characterize ME-associated reports, and investigate signals of disproportionate reporting (SDRs) on MEs in the Food and Drug Administration's Adverse Event Reporting System (FAERS).

Methods

FAERS data from 2004 to 2020 was used. ME reports were identified with the narrow Standardised Medical Dictionary for Regulatory Activities® (MedDRA®) Query (SMQ) for MEs. Drug names were converted to the Anatomical Therapeutic Chemical (ATC) classification. SDRs were investigated using the reporting odds ratio (ROR).

Results

In total 488,470 ME reports were identified, mostly (59%) submitted by consumers and mainly (55%) associated with females. Median age at time of ME was 57 years (interquartile range: 37-70 years). Approximately 1 out of 3 reports stated a serious health outcome. The most prevalent reported drug class was "antineoplastic and immunomodulating agents" (25%). The most common ME type was "incorrect dose administered" (9%). Of the 1,659 SDRs obtained, adalimumab was the most common drug associated with MEs, noting a ROR of 1.22 (95% confidence interval: 1.21 - 1.24).

Conclusion

This study offers a first of its kind characterization of MEs as reported to FAERS. Reported MEs are frequent and may be associated with serious health outcomes. This FAERS data provides insights on ME prevention and offers possibilities for additional in-depth analyses.

INTRODUCTION

The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) defines a medication error (ME) as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer" [3]. This definition is also adopted by the Food and Drug Administration (FDA) [70]. In addition, this definition excludes "the deliberate or intentional use (e.g., abuse, misuse, off label use) of a drug product in a manner that is inconsistent with FDA-required labeling" [2]. The World Health Organization initiated the third Global Patient Safety Challenge in 2017 titled "Medication Without Harm" for the purpose of promoting solutions to address problems concerning safety of medication practices, which includes dealing with MEs [25]. In 2012 it has been estimated that the worldwide annual costs of avoidable MEs were 42 billion dollars [36]. A systematic review from 2018 showed that the prevalence of MEs ranged from 2 to 94% among adults in various study populations around the world [4]. Reported prevalence numbers of MEs vary greatly due to heterogeneity in studied populations and variations in ME definitions [4,71]. A recent 2020 study estimated that annually 237 million MEs occurred in England alone [28]. Of these MEs, the researchers estimated that 28% were potentially clinically significant. Furthermore, the same study estimated that the adverse drug events (ADEs) stemming from MEs have led to an additional annual consumption of 181,626 hospital-bed-days and contributed up to 1,708 annual deaths. Another research estimated that annually 7,150 ME-related deaths are preventable for inpatients in the United States of America (USA) with a life-expectancy greater than 3 months [29]. Besides the economic burden and the healthcare impact, MEs also contribute to a lack of trust in the healthcare system and to patient dissatisfaction [72]. Hence, it is of high importance to gain more insights into reported MEs in order to prevent MEs in the future.

Limited studies have been performed on MEs using data from the spontaneous reporting systems. Newbould *et al.* studied MEs within the European Medicines Agency (EMA's) EudraVigilance database and reported that between 2005 and 2015 a total of 147,824 case reports were related to MEs causing adverse drug reactions (ADRs), of which 41,355 occurred within the European Economic Area with a proportional increase of submitted reports over time [73]. The results of this paper mainly focused on trends over time, geographical origin of reports, and quantification of MEs and associated drugs, while there were limited results on patient characteristics, drug-ME combinations (DMEs), and no results on associated clinical event outcomes or on signals of disproportionate reporting (SDRs). Carnovale *et al.* found 468,677 case reports on MEs within the FDA's Adverse Event Reporting System (FAERS) between 2004 and 2017, showing more detailed results on DMEs in multiple age strata with emphasis on SDRs [74]. However, this study provided limited information on patient characteristics and clinical outcomes of MEs. Furthermore, those studies did not

touch upon the topic of data quality or completeness of the Individual Case Safety Reports (ICSRs), while research on the data quality within FAERS appears scarce [75].

The objective of this paper was to provide an overview of ME reports from FAERS with emphasis on ME characteristics, associated patient characteristics, clinical outcomes, and SDRs of DMEs.

METHODOLOGY

Data source

FAERS is a database that contains spontaneous reports related to medication or medical devices, submitted to the FDA on adverse events (AEs), product quality complaints resulting in AEs, and MEs [46]. Anyone can freely send in a report through FDAs MedWatch Online Voluntary Reporting Form [76]. The Medical Dictionary for Regulatory Activities® (MedDRA®) is used to code AEs and MEs. This study uses MedDRA® version 23.1. The Legacy Adverse Event Reporting System (LAERS) is the predecessor of FAERS and it embodies earlier data from January 2004 up to September 2012 [77,78]. The database files from the newer FAERS database are published since October 2012. The publicly available database files from LAERS and FAERS were the primary data source for this study. In the remainder of the manuscript, we refer to the combined LAERS and FAERS database as "the FAERS database".

Data extraction and processing

The Adverse Event Open Learning through Universal Standardization (AEOLUS) system developed by Banda *et al.* was the cornerstone for extraction and processing of FAERS data [55]. The main functions of AEOLUS include standardization of FAERS data, deduplication of case reports, and generating SDRs. AEOLUS is available as a GitHub repository [79]. For this research, a forked version was used [80]. The original structured query language (SQL) scripts from AEOLUS were adjusted in such a way that all data files up to the end of 2020 could be downloaded. AIOLI, a drug mapping tool developed within the Medical Informatics department [81], allowed conversion of drug names to Anatomical Therapeutic Chemical (ATC) classification. Various age units encountered in the data were converted to years. Ages between 0 and 120 years were considered valid. The age variable was considered unknown in case of missing age, missing time format, or negative age.

ME case identification and characterization

ICSRs of MEs within FAERS were identified by using the preferred terms (PTs) from the narrow standardised MedDRA® Query (SMQ) for the key topic on MEs [82,83] (See supplementary Table S1 for a complete list of PTs). Characterization was performed on variables such as age, sex, drug use, indications and procedures, reporter type, country of origin, and clinical health outcomes. The clinical health outcomes were reported as "death," "life-threatening," "hospitalization (initial or prolonged)," "disability," "congenital anomaly," "required intervention to prevent permanent impairment or damage," and "other serious (important medical events)." The health outcome "other serious (important medical events)" is suggested by the FDA to be used in case that "the event [medication error] does not fit the other outcomes [i.e., death, life-threatening, etc.], but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes [i.e. death, life-threatening, etc.]" [84].

Disproportionality analysis

To assess the association between reported drug use and MEs, a disproportionality analysis was performed. DME-counts were performed by AEOLUS and shown in Table 1 [55].

Table 1. Contingency table representing the necessary counts needed to perform a disproportionality analysis.

	Report count for medication error	**Report count for all other events**
Report count for drug of interest	A	B
Report count for all other drugs	C	D

The reporting odds ratio (ROR) was calculated with the equation:

$$ROR = \frac{A/C}{B/D} = \frac{A \times D}{C \times B} \quad (1)$$

The respective 95% confidence intervals (CIs) were calculated with the equation:

$$95\%\ CI\ for\ ROR = e^{ln(ROR) \pm 1.96 \sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}} \quad (2)$$

Only drugs that were marked as primary suspects in the ICSRs were considered for analysis. Thresholds for displaying relevant SDRs were applied according to EMA: a lower bound of the 95%CI>1 and number of individual cases ≥3 [85]. Stratified disproportionality analyses were also performed based on sex and age.

RESULTS

The selection and the processing of ICSRs is displayed in Figure 1. A total of 14,919,552 reports were retrieved of which 10,651,341 (71%) were from the latest FAERS system. The AEOLUS system found 2,475,303 (17%) duplicates, leaving 12,444,249 (83%) reports for data processing. A total of 11,096,667 (89%) ICSRs had a valid ATC code for the primary suspect drugs. Using the narrow SMQ for MEs, 488,470 (4%) ICSRs were identified to be related to MEs. A total of 1,659 distinct DMEs could be classified under the narrow ME SMQ. About 25% of the DMEs met the criteria for disproportionality to be considered a SDR. Figure 2 shows how the number of spontaneous reports received by FAERS increased over the years from 204,538 in 2004 up to 1,588,017 in 2020, with a slight decrease in 2018. The proportion of ME reports followed a trend in which the proportion of MEs declined from 3.9% in 2004 to 1.7% in 2013, but increased up to 7.5% in 2020.

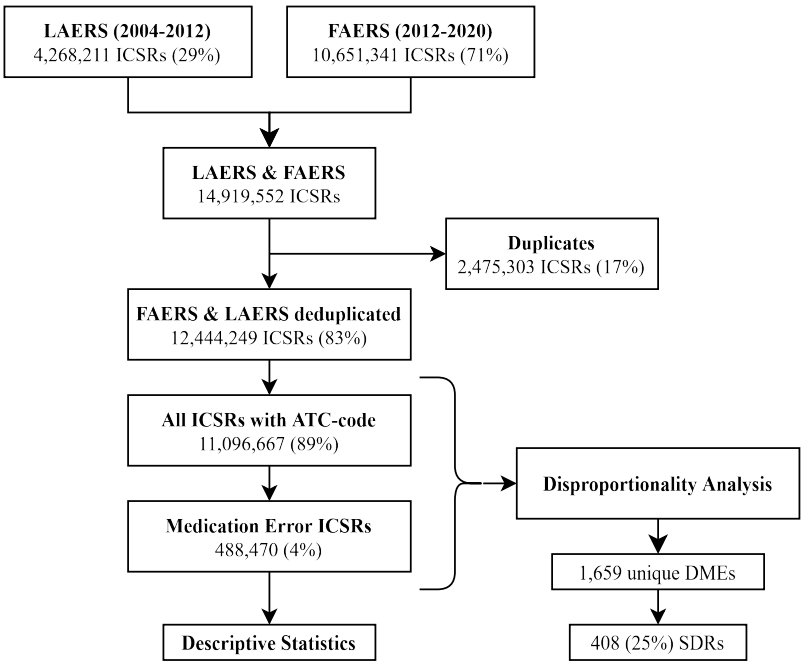

Figure 1. Flowchart for the selection and analysis of individual case safety reports. ATC - Anatomical Therapeutic Chemical classification; DME - Drug-medication error combination; FAERS - Food and Drug Administration's Adverse Event Reporting System; LAERS - Legacy Adverse Event Reporting System; SDR - Signal of disproportionate reporting.

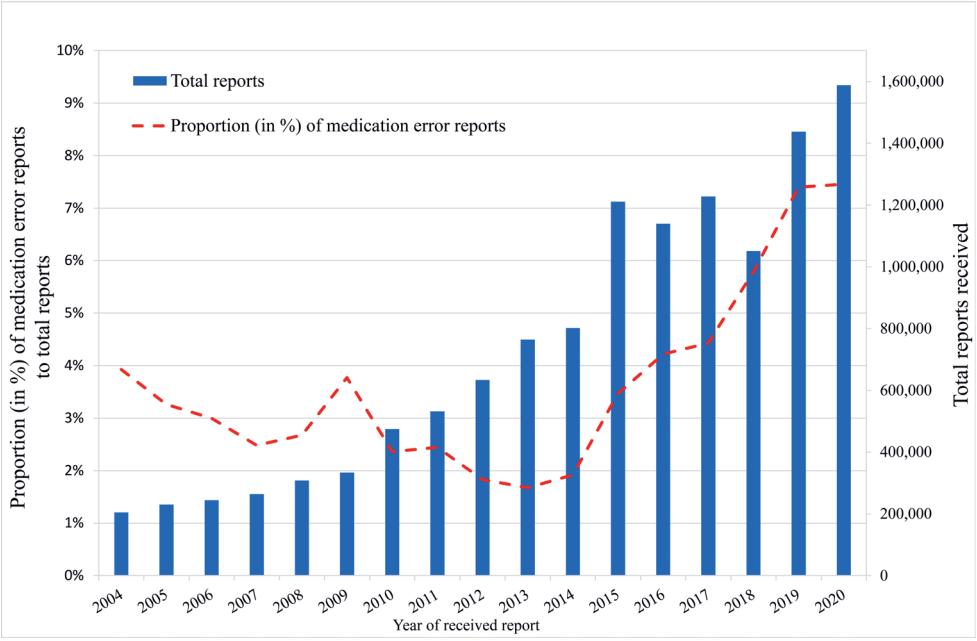

Figure 2. Proportion of medication error reports compared to the total number of reports received in FAERS between 2004 and 2020. FAERS - Food and Drug Administration's Adverse Event Reporting System.

Table 2 provides an overview of the report, reporter, and database characteristics of the 488,470 ICSRs related to MEs. About 419,931 (86%) of the cases originated from the latest FAERS database. In 269,032 (55%) cases, the sex of the user of the primary drug suspect was registered as female, 162,445 (33%) were male, and 56,993 (12%) was not reported. The median reported age was 57 years with an interquartile range of 37-70 years as presented in Table 3. More detailed age distributions of both the ME population and the entire FAERS population, additionally stratified by sex, are provided in supplementary Figures S1-S6. Consumers accounted for 286,469 (59%) of submitted ICSRs, healthcare professionals (HCPs) for 117,788 (24%), lawyers for 2,021 (<1%), and for 36,769 (8%) of ICSRs the reporter type was unknown. Most of the reports, being 387,656 (79%), originated from the USA and 29,640 (6%) were from unknown origin. The health outcome for most MEs was not reported, accounting for 338,744 (63%) reports. The most commonly reported health outcome was hospitalization in 65,369 (12%) reports. Health outcomes death, life-threatening, disability, congenital anomaly, and "required intervention to prevent permanent impairment or damage" were each reported in less than 5% of the cases. The majority of the ICSRs (337,640 reports; 69%) reported one drug per ICSR.

Table 2. Patient, reporter and data characteristics of medication error related individual case safety reports.

	Reports (%)
Total medication error reports	488,470 (100%)
Database	
FAERS	419,931 (86%)
LAERS	68,539 (14%)
Sex	
Female	269,032 (55%)
Male	162,445 (33%)
Not reported	56,993 (12%)
Health outcomes	
Hospitalization (initial or prolonged)	65,369 (12%)
Death	19,891 (4%)
Life-threatening	9,242 (2%)
Disability	5,207 (1%)
Required Intervention to prevent permanent impairment/damage	1,845 (<1%)
Congenital anomaly	156 (<1%)
Other serious (important medical event)	95,394 (18%)
Not reported	338,744 (63%)
Reporter	
Consumer	286,469 (59%)
Physician	81,365 (17%)
Pharmacist	36,423 (7%)
Other health-professional	45,423 (9%)
Lawyer	2,021 (<1%)
Not reported	36,769 (8%)
Reporter country	
United States of America	387,656 (79%)
152 countries, each contributing <5%	71,174 (15%)
Not reported	29,640 (6%)
Unique drugs per report	
1	337,640 (69%)
2	56,900 (12%)
3	26,760 (5%)
4	16,434 (3%)
5	11,589 (2%)
6 or more	39,147 (8%)

FAERS - Food and Drug Administration Adverse Event Reporting System; LAERS - Legacy Adverse Event Reporting System.

Table 3. Age characteristics of individuals from the medication error related individual case safety reports.

	Reports (proportion)
Reports with valid age	272,655 (55.8%)
Reports with invalid age	215,815 (44.2%)
Median age, in years (IQR)	57 (37-70)
Age groups	**Reports (proportion)**
Neonates (0 - 28 days)	1,603 (<1%)
Infants (29 days - 1 year)	2,826 (1%)
Children (2 - 11 years)	13,685 (3%)
Adolescent (12 - 17 years)	11,147 (2%)
Adults (18 - 64 years)	161,190 (33%)
Elderly (≥ 65 years)	97,731 (20%)
Not reported	200,288 (41%)

IQR - Interquartile range.

From the 488,470 ICSRs on MEs, there were 302,325 (62%) ICSRs which listed an indication for the primary drug suspect. The most frequent system organ classes (SOCs) corresponding with the indications of the primary drug suspect were "Musculoskeletal and connective tissue disorders" (46,129 reports; 15%), "Metabolism and nutrition disorders" (35,151 reports; 12%), "Nervous system disorders" (25,042 reports; 8%), "Skin and subcutaneous tissue disorders" (24,689 reports; 8%), and "Surgical and medical procedures" (23,062 reports; 8%), accounting for 51% of all SOCs. More details are provided in supplementary Figure S7.

A total of 512,933 DMEs were found among the 488,470 ME-related ICSRs as seen in Figure 3. About 70% of all DMEs were associated with "Antineoplastic and Immunomodulating agents" (129,588 DMEs; 25%), drugs from the "Nervous system" (90,090 DMEs; 18%), drugs involved in the "Alimentary tract and metabolism" (76,351 DMEs; 15%), and drugs for the "Respiratory system" (61,941 DMEs; 12%).

The most frequently reported PTs were "Incorrect dose administered" (90,903; 9%), "Wrong technique in product usage process" (84,642; 8%), and "Inappropriate schedule of product administration" (46,250; 5%) as seen in Table 4.

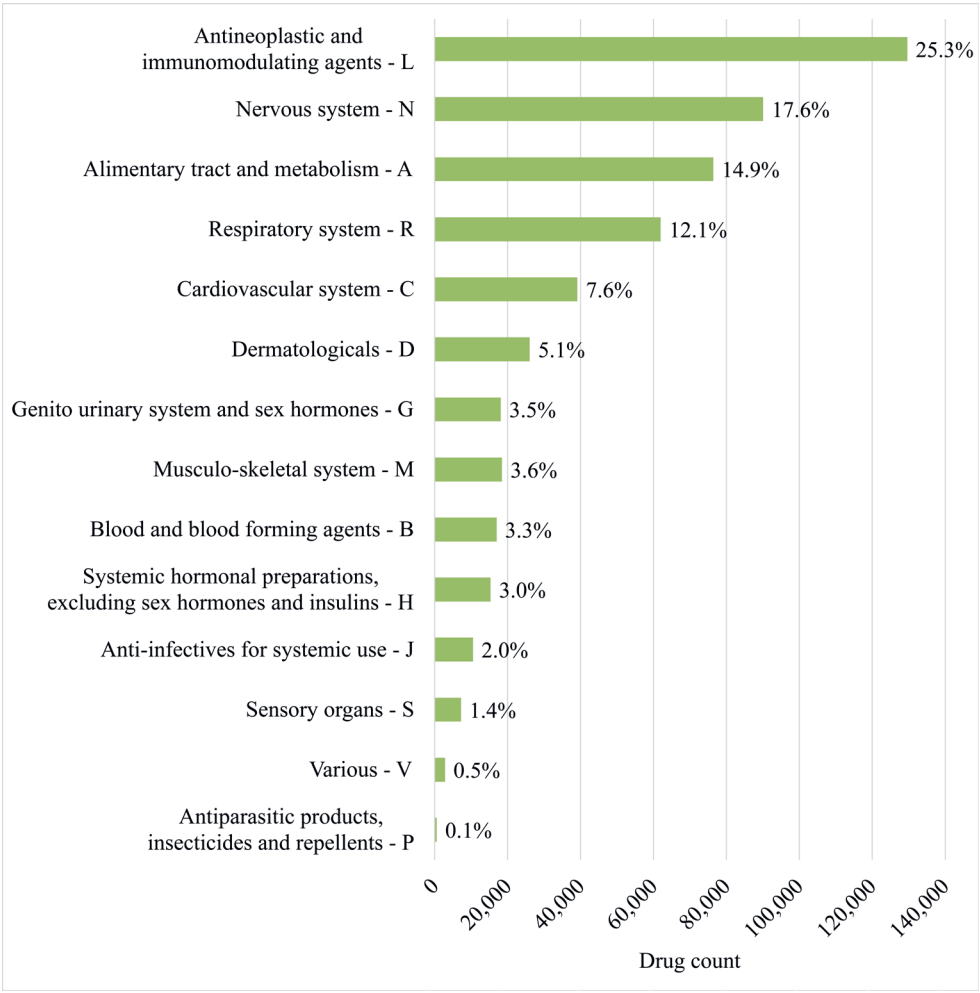

Figure 3. The drug count forthcoming from a total count of 512,933 drug-medication error combinations found in the 488,470 medication error-related individual case safety reports represented on level 1 of the Anatomical Therapeutic Chemical classification.

Disproportionality results are displayed in Table 5. Adalimumab (ATC: L04AB04) was the drug with most MEs reported, accounting for 25,678 ICSRs, and represented a ROR of 1.22 (95%CI: 1.21 - 1.24). The second most frequently reported drug with a stronger SDR was attributed to salbutamol, accounting for 17,175 ICSRs and a ROR of 14.77 (95%CI: 14.52 - 15.02). An almost equally frequent and strong SDR was shown for pegfilgrastim (ATC: 15,089), accounting for 15,089 ICSRs and a ROR of 14.23 (95%CI: 13.98 - 14.49). Notably, the route of administration for most drugs displayed in Table 5 was parenteral.

Table 4. Top 10 most common narrow medication errors reported.

	Occurrence	(proportion)
Total drug-medication error combinations	512,933	(100%)
Reported type of medication error		
Incorrect dose administered	90,903	(9%)
Wrong technique in product usage process	84,642	(8%)
Inappropriate schedule of product administration	46,250	(5%)
Accidental exposure to product	31,922	(3%)
Medication error	30,910	(3%)
Accidental overdose	19,692	(2%)
Device use error	19,682	(2%)
Product storage error	19,337	(2%)
Expired product administered	17,443	(2%)
Wrong technique in device usage process	14,758	(1%)

Table 5. The **10 most frequent** drug-medication error combination resulting in a signal of disproportionate reporting.

ATC level 5 code	Generic drug name; route of administration	Reports	ROR	95% CI
L04AB04	Adalimumab; parenteral	25,678	1.22	1.21 - 1.24
R03AC02	Salbutamol; inhalant	17,175	14.77	14.52 - 15.02
L03AA13	Pegfilgrastim; parenteral	15,089	14.23	13.98 - 14.49
C10AX13	Evolocumab; parenteral	14,544	7.55	7.42 - 7.68
D10AD03	Adapalene; topical	11,812	2.32	2.28 - 2.37
N02CD01	Erenumab; parenteral	11,223	15.48	15.16 - 15.80
A10AE04	Insulin glargine; parenteral	11,172	4.59	4.50 - 4.68
A10AB04	Insulin lispro; parenteral	10,681	5.02	4.92 - 5.12
A10BJ01	Exenatide; parenteral	8,721	2.46	2.41 - 2.51
N02BE01	Paracetamol; systemic, rectal	8,719	4.55	4.46 - 4.66

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

Disproportionality results based on highest ROR are displayed in Table 6. Triprolidine (ATC: R01AX03) showed the strongest signal with a ROR of 48.08 (95%CI: 10.76 - 214.82), but the number of reports was three. Stratified results based on sex and age groups showed some overlap, but overall there was a wide variety regarding the top 10 strongest SDRs. The stratified results are available in ESM, Table S2-S9.

Table 6. The **10 strongest** signals of disproportionate reporting related to medication errors.

ATC level 5 code	Generic drug name; route of administration	Reports	ROR	95% CI
R01AX03	Triprolidine; oral	3	48.08	10.76 - 214.82
D08AX07	Sodium hypochlorite; topical	7	40.79	15.81 - 105.24
A10BJ04	Albiglutide; parenteral	7,837	40.38	39.25 - 41.54
R06AX07	Phenylephrine; ophthalmic	3	38.46	9.19 - 160.95
S01GA05	Potassium acetate; parenteral	7	22.44	9.49 - 53.06
L03AA13	Zoster, live attenuated; systemic	50	19.79	14.41 - 27.17
A06AD15	Sodium acetate; parenteral	12	19.72	10.33 - 37.67
R01AX06	Tetracaine; topical	4	18.32	6.03 - 55.64
N02BA51	Ipratropium bromide; nasal	3	16.03	4.52 - 56.79
R03BX	Erenumab; parenteral	11,223	15.48	15.16 - 15.80

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

DISCUSSION

In this study we investigated the frequency of MEs, it's characteristics and signals of disproportionality. We observed an increase in reporting of MEs over time, almost half of the MEs were associated with serious health outcomes and MEs among antineoplastic and immunomodulating agents are reported most frequently.

The observed increased reporting rate in FAERS can be related to increased healthcare access, utilization due to the Affordable Care Act enacted in 2010 [86–88], and the introduction of the reporting form FDA3500B, released in 2013, which aided consumers in voluntary reporting in addition to online reporting via MedWatch [42]. Also, public health campaigns on medication safety might have contributed to awareness on the necessity of reporting and therefore increased reporting [89,90]. The fact that FAERS ICSRs were mostly submitted by consumers rather than HCPs resonates with literature emphasizing many limiting factors for HCPs, such as lack of time, difficulties determining the cause of ADE, poor reporting systems and uncertainty about the reporting procedures [91]. Furthermore, other research reported that consumers were motivated to self-report if they were under the impression that HCPs did not (have the time to) report an ADR, did not take their ADR seriously, or if HCPs asked consumers to report themselves [92]. Also, we assume that MEs might not be recognized or considered as AEs by the HCP, because the patient never mentions them or does not seek HCP guidance. Interestingly, the proportion and the amount of ME-related ICSRs also increased over time. Possible causes might be due to an increase in (i) dispensed prescriptions [93] (ii) aging population [94,95] (iii) novel drug approvals (iv) healthcare complexity [95] and (v) polypharmacy [96–98].

Most described demographic attributes correspond with what is observed among the general population of health consumers. Most subjects in ME ICSRs were women, who receive more drug prescriptions and have a higher healthcare consumption than men [99,100]. Ageing coincides with an increased risk of disease development and thus increased drug use [98]. Despite lower amount of reports among the pediatric population in this study, the risk of MEs in children should not be underestimated; a systematic review reported that MEs occurred in up to 27% of treated children [101]. The observed ME health outcomes from this study as described in Table 2 show similarities with especially the moderate and severe health outcomes of MEs from a systematic review focusing on MEs among nursing home residents, mostly in the USA [102]. It seems that polypharmacy individuals were underrepresented in our study as less than one-third of the ICSRs reported individuals using 2 or more unique drugs at the time of the ME, while literature suggests that half of the medication users in the USA use 2 or more drugs concomitantly [96].

Literature on MEs related to drug use is limited. Only a few recent studies that were performed outside of the USA emphasize the issue of frequent MEs among cancer patients [103–105]. The overall proportions of drugs on ATC level 1 related to MEs from the narrow SMQ in our study were largely similar to findings from Carnovale *et al.* [74]. Disproportionality findings by Newbould *et al.* based on EudraVigilance data showed that MEs were mainly reported for drugs belonging to the "nervous system" drug group, similar to our findings in FAERS [73]. Vaccines (ATC: J07) were most commonly reported in EudraVigilance, but rarely in FAERS data, as vaccine-related reports are primarily submitted to the Vaccine Adverse Event Reporting System (VAERS) in the USA. Findings from spontaneous reporting systems do not necessarily reflect findings from research focused on active identification of MEs [106,107], which emphasizes the underreporting problem and thus the lack of a complete overview of MEs within a database with spontaneous reports on ADRs. The most frequently reported MEs by Carnovale *et al.* and Newbould *et al.* correspond with our findings, although the exact frequencies or proportions were not provided in the paper of Carnovale *et al.* [73,74].

Not all of the most frequent and strongest SDRs observed in this study could be confirmed by literature. For instance, there is no focused literature on the association between adapalene use and the risk or causes of MEs. While there are studies published on adapalene adherence, there is no information regarding MEs [108,109]. Narratives of received ICSRs, provided by the FDA, show how patients have overdosed on over-the-counter (OTC) adapalene, without providing further background information on what was the root-cause of overdosing.

For the drug pegfilgrastim, MEs were mostly related to issues with (handling of) the device. Previous studies reported failure rates between 1.3% and 6.9%, in particular for the on-body injector formulation [110–114]. However, it is unclear whether this represents MEs or product quality issues. Received narratives from the FDA show a variety of circumstances under

which pegfilgrastim-related MEs occurred, emphasizing the necessary caution when dealing with such drugs, especially in complex healthcare settings.

For triprolidine, which had the strongest SDR (but with low number of reports), there was no literature confirming this association. Limited literature was available on the second strongest SDR forthcoming from sodium hypochlorite in relation to MEs [115–118]. Albiglutide was overall found to be a relatively frequent and strong signal in terms of narrow PTs within FAERS, however, scientific literature on albiglutide was limited [119], and the drug has been discontinued for commercial grounds since 2018 [120]. The inhalation medication salbutamol produced a strong SDR, backed with a high frequency of ME occurrence. It is a commonly used drug among patients with a respiratory disease and it is known that MEs occur frequently among patients using inhaler devices, while sometimes HCPs can be also at fault for inhaler related MEs [121–124].

Strengths and limitations

As for all observational studies, our study has strengths and limitations. Despite the increased reporting of MEs over time, findings in literature suggest that barriers remain in healthcare practices for reporting MEs which lead to (i) underreporting as well as selective reporting [125,126]. It is already known that FAERS in general has an underreporting problem similar to all other spontaneous reporting systems [127]. (ii) Vaccine-related-ADRs are not included in the database (as these are not part of FAERS) and unmapped RxNorm names could not be included in the disproportionality analysis, which might bias the results and also make the results less comparable with findings from other spontaneous reporting systems [73,74]. (iii) MedDRA® PTs are by itself debatable in the sense that some describe similar concepts or seem generally too vague to interpret. On top of that, MedDRA® PTs might not have been properly chosen for ICSRs which indeed has already been described in practice [128]. (iv) Despite all efforts of the code-developers for the deduplication of the FAERS data, there might be some duplicate cases present in the data. (v) Missing data in FAERS limits the interpretability of some results and might prohibit stratified analyses. (vi) Finally, the disproportionality analysis only emphasizes the disproportionality of a given DME rather than true causality. Further causality analysis is necessary for an in depth interpretation of a SDR. The strengths of our study are that we provided details on ICSRs for MEs in terms of patient characteristics, health outcomes, and reporter details. Also, this study provides more information on unreported data within the ME population which is important to consider when conducting subsequent research on MEs. Finally, this study contributes to the body of knowledge on reported MEs, providing insights on which MEs were commonly reported and what future focus areas should be for prevention of MEs.

CONCLUSION

This study offers a first of its kind characterization of MEs as reported to FAERS. MEs were increasingly being reported, mostly by consumers. Most reported MEs were associated with adults and females. About 1 out of 3 of the reported MEs resulted in a serious health outcome. A wide variety of DMEs were found, some not or rarely reported in literature, most often involving parenteral drugs. This FAERS data provides insights on ME prevention and offers possibilities for additional in-depth analyses.

DECLARATIONS

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Conflict of interest statement

The research group from the Department of Medical Informatics receives/received unconditional research grants from Chiesi, GlaxoSmithKline (GSK), UCB, and Amgen, Johnson and Johnson, and the European Medicines Agency, none of which relate to the content of this manuscript. Outside this submitted work, the institution of LL received fees for lectures (IPSA vzw) and external expert consultation (AstraZeneca).

SUPPLEMENTARY MATERIAL

Table S1. Preferred Terms from the narrow standardised Medical Dictionary for Regulatory Activities® Query for medication errors, version 23.1, September 2020.

Preferred Term	Code
Accidental device ingestion	10072950
Accidental device ingestion by a child	10072951
Accidental exposure to product	10073317
Accidental exposure to product by child	10073318
Accidental exposure to product packaging	10077659
Accidental exposure to product packaging by child	10077660
Accidental overdose	10000381
Accidental poisoning	10000383
Accidental underdose	10074904
Accidental use of placebo	10073758
Booster dose missed	10073205
Circumstance or information capable of leading to device use error	10074266
Circumstance or information capable of leading to medication error	10064385
Contraindicated device used	10077678
Contraindicated product administered	10078504
Contraindicated product prescribed	10081744
Deprescribing error	10081029
Device dispensing error	10080357
Device monitoring procedure not performed	10077720
Device programming error	10080718
Device use confusion	10083151
Device use error	10072878
Discontinued product administered	10078505
Documented hypersensitivity to administered product	10076470
Dose calculation error	10076874
Drug administered in wrong device	10070470
Drug dispensed to wrong patient	10065634
Drug dose omission by device	10080648
Drug dose titration not performed	10074906
Drug monitoring procedure incorrectly performed	10075461
Drug monitoring procedure not performed	10075462
Drug titration error	10074853
Duplicate therapy error	10080422
Expired device used	10073594
Expired product administered	10074902
Exposure via direct contact	10071411
Exposure via eye contact	10073336

Table S1. Preferred Terms from the narrow standardised Medical Dictionary for Regulatory Activities® Query for medication errors, version 23.1, September 2020. (*continued*)

Preferred Term	Code
Exposure via skin contact	10071430
Extra dose administered	10064366
Failure of child resistant product closure	10084008
Failure to suspend medication	10080933
Inadequate aseptic technique in use of product	10072608
Inappropriate schedule of product administration	10081572
Incomplete course of vaccination	10072103
Incorrect disposal of product	10078390
Incorrect dosage administered	10073768
Incorrect dose administered	10064355
Incorrect dose administered by device	10068945
Incorrect dose administered by product	10080804
Incorrect drug administration rate	10064306
Incorrect product administration duration	10081581
Incorrect product dosage form administered	10081574
Incorrect product formulation administered	10074946
Incorrect route of product administration	10081202
Intercepted accidental exposure to product by child	10079333
Intercepted medication error	10064382
Intercepted product administration error	10081573
Intercepted product dispensing error	10081742
Intercepted product monitoring error	10079334
Intercepted product preparation error	10079213
Intercepted product prescribing error	10081743
Intercepted product selection error	10076544
Intercepted product storage error	10079212
Intercepted wrong patient selected	10065645
Labelled drug-disease interaction medication error	10064381
Labelled drug-drug interaction medication error	10064373
Labelled drug-food interaction medication error	10064374
Lack of administration site rotation	10076087
Lack of application site rotation	10076088
Lack of infusion site rotation	10076089
Lack of injection site rotation	10073752
Lack of vaccination site rotation	10076090
Medical device monitoring error	10077672
Medication error	10027091
Multiple use of single-use product	10072342
Out of specification product use	10083420

Table S1. Preferred Terms from the narrow standardised Medical Dictionary for Regulatory Activities® Query for medication errors, version 23.1, September 2020. (*continued*)

Preferred Term	Code
Paravenous drug administration	10075353
Product administered at inappropriate site	10080753
Product administered by wrong person	10084371
Product administered to patient of inappropriate age	10081578
Product administration error	10081576
Product appearance confusion	10080000
Product barcode issue	10069269
Product confusion	10082712
Product design confusion	10080827
Product dispensing error	10080359
Product dosage form confusion	10071587
Product dose omission in error	10084404
Product label confusion	10069273
Product monitoring error	10081575
Product name confusion	10069332
Product packaging confusion	10074776
Product preparation error	10076869
Product prescribing error	10081770
Product selection error	10076542
Product storage error	10079843
Product substitution error	10078984
Recalled product administered	10081540
Single component of a two-component product administered	10080977
Therapeutic drug monitoring analysis incorrectly performed	10073703
Therapeutic drug monitoring analysis not performed	10073702
Transcription medication error	10076245
Transfusion with incompatible blood	10044360
Unintentional use for unapproved indication	10076589
Vaccination error	10063972
Wrong device used	10070468
Wrong dosage form	10080302
Wrong dosage formulation	10080975
Wrong dose	10080304
Wrong drug	10080306
Wrong patient	10084399
Wrong patient received product	10081577
Wrong product administered	10081579
Wrong product procured	10080974
Wrong product stored	10080001

Table S1. Preferred Terms from the narrow standardised Medical Dictionary for Regulatory Activities® Query for medication errors, version 23.1, September 2020. (*continued*)

Preferred Term	Code
Wrong rate	10080934
Wrong route	10084398
Wrong schedule	10080303
Wrong strength	10080305
Wrong technique in device usage process	10077040
Wrong technique in product usage process	10076573

Table S2. Top 10 strongest signals of disproportionate reporting, **among men**.

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
A10BJ04	Albiglutide; parenteral	3,317	46.19	44.18 - 48.29
N02CD01	Erenumab; parenteral	1,842	27.14	25.70 - 28.66
V04CX07	Edrophonium	3	24.71	6.55 - 93.13
C01BD05	Ibutilide; parenteral	4	16.47	5.51 - 49.27
A02BA53	Famotidine, combinations	94	16.22	12.94 - 20.33
R03AC02	Salbutamol; inhalant	5,580	15.19	14.74 - 15.64
L03AA13	Pegfilgrastim; parenteral	3,990	14.97	14.46 - 15.50
G04BE01	Alprostadil; parenteral, urethral	83	12.61	9.97 - 15.94
D10AF02	Erythromycin; topical	4	12.55	4.31 - 36.56
V04CC03	Sincalide	8	12.55	5.89 - 26.73

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

Table S3. Top 10 strongest signals of disproportionate reporting, **among women**.

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
R06AX07	Triprolidine; oral	3	50.3	11.26 - 224.76
A10BJ04	Albiglutide; parenteral	4,445	40.72	39.23 - 42.27
R03BA09	Fluticasone furoate; inhalant	6	23.67	9.33 - 60.04
N02CD01	Erenumab; parenteral	9,076	18.7	18.26 - 19.14
R03AC02	Salbutamol; inhalant	10,920	16.62	16.27 - 16.98
L01DB09	Valrubicin	21	15.48	9.63 - 24.88
J01AA15	Omadacycline; oral	36	14.55	10.15 - 20.86
L03AA13	Pegfilgrastim; parenteral	8,588	14.54	14.20 - 14.89
R01BA52 & R06AA52	Pseudoephedrine with diphenhydramine; oral	3	13.41	3.88 - 46.34
D01AE18	Tolnaftate; topical	6	12.98	5.42 - 31.12

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

Table S4. Top 10 strongest signals of disproportionate reporting **among children aged ≤ 27 days**.

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
N06BC01	Caffeine; systemic	7	109.22	38.27 - 311.75
N01BB52	Lidocaine, combinations	3	46.7	12.06 - 180.74
R06AD02	Promethazine; systemic, rectal	19	45.44	26.57 - 77.72
J01CE01	Benzylpenicillin; parenteral	7	38.23	16.14 - 90.52
G04BE01	Alprostadil; parenteral, urethral	3	36.32	9.82 - 134.27
R05CA03	Guaifenesin; systemic	3	36.32	9.82 - 134.27
G02AB01	Methylergometrine; systemic	13	35.62	19.02 - 66.73
A10BB07	Glipizide; oral	8	29.14	13.34 - 63.66
A12AA03	Calcium gluconate; systemic	4	29.07	9.64 - 87.69
A12AA07	Calcium chloride; parenteral	7	20.66	9.20 - 46.41

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

Table S5. Top 10 strongest signals of disproportionate reporting**, among children aged 28 days – 23 months.**

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
J01DH03	Ertapenem; parenteral	4	101.64	11.36 - 909.67
A07DA53	Loperamide, combinations; oral	3	76.21	7.92 - 732.84
J02AB02	Ketoconazole; oral	3	76.21	7.92 - 732.84
N02CC02	Naratriptan; oral	3	76.21	7.92 - 732.84
A02BA53	Famotidine, combinations	15	29.42	13.99 - 61.89
G04BD04	Oxybutynin; oral, transdermal	3	25.4	5.12 - 125.91
C09CA04	Irbesartan; oral	8	22.61	8.72 - 58.65
L01BC06	Capecitabine	7	19.78	7.36 - 53.15
R06AX13	Loratadine; oral	129	17.22	13.75 - 21.56
R05CA03	Guaifenesin; systemic	8	14.54	6.09 - 34.68

ATC - Anatomical Therapeutic Chemical classification; CI - confidence interval; ROR - Reporting odds ratio.

Table S6. Top 10 strongest signals of disproportionate reporting, **among children aged 2-11 years.**

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
C03CA04	Torasemide; systemic	3	101.24	10.53 - 973.35
J05AP05	Simeprevir; oral	3	50.62	8.46 - 302.97
A02BA53	Famotidine, combinations	65	34.42	24.36 - 48.63
A01AA04	Stannous fluoride; oral	4	27	7.25 - 100.55
N02AX06	Tapentadol; oral	18	26.44	14.26 - 49.00
C02KX05	Riociguat; oral	3	25.31	5.66 - 113.10
C09CA07	Telmisartan; oral	4	22.5	6.35 - 79.74
N06AX24	Vilazodone	9	20.26	8.86 - 46.29

Table S6. Top 10 strongest signals of disproportionate reporting, **among children aged 2-11 years.** (*continued*)

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
G03AD01	Levonorgestrel; oral	3	20.25	4.84 - 84.73
N07BC01	Buprenorphine; sublingual	3	20.25	4.84 - 84.73

ATC - Anatomical Therapeutic Chemical classification; CI - confidence interval; ROR - reporting odds ratio.

Table S7. Top 10 strongest signals of disproportionate reporting, **among children aged 12-17 years**.

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
G02AD02	Dinoprostone; oral, vaginal	3	154.93	16.11 - 1489.61
C02DB02	Hydralazine; oral	3	77.47	12.94 - 463.66
C01DA14	Isosorbide mononitrate; oral	5	51.65	14.95 - 178.45
J01AA15	Omadacycline; oral	3	25.82	6.46 - 103.26
N02CD01	Erenumab; parenteral	62	18.5	13.83 - 24.73
C01CA03	Norepinephrine; parenteral	7	15.72	6.75 - 36.65
A10BB07	Glipizide; oral	7	14.46	6.26 - 33.45
A07DA53	Loperamide, combinations; oral	5	13.59	5.07 - 36.41
N02AA59 & R06AD52	Codeine with promethazine	3	11.07	3.18 - 38.51
C10AX13	Evolocumab; parenteral	7	10.96	4.85 - 24.78

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

Table S8. Top 10 strongest signals of disproportionate reporting, **among people aged 18-64 years.**

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
A10BJ04	Albiglutide; parenteral	3,166	50.28	48.11 - 52.56
V04CX07	Edrophonium	3	24.81	6.83 - 90.16
N02CD01	Erenumab; parenteral	7,893	24.5	23.88 - 25.13
C01BD05	Ibutilide; parenteral	4	23.63	7.78 - 71.80
J01AA15	Omadacycline; oral	38	21.24	14.87 - 30.34
L03AA13	Pegfilgrastim; parenteral	5,232	17.86	17.33 - 18.40
V04CC03	Sincalide	24	16.14	10.42 - 25.00
L01DB09	Valrubicin	7	15.24	6.80 - 34.12
A06AD15	Macrogol; oral	1,815	11.49	10.94 - 12.07
G04BE01	Alprostadil; parenteral, urethral	10	11.03	5.70 - 21.33

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

Table S9. Top 10 strongest signals of disproportionate reporting, **among people aged ≥ 65 years.**

ATC level 5 code	Generic drug name; route of administration	Count	ROR	95% CI
B05XA17	Potassium acetate; parenteral	3	34.65	8.66 - 138.53
A10BJ04	Albiglutide; parenteral	888	33.51	30.93 - 36.31
N02CD01	Erenumab; parenteral	1,611	24.8	23.42 - 26.26
L03AA13	Pegfilgrastim; parenteral	4,155	17.33	16.74 - 17.93
G04BE01	Alprostadil; parenteral, urethral	30	13.95	9.43 - 20.66
J07BK02	Zoster, live attenuated; systemic	5	13.86	5.31 - 36.20
D10AF01	Clindamycin; topical	3	13.86	4.01 - 47.87
S01AA27	Cefuroxime; ophthalmic	53	13.36	9.96 - 17.93
J01AA15	Omadacycline; oral	16	13.36	7.82 - 22.81
R01AX10	Various; inhalant, nasal	12	12.23	6.62 - 22.59

ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

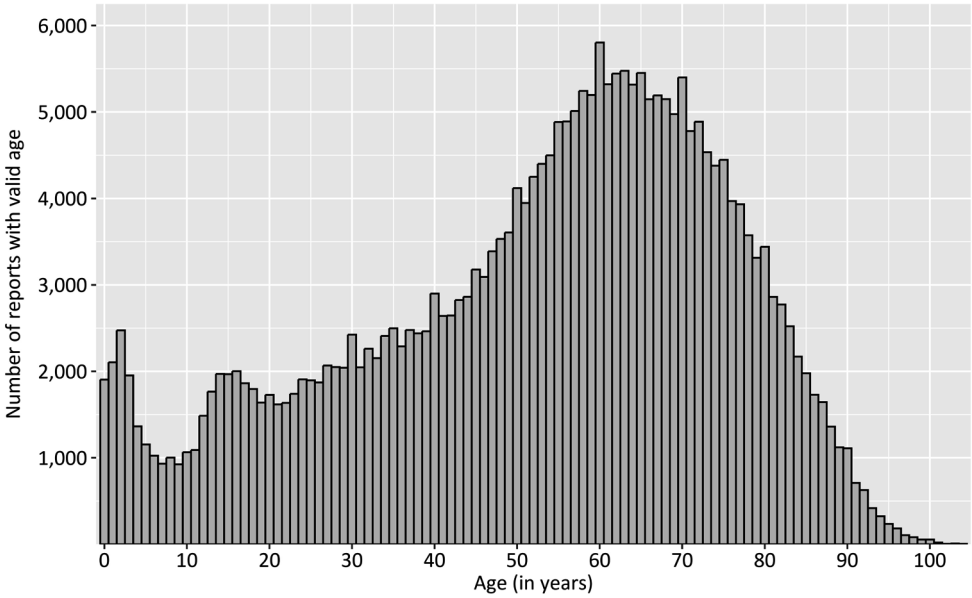

Figure S1. Age distribution of reported age for 272,655 medication error reports.

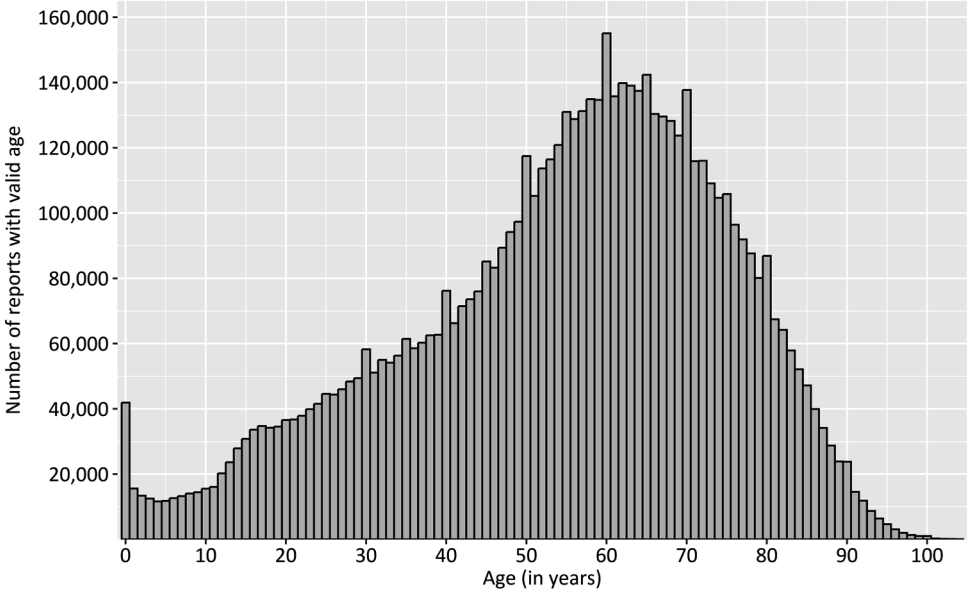

Figure S2. Age distribution of reported age for 6,473,930 reports from the entire spontaneous reporting database from the Food and Drug Administration.

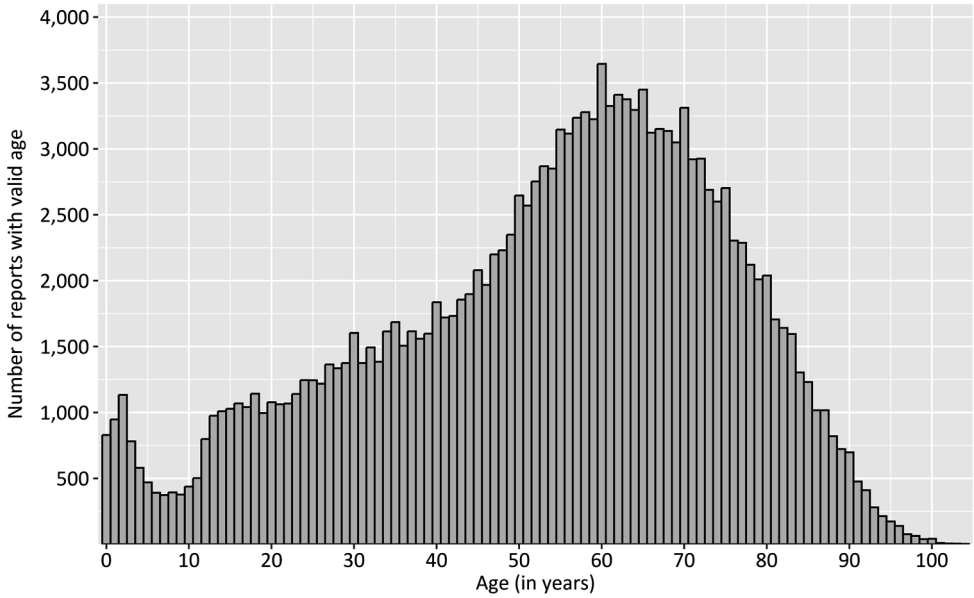

Figure S3. Age distribution of reported age **among females** for 166,978 medication error reports.



Figure S4. Age distribution of reported age **among females** for 3,881,075 reports from the entire spontaneous reporting database from the Food and Drug Administration.

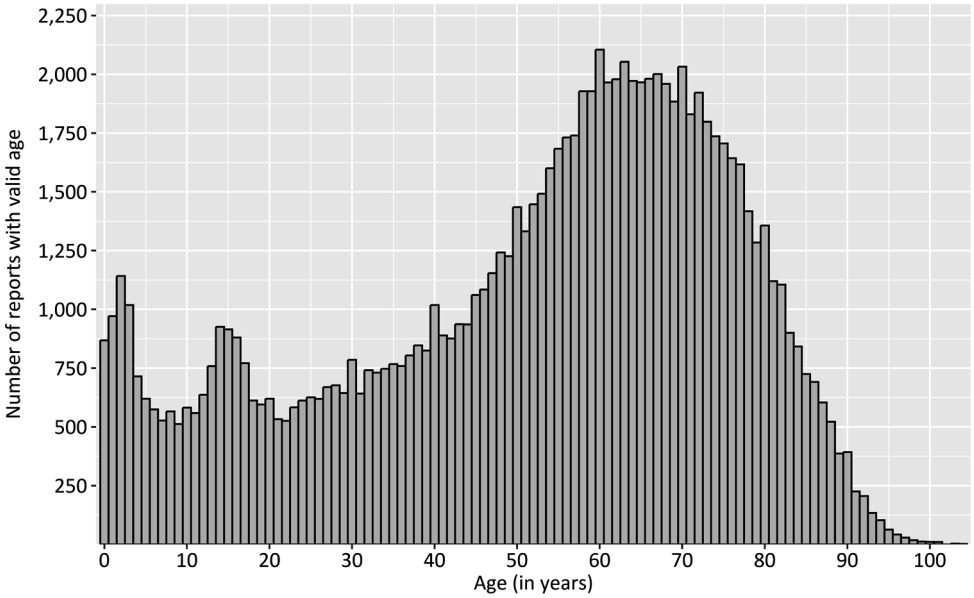

Figure S5. Age distribution of reported age **among males** for 101,606 medication error reports.

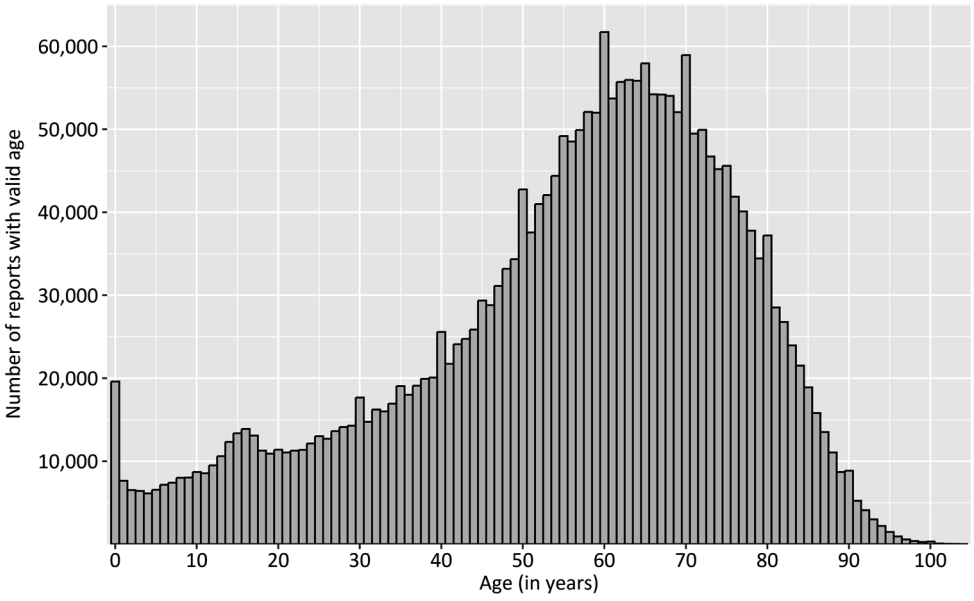

Figure S6. Age distribution of reported age **among males** for 2,475,608 reports from the entire spontaneous reporting database from the Food and Drug Administration.

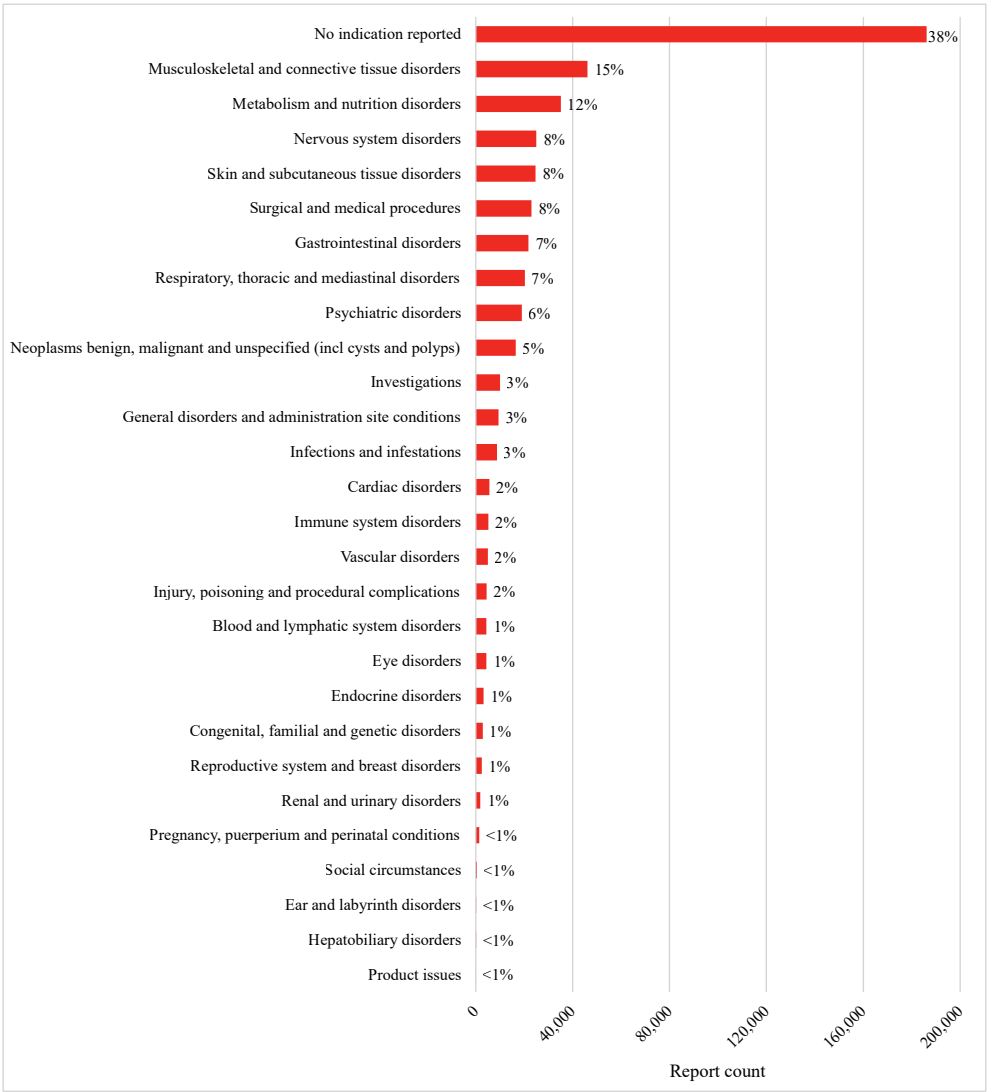

Figure S7. Graphical representation of indications reported for the primary drug suspect within the retrieved medication error reports, grouped by MedDRA® System Organ Classes. MedDRA® - Medical Dictionary for Regulatory Activities.



Chapter 4

Disproportionality Analysis and Characterization of Medication Errors in EudraVigilance: Exploring Findings on Sexes and Age Groups

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ABSTRACT

Background

While medication errors (MEs) have been studied in the European Medicines Agency's (EMA) EudraVigilance, extensive characterization and signal detection based on sexes and age groups have not been attempted.

Objectives

The aim of this study was to characterize all ME-related individual case safety reports (ICSRs) in EudraVigilance and explore notable signals of disproportionate reporting (SDRs) among sexes and age groups for the 30 most frequently reported drugs.

Methods

ICSRs were used from EudraVigilance reported between 2002-2021. An ME was defined as any preferred term from the narrow Standardised Medical Dictionary for Regulatory Activities® (MedDRA®) Query (SMQ). SDRs were selected based on a lower boundary of the 95% confidence interval (CI) ≥ 1 of the reporting odds ratio (ROR), and at least 3 ICSRs. Analyzed subgroups were females, males, and age groups 0-1 month, 2 months-2 years, 3-11 years, 12-17 years, 18-64 years, 65-85 years, and ≥86 years. Heatmaps were utilized as a visual aid to identify striking SDRs.

Results

Of the 9,662,345 EudraVigilance reports, 267,262 (2.8%) contained at least one ME, with a total of 300,324 MEs, for 429,554 drugs. The most reported ME was "Inappropriate schedule of product administration" (52,646; 17.5%), followed by "Incorrect dose administered" (32,379; 10.8%), and "Wrong technique in product usage process" (26,831; 8.9%). ICSRs with MEs were most frequently related to females (148,009; 55.4%), most often submitted by healthcare professionals (155,711; 58.3%), originated predominantly from the United States of America (98,716; 36.9%), followed by France (26,678; 10.0%), and showed a median reported age of 50 years (interquartile range: 26-68). Most ME ICSRs (158,991; 59.5%) were associated with a serious health outcome. A total of 847 SDRs were identified, based on the entire EudraVigilance database; for subgroups, the number of SDRs ranged from 84 for the age group 0-1 month to 749 for females. SDRs for females and males were very similar. Most MEs were reported for the vaccine against human papillomavirus (ATC: J07BM01; 11,086 MEs, 57% being "inappropriate schedule of product administration"), with RORs ranging from 1.5-47.0 among age groups. The SDR for the live-attenuated vaccine against Herpes Zoster (ATC: J07BK02) had an ROR ranging from 26.6-78.1 among all subgroups. SDRs for oxycodone (ATC: N02AA05; 847 cases of "Accidental overdose", 35%), risperidone (ATC: N05AX08; 469 cases "Inappropriate schedule of product administration", 22.3%), and rivaroxaban (ATC: B01AF01; 1,377 cases of "Incorrect dose administered", 34.6%) stood out with higher magnitude SDRs for the age group 2 months – 2 years, with

an ROR ranging between 8.2-10.7, while for the entire EudraVigilance the ROR ranged between 1.3-1.6 for the same drugs.

Conclusion

This exploratory research provides an overview of characterized ME ICSRs and SDRs from the EudraVigilance database. Most conspicuous SDRs were identified in specific age groups. SDRs, not described in the literature, were found for vaccines, oxycodone, rivaroxaban, and risperidone, and may prompt further examination by stakeholders. Top-reported MEs ("Inappropriate schedule of product administration", "Incorrect dose administered", and "Wrong technique in product usage process") emerged as a general priority focus to perform further root-cause analysis involving healthcare providers, manufacturers, and regulatory bodies, to improve understanding and prevention of MEs.

INTRODUCTION

A medication error (ME) is defined by the European Medicines Agency (EMA) as "an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient" [1]. Previous research showed that MEs are increasingly reported over time [64,73]. Increased reporting may be, not exclusively, attributed to the extended definition of adverse drug reactions (ADRs) introduced in European pharmacovigilance legislation in 2012 [129]. Despite known risk factors [4] and many preventative recommendations and guidelines [130–132], MEs persist worldwide up to this day [133–136].

While some MEs are harmless, other MEs may cause fatal outcomes such as death among various patient populations. It has been previously reported that 37% of individual case safety reports (ICSRs) on MEs were co-reported with a serious health outcome, of which 4% were co-reported with death [64]. A study from the United States of America (USA) found that in an outpatient setting, 15 ME-related adverse drug events (ADEs) per 1,000 person years were preventable [137].

Besides health implications, MEs also impose a financial burden. For example, studies reported that the cost of an ME can be as low as €2.58 in Iraq, in case of an invalid immunization dose for a child [138], or as high as €6,432 for in-hospital preventable ADEs in the Netherlands [139].

The prevalence of MEs in community settings ranged from 2% up to 94% [4]. This wide prevalence range is due to (i) variability in the studied types of MEs, (ii) different ME definitions, (iii) specific selection of study population, (iv) varied study settings, and (v) use of various ME detection tools, while there is no established gold standard [4]. A meta-analysis on ME prevalence among paediatric inpatients reported that MEs occurred at a rate between 45 and 167 per 1,000 patient days [140]. That same research found that prescribing errors were the most frequent of all studied MEs, with proportions between 4.1 and 58.1 per 100 orders [140]. Numerous factors contribute to MEs in the peadiatric population such as errors in dose calculations based on age or body weight, lack of dosing information specifically for children, lack of the appropriate formulations, or the inevitable use of off-label products [141].

Previous efforts have been made to characterize MEs from ICSRs submitted to EMA's EudraVigilance database including data up to the year 2015 [73]. However, there was no data published on other subjects of interest, such as patient characteristics, seriousness of ME ICSRs, and signals of disproportionate reporting (SDRs), especially among subgroups based on sex and age. In the context of this exploratory study, it was of interest to observe whether conspicuous findings would emerge when performing analyses on subgroups based on sex and age. Recently, we described ME characteristics and SDRs using data

from the Food and Drug Administrations (FDA) Adverse Event Reporting System (FAERS) for MEs submitted up to the year 2020 [64]. However, the ME-related FAERS data mostly (79%) consists of reports from the USA [64], while EMA's EudraVigilance has a higher representation for MEs reported from the European continent (29%) [73]. Exploring MEs in EudraVigilance will contribute to a broader perspective on MEs reported worldwide in addition to previously performed research. The objective of the current research was to provide an up-to-date characterization of MEs reported in EudraVigilance and explore notable SDRs when performing subgroup analyses based on sex and age groups.

METHODS

EudraVigilance and data access

The data source for this research was EMA's EudraVigilance database, which is a database that contains information from submitted ICSRs on ADRs, ADEs, and MEs from sponsors of clinical trials, marketing authorization holders, and national competent authorities in the European Economic Area (EEA) and beyond [73,142,143]. Different stakeholders, including regulatory authorities, academia, healthcare professionals (HCPs), and patients, can request data access to EudraVigilance according to EMA's access policy [144] or view the (limited) data which is publicly available [145]. The required data to perform analyses was supplied for ICSRs submitted to EudraVigilance from the 1st of January 2002 up to 31st of December 2021. Only drugs which were marked by the EMA as "Suspect" (the main drug suspected to be associated with the reported events) for the reported Preferred Term (PT) within the ICSRs were provided. The Medical Dictionary for Regulatory Activities® (MedDRA®) is used as a standardised medical terminology for the registration of a wide variety of events, including MEs, described in ICSRs.

Medication errors

An ME was defined as a MedDRA® PT represented under the narrow Standardised MedDRA® Query (SMQ) for MEs, under MedDRA® version 24.1, published in September 2021. The narrow SMQ facilitates obtaining cases that are highly likely to represent MEs, focusing on specificity, which is in contrast with the broad SMQ that yields results with a higher sensitivity [146].

Data processing and analysis

An overview of the data processing and analysis is displayed in Figure 1. The data was imported in a PostgreSQL database running on version 16.1. Aioli [81] is an extension of the Adverse Event Open Learning through Universal Standardization (AEOLUS) system [55], which was developed to standardize data from the FDA Adverse Event Reporting System, but did not map drug names to Anatomical Therapeutical Chemical (ATC) classification system [147] codes. If for a given drug multiple ATC codes were available for different

therapeutic use, the Aioli system determined the best fit using available information on drug strength and route of administration. If there was not sufficient information to distinguish between multiple ATC codes, or if no ATC code existed for the given substance, no ATC code was assigned.

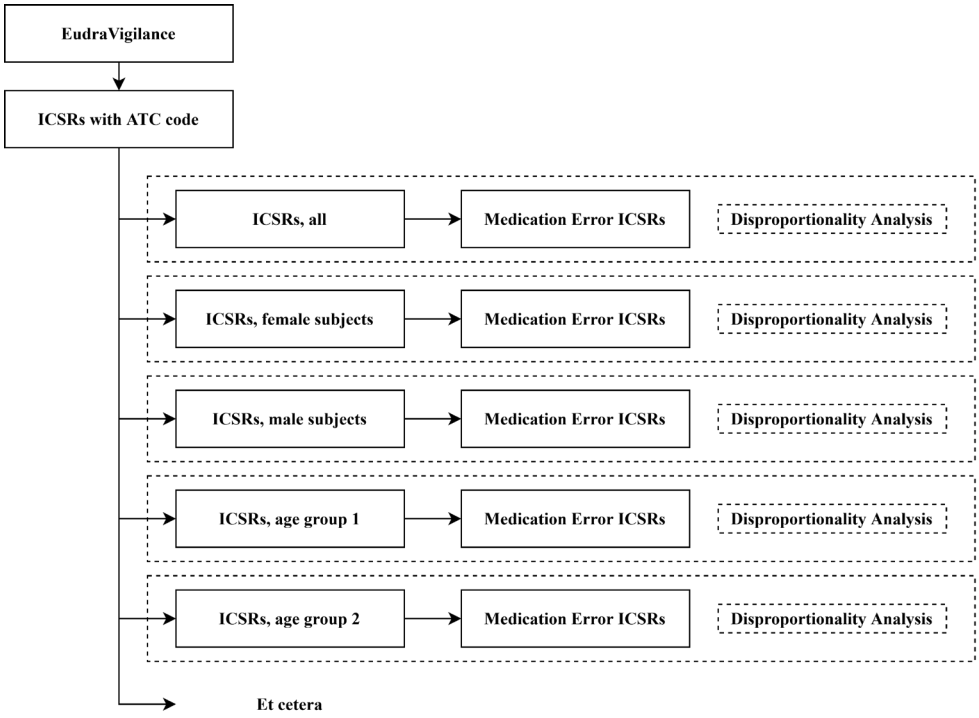

Figure 1. Methodological overview on the selection of ICSRs for analysis, including examples of analysis based on sexes and age groups. ICSR - Individual case safety report; ATC - Anatomical Therapeutic Chemical classification.

SDRs were calculated with adapted SQL scripts from the AEOLUS system [55,80]. SDRs were expressed by calculating the Reporting Odds Ratio (ROR) with a 95% confidence interval (95% CI). The following counts of drug-event combinations were used as input for the disproportionality analysis: A) drug of interest - ME, B) drug of interest - other event, C) other drugs - ME, and D) other drugs - other events (Table 1).

Table 1. Overview of report counts based on various drug-event combinations expressed by the letters A, B, C, and D.

	Any PT from narrow ME SMQ	**Other events**
A drug of interest	A	B
All other drugs	C	D

ME - Medication Error; MedDRA® - Medical Dictionary for Regulatory Activities®; PT - Preferred Term; SMQ - Standardised MedDRA® Query.

From every unique ICSR, each registered PT from the narrow ME SMQ contributes to the ME counts as seen for counts A and C. The ROR and 95% CI were then calculated as follows:

$$ROR = \frac{A/C}{B/D} \quad (1)$$

$$95\%\ CI = e^{ln(ROR) \pm 1.96 \sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}} \quad (2)$$

A signal was regarded as disproportionate if the case count was at least 3 and the lower boundary of the 95% CI was greater than 1, as stated by the EMA [85].

Multiple reporters and reporter countries may have been noted under a unique ICSR if the same case was reported by multiple reporters from possibly different countries. For the descriptive statistics on reporters and corresponding reporting country, the column "Primary Source for Regulatory Purposes" (column code: C.2.r.5) [148] was used to prevent a unique ICSR contributing multiple times.

Seriousness of health outcomes in ICSRs with MEs

The seriousness was described in the REACTION table provided by the EMA, by separate columns for "Death" (column code: E.i.3.2a), "Life threatening" (column code: E.i.3.2b), "Caused or prolonged hospitalisation" (column code: E.i.3.2c), "Disabling / Incapacitating" (column code: E.i.3.2d), "Congenital Anomaly / Birth Defect" (column code: E.i.3.2e), and "Other medically important condition" (column code: E.i.3.2f). The last category is defined as "other situations that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed [e.g. "Death", "Life threatening", etc.] [149]. Multiple columns for the seriousness may have been marked in an ICSR.

Processing and displaying of signals of disproportionate reporting

Due to a large output of results, SDRs were selected and displayed in the following way. A selection was made of 30 SDRs based on the most frequently reported drugs with co-occurring MEs within the entire EudraVigilance database. These SDRs were sorted based on descending RORs. If the criteria were met (case count at least 3 and lower boundary 95% CI greater than 1), corresponding SDRs for females, males, and age groups 0-1 month, 2 months-2 years, 3-11 years, 12-17 years, 18-64 years, 65-84 years, and ≥85 years, were displayed right next to the SDRs based on the total population.

The final results for SDRs and counts for various types of MEs are displayed in heatmaps. While heatmaps are mostly popular in the field of biology for displaying high-throughput data [150], they have also been shown to be useful for visualization of disproportionality results [151]. The heatmaps represent values of interest (i.e. RORs and case counts) for the selected SDRs as previously described. Shades of colors, ranging from white to red, represented values in which the brightest red cells represent the highest value, while lighter shades of yellow and white represent lower values. Interactive heatmaps with additional data are also provided online as supplementary material. Heatmaps were made with the R package heatmaply, version 1.4.2 [152].

Alternatively, top 10 findings for the entire database, not restricted to EMA's case count or ROR criteria, were displayed by ordering based on A) the most frequently reported drugs in association with MEs, and B) the drugs with the highest lower boundary 95% CI of the ROR, accompanied by the top 3 MEs for each drug.

RESULTS

General findings on medication error ICSRs

Of the total of 9,662,345 ICSRs as provided by the EMA, there were 267,262 (2.8%) ICSRs containing information on at least 1 narrow ME, with a total of 300,324 reported MEs. The yearly proportion of ICSRs on MEs has been steadily increasing since 2004 (274 ICSRs; 1.1%) up to 2020 (27,549 ICSRs; 3.7%) as displayed in Figure 2. In 2021 the number of ME-related ICSRs submitted to EudraVigilance (48,958 ICSRs) had almost doubled compared to 2020.

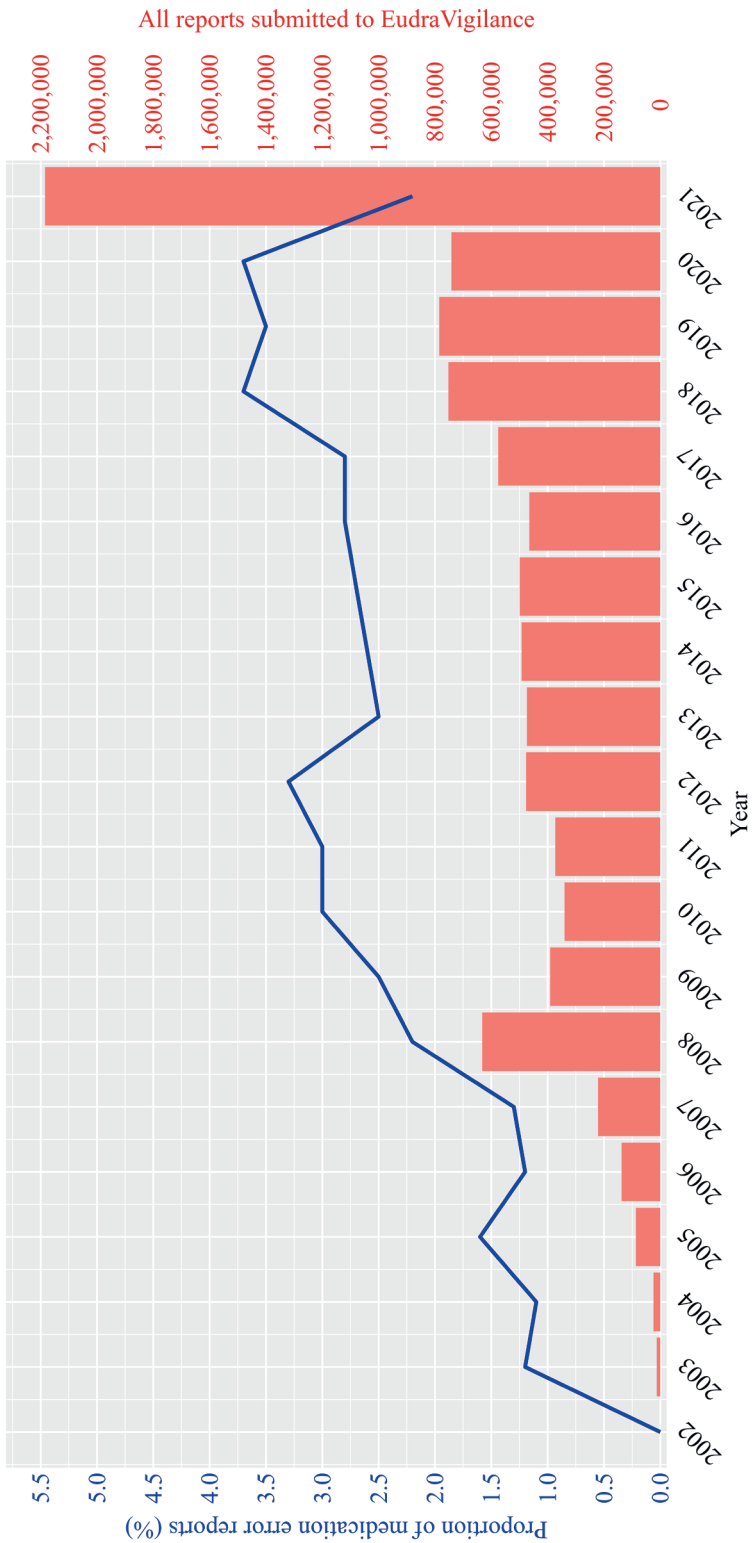

Figure 2. Overview of all reports submitted to EudraVigilance (represented by the red bar chart, number of reports on the right Y-axis) and the proportion of reports submitted mentioning a medication error (represented by the blue line chart, proportions noted on the left Y-axis).

An overview of the most frequently reported MEs is displayed in Table 2. The five most frequently reported PTs for ME account for more than half of all MEs, being "Inappropriate schedule of product administration" (52,646; 17.5%), "Incorrect dose administered" (32,379; 10.8%), "Wrong technique in product usage process" (26,831; 8.9%), "Medication error" (21,394; 7.1%), and "Product administration error" (16,538; 5.5%). Characteristics were separately provided for ICSRs noting "Inappropriate schedule of product administration" and "Incorrect dose administered" in supplementary Tables S1-S3.

Table 2. An overview of the 15 most frequently reported medication errors in the EudraVigilance database.

	Occurrence (%)
Total amount of reported medication errors	**300,324 (100%)**
Inappropriate schedule of product administration	52,646 (17.5%)
Incorrect dose administered	32,379 (10.8%)
Wrong technique in product usage process	26,831 (8.9%)
Medication error	21,394 (7.1%)
Product administration error	16,538 (5.5%)
Accidental overdose	15,011 (5%)
Incorrect route of product administration	14,017 (4.7%)
Incorrect product administration duration	10,733 (3.6%)
Product storage error	10,197 (3.4%)
Expired product administered	9,137 (3%)
Accidental exposure to product	8,452 (2.8%)
Product prescribing error	8,208 (2.7%)
Contraindicated product administered	8,059 (2.7%)
Wrong product administered	7,114 (2.4%)
Product dispensing error	6,066 (2%)

The highest proportion of MEs was found in the age group 2 months – 2 years (12,694 ME ICSRs; 6.1% of 208,763 group total ICSRs), while the lowest proportion of MEs were found in the age group 18-64 years (94,979 ME ICSRs; 2.2% of 4,355,919 group total ICSRs), as seen in Table 3. The majority of ME-related ICSRs (215,133 ICSRs; 80.5%) had one drug marked as the main "suspect" within the corresponding ICSR (Table 3). The total amount of suspect drugs for MEs was 429,554, of which 353,852 (82.4%) could be mapped to an ATC code. A list of unmapped drugs within the entire EudraVigilance database is provided in supplementary Table S4.

Table 3. Count overview of suspect drugs reported in reports on medication errors.

Analyzed group	ICSRs on MEs / Total (Proportion)
Entire EudraVigilance	267,262 / 9,662,345 (2.8%)
Female	148,009 / 5,416,701 (2.7%)
Male	94,436 / 3,649,560 (2.6%)
0-1 month	1,766 / 35,532 (5.0%)
2 months - 2 years	12,694 / 208,763 (6.1%)
3-11 years	10,254 / 192,970 (5.3%)
12-17 years	7,929 / 199,299 (4.0%)
18-64 years	94,979 / 4,355,919 (2.2%)
65-85 years	50,441 / 2,075,852 (2.4%)
Above 85 years	8,891 / 292,903 (3.0%)
ICSRs on MEs	267,262 (100%)
Suspect drugs per report, n (%)	
1	215,133 (80.5%)
2	30,145 (11.3%)
3	8,468 (3.2%)
4	3,588 (1.3%)
5 or more	9,912 (3.7%)
Suspect drugs found, n (%)	**429,554 (100%)**
Suspect drugs mapped to ATC	353,852 (82.4%)

ATC - Anatomical Therapeutic Chemical classification; ICSR - Individual case safety report; ME - Medication error.

Person characteristics

The ICSRs on MEs concerned more frequently females (148,009; 55.4%) than males (94,436; 35.3%), while sex was unknown in 24,817 (9.3%) ICSRs (Table 4). The median reported age was 50 years (interquartile range: 26-68) and the age category of 18-64 years (94,979 ICSRs; 35.5%) was most frequently reported within the ICSRs on MEs (Table 4). The age category was missing in 80,308 ICSRs (30.0%).

Table 4. EudraVigilance person characteristics of medication error-related reports.

	Count (Proportion)
ICSRs on medication errors	**267,262 (100%)**
Sex	
Female	148,009 (55.4%)
Male	94,436 (35.3%)
Not reported	24,817 (9.3%)
Age category	
0-1 month	1,766 (0.7%)
2 months - 2 years	12,694 (4.7%)
3-11 years	10,254 (3.8%)
12-17 years	7,929 (3.0%)
18-64 years	94,979 (35.5%)
65-85 years	50,441 (18.9%)
Above 85 years	8,891 (3.3%)
Not reported	80,308 (30.0%)
Median age, in years (IQR)	**50 (26-68)**

ICSR - Individual case safety report; IQR - Interquartile range.

Reporter and reporter country characteristics

Most ICSRs on MEs were reported by healthcare professionals accounting for 155,711 (58.3%) ICSRs (Table 5). Also, a considerable amount of 103,128 (38.6%) ICSRs were submitted by consumers and non-HCPs. Most ICSRs (98,716; 36.9%) originated from the USA. Countries from the European Union that reported most MEs, were France (26,678 ICSRs; 10.0%), Germany (25,117 ICSRs; 9.4%), and Spain, (5,706 ICSRs; 2.1%). Many other countries from outside of Europe also submitted a considerable amount of ME ICSRs, such as the United Kingdom, Canada, Brazil, Japan, Australia, and China (Table 5).

Seriousness of reported medication errors

In 159,670 (59.7%) of the ICSRs, at least one category representing the seriousness of the reported ME was noted (Table 6). The most reported category was "Other medically important condition" for 108,557 (40.6%) ICSRs. The second most frequently reported category was "Hospitalization" in 59,993 (22.4%) ICSRs. For 107,592 (40.3%) ICSRs none of the seriousness categories were reported.

Table 5. EudraVigilance reporter and reporter country characteristics in individual case safety reports on medication errors.

Reports on medication errors	267,262 (100%)
Reporter type	**Count (Proportion)**
Consumer or other Non-Health Professional	103,128 (38.6%)
Physician	64,810 (24.2%)
Other health professional	57,325 (21.4%)
Pharmacist	33,576 (12.6%)
Lawyer	7,329 (2.7%)
Unknown	1,094 (<1%)
Reporter country	**Count (Proportion)**
United States of America	98,716 (36.9%)
France	26,678 (10%)
Germany	25,117 (9.4%)
United Kingdom of Great Britain and Northern Ireland	21,394 (8%)
Canada	16,743 (6.3%)
Brazil	9,885 (3.7%)
Japan	9,176 (3.4%)
Spain	5,706 (2.1%)
Italy	4,581 (1.7%)
Australia	4,442 (1.7%)
China	4,315 (1.6%)
Sweden	4,165 (1.6%)
Netherlands	2,747 (1%)
161 countries contributing <1%	33,597 (12.6%)

Table 6. Reported seriousness of the health outcomes for individual case safety reports including medication errors.

	Count (Proportion)
Report of serious health outcome	159,670 (100%)
Type of seriousness	
Caused or prolonged hospitalisation	59,993 (22.4%)
Death	12,245 (4.6%)
Life threatening	7,857 (2.9%)
Disabling / Incapacitating	6,090 (2.3%)
Congenital Anomaly / Birth Defect	127 (<1%)
Other medically important condition, unspecified	108,557 (40.6%)

Identified SDRs and subpopulation differences

A total of 2,221 drug-ME combinations were found, of which 847 (38.1%) met the criteria for disproportionality based on the entire EudraVigilance database (Table 7). The amount of SDRs was as low as 84 for the age group of 0-1 month and as high as 749 for females. Most MEs were reported for papillomavirus vaccine (human types 6, 11, 16, 18; ATC: J07BM01; 11,086 MEs), followed by infliximab (ATC: L04AB02; 9,236 MEs) and varicella, live attenuated (ATC: J07BK01; 5,623 MEs) as seen in Table 8. Sex-based subgroup SDRs showed minor differences between the sexes and also when compared to SDRs based on the overall EudraVigilance database, as shown in the SDR heatmap (Figure 3 and online interactive supplementary file2). When further analyzing the heatmap of SDRs, the most distinct result in terms of age was found for etonogestrel (ATC: G03AC08) which showed an ROR of 60.4 (95% CI: 14.4-252.8; 3 cases) for the age group 65-85 years. Of the total of 4,501 MEs identified for etonogestrel, the most commonly reported ME was "Incorrect product administration duration" (2,639 cases; 59%) as seen in the heatmap represented by Figure 4 (and online interactive supplementary file3).

Table 7. Amount of identified signals meeting the disproportionality criteria for the entire EudraVigilance database and groups based on sexes and age groups.

Analysed group	DMECs	SDRs meeting criteria (proportion)
Entire EudraVigilance	2,221	847 (38.1%)
Females	2,048	749 (36.6%)
Males	1,938	676 (34.9%)
0 – 1 month	314	84 (26.8%)
1 month – 2 months	980	401 (40.9%)
2 – 11 years	975	334 (34.3%)
12 – 18 years	815	165 (20.2%)
19 – 64 years	1,923	636 (33.1%)
65 – 85 years	1,627	517 (31.8%)
86 years and above	976	250 (25.6%)

DMEC - Drug-medication error combination; SDR - Signal of disproportionate reporting.

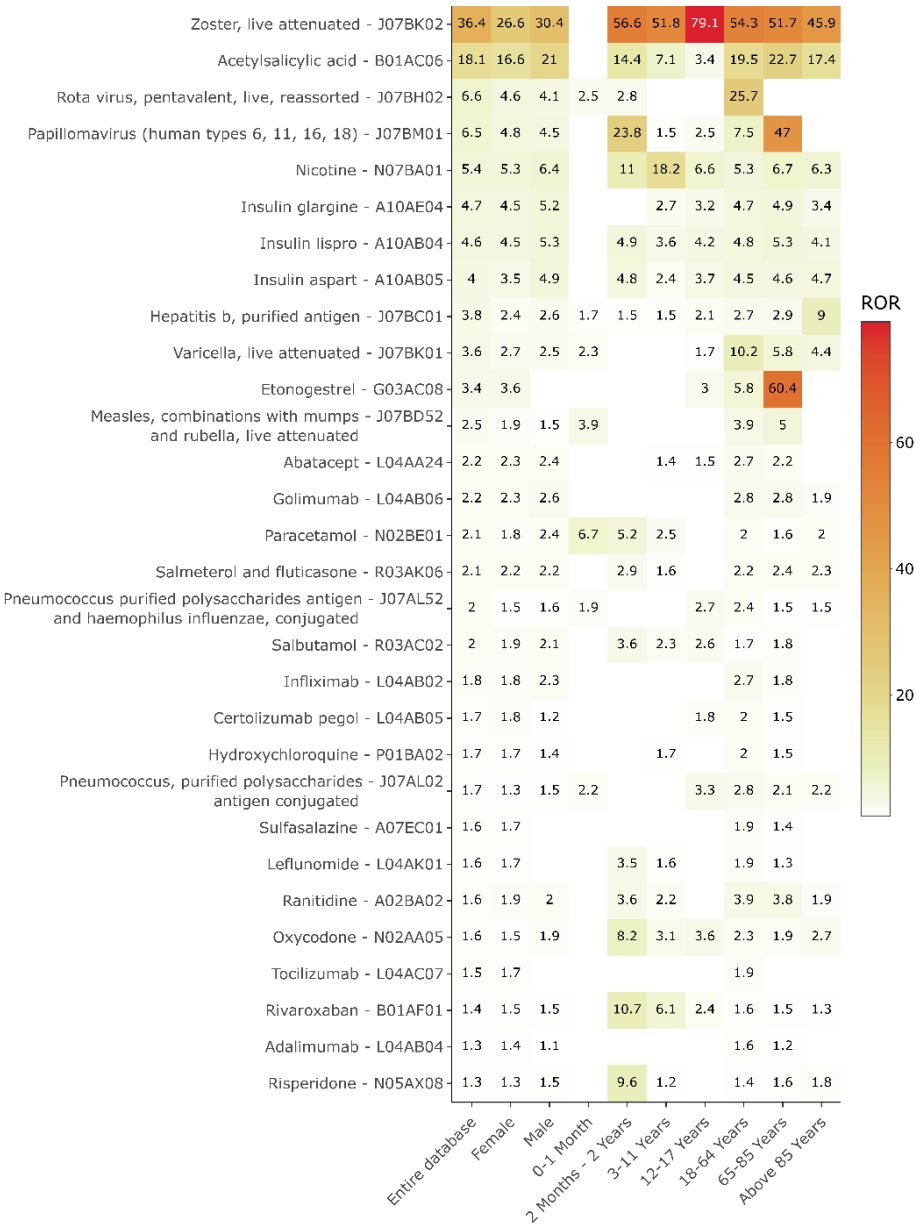

Figure 3. The 30 most commonly reported drugs with their corresponding code from the Anatomical Therapeutic Chemical (ATC) classification system, associated with medication errors, ordered by the magnitude of disproportionality based on the values obtained when analyzing the entire EudraVigilance database. Values of the reporting odds ratio are displayed where available for all the subgroups based on sexes and age-groups. An empty cells signifies either no medication errors found or disproportionality criteria were not met. Interactive figure available in online supplementary material file2. ROR = reporting odds ratio

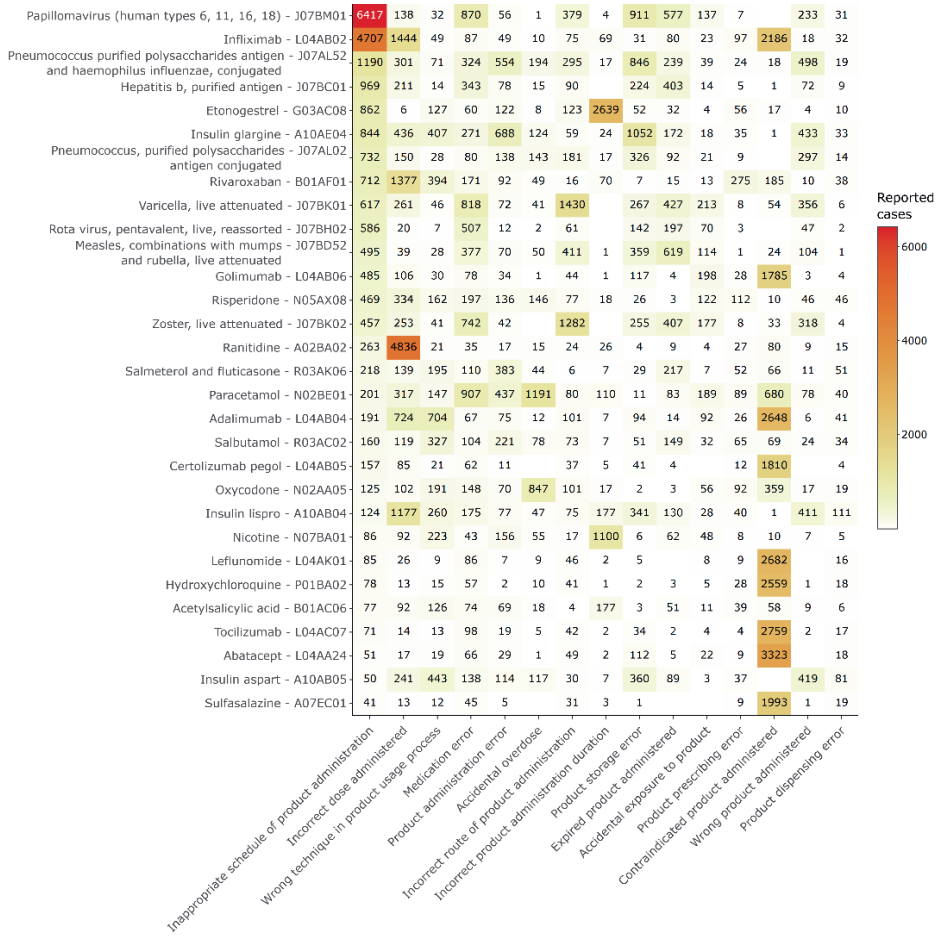

Figure 4. The 15 most commonly reported medication errors highlighted and quantified for the 30 most commonly reported drugs associated with medication errors based on the entire EudraVigilance database. Values of the amount of reported cases are displayed where available. An empty cell signifies that the corresponding type of medication error was not reported for a drug. Interactive figure is available in online supplementary material file3.

Differences among age subgroups were also observed for vaccination against human papillomavirus (HPV, human types 6, 11, 16, 18; ATC: J07BM01), showing an ROR as low as 1.5 (95% CI: 1.3-1.7; 314 cases) for the age group 3-11 years, a higher ROR of 23.8 (95% CI: 18.2-31.2; 78 cases) for age group 2 months – 2 years, and an even higher ROR of 47.0 (95% CI: 19.2-115.2; 7 cases) for the age group 65-85 years. The HPV vaccine was also the most commonly reported drug associated with MEs, accounting for 11,086 reported MEs, of which 6,417 (58%) were attributed to "Inappropriate schedule of product administration".

It was also notable that the SDR for the vaccine against herpes zoster (live attenuated; ATC: J07BK02) was stronger in all age groups, except age group 0-1 month, than for the entire

EudraVigilance population. The ROR ranged between 45.9-79.1 among subgroups, while for the entire database the ROR was 36.4 (95%CI: 35.2 – 37.7; 4,756 cases). For females and males the ROR was lower, being respectively 26.6 (95%: 25.3 – 28.0; 1,967 cases) and 30.4 (95% CI: 28.3 – 32.6; 1,028 cases). The most commonly reported ME was "Incorrect route of product administration" (1,282 cases; 27.0%).

Analysis on age subgroups showed conspicuous SDRs for the age group 2 months – 2 years for the drugs oxycodone (ATC: N02AA05; ROR = 8.2; 95% CI: 6.4-10.5; 73 cases), rivaroxaban (ATC: B01AF01; ROR = 10.7; 95% CI: 4.7-24.1; 7 cases), and risperidone (ATC: N05AX08; ROR = 9.6; 95% CI: 7.2-12.7; 57 cases). Very few SDRs for the most frequently reported drugs were found for the age group 0-1 months, but notably the SDR for paracetamol (ATC: N02BE01) stood out showing an ROR of 6.7 (95% CI: 5.5-8.3; 100 cases). The most reported ME for oxycodone was "Accidental overdose" (847 cases; 35%), for risperidone "Inappropriate schedule of product administration" (469 cases; 22.3%), for rivaroxaban "Incorrect dose administered" (1,377 cases; 34.6%), and for paracetamol "Accidental overdose" (1,191 cases, 23%).

Type of medication errors among SDRs

Based on the results displayed in the heatmap in Figure 4, several MEs stand out for a couple of drugs not yet mentioned above. For infliximab (ATC: L04AB02) there were 4,707 out of a total of 9,236 MEs (51%) attributed to "Inappropriate schedule of product administration". The ME "Incorrect dose administered" accounted for 4,836 (89%) out of 5,433 MEs for ranitidine (ATC: A02BA02). The ME "Contraindicated product administered" was reported in a range of 1,785- 3,323 MEs for (in ascending order) golimumab (ATC: L04AB06; 60.1% of MEs), certolizumab pegol (ATC: L04AB05; 78.3%), sulfasalazine (ATC: A07EC01; 89.6%), infliximab (ATC: L04AB02; 23.7%), hydroxychloroquine (ATC: P01BA02; 88.1%), adalimumab (ATC: L04AB04; 53.3%), tocilizumab (ATC: L04AC07; 88.0%), and abatacept (ATC: L04AA24; 87.9%).

Frequent medication errors among frequently reported drugs and strongest SDRs

Table 9 and 10 display the top-10 findings, not restricted to EMA's case count or ROR criteria, when ordering based on A) the most-frequently reported drugs in association with MEs, and B) the drugs with the highest lower boundary 95% CI of the ROR, accompanied by the top 3 MEs. A noteworthy result was the vaccine against the coronavirus disease of 2019 (COVID-19) (ATC: J07BN01), which was the second most-reported drug on MEs (10,150 ICSRs) in the database, predominantly because of the ME "Inappropriate schedule of product administration" (7,510 cases; 74%). Another noteworthy result was etanercept (ATC: L04AB01) accounting for 8,286 reported MEs, of which the most frequent ME was "Contraindicated product administered" (3,135 cases; 37.8%). The drug with the highest lower boundary of the 95% CI of the ROR was sodium lauryl sulfoacetate, incl. combina-

tions (ATC: A06AG11; 17 MEs; ROR with 95% CI: 95, 48 - 189), with "Accidental device ingestion" (10 cases; 58.8%) being the most-reported ME.

DISCUSSION

Signals of disproportionate reporting and medication errors

In this paper, we extensively characterized ME ICSRs, as these were underexposed in previous research [73], and explored SDRs for MEs, demonstrating notable differences in SDRs when stratifying by age. A reason why more differences were found between age groups than between sexes might be due to age being a more prominent factor than sex in altering medication needs for different age groups, e.g., by age-related dosing regimens, age-related diseases, increased polypharmacy over time, and more complex healthcare for the youngest and oldest populations. Heatmaps proved to be a convenient graphical tool to give a quick overview of SDRs on MEs, and compare the SDRs for different sexes and age groups.

Disproportionality analysis as a prioritization method

We showed that there are multiple ways to organize, sort, and display the data, which brings both challenges and opportunities to discover new insights. The disproportionality analysis may be viewed in the context of this research as a prioritization tool when dealing with an abundance of data. While sorting solely based on counts provides insight into the most frequently reported MEs, the disproportionality analysis provides more context given all the drugs and PTs reported in the EudraVigilance database. The disproportionality measure provides insight in drug-ME combinations that are more often reported than expected, given the data in EudraVigilance, which is a feature not present when solely sorting by counts. Sorting additionally on only counts showed how the COVID-19 vaccine (ATC: J07BN01) was the second most-reported drug on MEs, however, the low ROR (and narrow 95% CIs) could indicate that other PTs not related to MEs might have been disproportionately reported for the COVID-19 vaccine. Sorting based on the lower boundary 95% CI highlighted other drugs for which MEs were reported disproportionally, but simultaneously showed that most findings were subject to a low case count, questioning the impact of these findings. By highlighting these different methodologies we showed how different results may be obtained. These complementary results show the value of utilizing different methodologies, and in particular the disproportionality analysis.

SDRs previously described in literature

Observations based on the heatmap revealed findings which relate to previous publications on MEs for specific drugs, such as various types of insulin (ATC: A10AE04, A10AB04, A10A05) [153], rivaroxaban (ATC: B01AF01) [154], and oxycodone (N02AA05) [155,156]. Nicotine replacement therapy (ATC: N07BA01) is also known to be frequently reported in the context of MEs [157], however, misuse might play a major role when considering

disproportionality rates that were found among individuals <18 years in our study. While the varicella zoster vaccine live (Zostavax®, ATC: J07BK02) was only approved for people aged 50 years and above [158], we identified SDRs for infants, children, and adolescents. In 2015, the New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) received five reports on MEs related to the varicella zoster virus vaccines, of which four reports indicated that Zostavax® was erroneously administered to children [159]. The Vaccine Adverse Event Reporting System (VAERS) data, consulted via Centers for Disease Control's Wonder search engine, showed 140 reports submitted on Zostavax® being administered to patients of inappropriate age [160]. A possible reason for these MEs as reported in literature might be a mix-up with other vaccines which are stored together such as Varivax®, Varilrix®, Shingrix®, and Zostavax® [159,161,162].

Known SDRs with unknown root-cause

Other findings based on the heatmap show SDRs previously described in literature, however, without a described root-cause for MEs. Based on VAERS data, it has been found that the HPV vaccines have been administered to children of inappropriate age, namely 0-8 years [163], corresponding to our findings as well. However, it is unclear how this may have happened. Similarly, it appears that the pentavalent Rota virus vaccine has been given to individuals in the inappropriate age category 18-64 years, generating an SDR for MEs. Previous literature has described how this vaccine was administered to children of inappropriate age [164], however, it is unclear how vaccination has occurred among an adult population not to be expected to receive this vaccine. It has also been previously reported that between 2001 – 2012, 160 ICSRs were submitted to the French poison centers on MEs among children exposed to risperidone (ATC: N05AX08) [165]. Most children (112) received an incorrect dose, of which 20 children were younger than 5 years, while risperidone was wrongly administered to 21 children [165]. From that publication it is not clear how many children were found in the age category 2 months – 2 years, but the median reported age was 8 years with a range of 0.9-12 years. Risperidone was FDA approved for children of age 5 years and above [166], and it is concerning to see a disproportionate reporting among the age group 2 months - 2 years.

New SDRs, not known in literature

Based on the heatmaps, also some previously unknown SDRs on MEs were found. Notably, six drugs (i.e. infliximab [ATC: L04AB02], adalimumab [ATC: L04AB04], golimumab [ATC: L04AB06], certolizumab [ATC: L04AB05], tocilizumab [ATC: L04AC07], and abatacept [ATC: L04AA24]), classified as disease-modifying antirheumatic drugs (DMARDs) and more specifically biological DMARDs (bDMARDs), were disproportionately reported, with the ME "Contraindicated product administered" being most frequent. While so far no research has been published on MEs for these drugs, it is known that bDMARDs increase the risk of infections for individuals with rheumatoid arthritis [167–170], and guidelines state that bDMARDs should not be prescribed in the presence of a serious active infection [168].

Similar findings were identified for SDRs on the DMARDs sulfasalazine (ATC: A07EC01) and hydroxychloroquine (ATC: P01BA02). These DMARDs are known to be used for the treatment of rheumatoid arthritis as part of complex guidelines [171], which might make these drugs more prone to MEs.

Strengths

This is the first study that highlighted the importance of subgroup analysis, especially based on age, when examining SDRs for MEs within the EudraVigilance database. Differences between age groups may motivate further investigation of findings for specific age groups. The graphical representation of SDRs and providing an interactive version to further explore the data offers the possibility to get a clear overview of the obtained results, visualize notable results, and explore undiscussed SDRs. The disproportionality analysis may be seen as a method to sort results and prioritize further investigation of SDRs previously not known in literature, might trigger stakeholders to further examine these findings. This exploratory study showed several of many possibilities to sort the findings, and could inspire follow-up research on the ME topic or specific ME findings.

Limitations

A well-known inherent limitation of all spontaneous reporting systems, including EudraVigilance, is under-reporting [43]. On top of that, the rate of under-reporting may vary depending on specific drugs, the type of event, and the severity of an event [172], which further biases the results. A true estimate of the actual incidence and prevalence of MEs is not possible as our information is based on ICSRs only. The lack of data on age and sex in many ICSRs inhibits the use of all ICSRs for subgroup analyses, and therefore the disproportionality analyses on the subgroups may have produced biased SDRs. At the same time, the abundance of data provides a challenge in prioritizing, selecting, sorting, and displaying the data. An analysis based on country-level is of interest and could provide interesting findings in future research. Furthermore, the ROR and its 95% CI should be carefully interpreted, especially if a low number of ICSRs contributes to the SDR. While it is beyond the scope of this paper, the unavailability of easily accessible ICSR narratives hinders further in-depth investigation of newly found SDRs for MEs. Due to the study design, we only analyzed the MEs presented as PTs in the ICSRs, while based on the raw data there might have been more MEs present. For example, identification of contra-indications, wrong dosing, and inappropriate polytherapy would have required additional analysis on more data such as (assessing appropriate) age, presence of pregnancy, use of concomitant medications, etc. While most ICSRs mention 1 suspect drug, 20% of the ICSRs mention 2 or more suspect drugs. It is important to note that not all the suspect drugs within a given report might be associated with multiple MEs in the same report, however, the disproportionality analysis mitigates this issue. Additionally, a unique ICSR may contain multiple PTs describing the same ME, which might contribute to overestimation of a reported MEs in some cases. Some

drugs, for which multiple ATC codes were available, could not be mapped to a single ATC code due to lack of information, which might further contribute to potentially biased results.

CONCLUSION

This research provides an overview of MEs and SDRs from the EudraVigilance database. A large number of SDRs were identified, part of which are not described in the literature and may prompt further investigation by stakeholders. For drugs with the most reported MEs, the most conspicuous SDRs were identified in specific age groups, especially for vaccines, paracetamol, oxycodone, rivaroxaban, and risperidone. New SDRs were identified for DMARDs for which the ME "Contraindicated product administered" was most often reported.

DECLARATIONS

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Ethics Approval / Consent to Participate / Consent for Publication / Code Availability

Not applicable.

Conflict of interest

The research group from the Department of Medical Informatics received unconditional research grants from Chiesi, UCB, Amgen, Johnson and Johnson, and the European Medicines Agency (EMA), none of which relate to the content of this manuscript.

Availability of data and materials

An agreement has been made with the EMA not to transfer or dispose of the ICSR data set Level 2A for which access is provided under the condition of the Confidentiality Undertaking to any third party. It is agreed not to permit any third party to access, study, analyze, refer to or otherwise use the data or permit any party to reproduce any ICSR data. A publicly available version of this database is available here: https://www.adrreports.eu/en/index.html. Further inquiries can be directed to the corresponding author.

Author contributions

VP: Conceptualization, Formal Analysis, Visualization, Writing–original draft, Writing–review and editing, Methodology, Visualization. JK: Software, Writing–review and editing. EV: Software, Writing–review and editing. MdW: Software, Writing–review and editing. PR: Supervision, Writing–review and editing. KV: Conceptualization, Supervision, Writing–review and editing.

SUPPLEMENTARY MATERIALS

Table S1. EudraVigilance person characteristics of medication errors reports on "Inappropriate schedule of product administration" and "Incorrect dose administered."

Medication Error	Inappropriate schedule of product administration	Incorrect dose administered
ICSRs, n (proportion)	**52,646 (100%)**	**32,379 (100%)**
Sex, n (proportion)		
Female	31,483 (59.8%)	16,903 (52.2%)
Male	16,279 (30.9%)	13,730 (42.4%)
Not reported	4,884 (9.3%)	1,746 (5.4%)
Age category, n (proportion)		
0-1 Month	191 (<1%)	154 (<1%)
2 Months - 2 Years	1,749 (3.3%)	636 (2%)
3-11 Years	872 (1.7%)	915 (2.8%)
12-17 Years	2,071 (3.9%)	639 (2%)
18-64 Years	23,961 (45.5%)	13,098 (40.5%)
65-85 Years	8,079 (15.3%)	7,699 (23.8%)
Above 85 Years	1,121 (2.1%)	1,156 (3.6%)
Not reported	14,602 (27.7%)	8,082 (25%)
Median age, in years (IQR)	44 (26-63)	57 (34-71)

ICSR - Individual case safety report; IQR - interquartile range; n - amount of ICSRs.

Table S2. EudraVigilance reporter and reporter country characteristics of individual case safety reports on medication errors "Inappropriate schedule of product administration" and "Incorrect dose administered."

	Inappropriate schedule of product administration	Incorrect dose administered
ICSRs, n (proportion)	**52,646 (100%)**	**32,379 (100%)**
Reporter type, n (proportion)		
Consumer or other Non-Health Professional	22,392 (69.2%)	12,108 (37.4%)
Lawyer	721 (2.2%)	5,200 (16.1%)
Pharmacist	3,777 (11.7%)	3,490 (10.8%)
Physician	12,407 (38.3%)	6,619 (20.4%)
Other health professional	13,284 (41%)	4,926 (15.2%)
Unknown	65 (<1%)	36 (<1%)
Reporter country, n (proportion)		
United States of America	18,968 (58.6%)	14,779 (45.6%)
Canada	6,409 (19.8%)	2,052 (6.3%)
United Kingdom of Great Britain and Northern Ireland	6,069 (18.7%)	1,696 (5.2%)
Germany	4,532 (14%)	2,225 (6.9%)
France	3,076 (9.5%)	3,745 (11.6%)
Brazil	2,064 (6.4%)	1,159 (3.6%)
Japan	1,863 (5.8%)	629 (1.9%)
Sweden	1,143 (3.5%)	431 (1.3%)
China	657 (2%)	597 (1.8%)
Australia	636 (2%)	452 (1.4%)
Spain	635 (2%)	667 (2.1%)
Austria	434 (1.3%)	196 (<1%)
Greece	386 (1.2%)	285 (<1%)
Korea (Republic of)	341 (1.1%)	95 (<1%)
Italy	337 (1%)	297 (<1%)
Portugal	336 (1%)	129 (<1%)
Netherlands	317 (1%)	250 (<1%)
Belgium	312 (1%)	223 (<1%)

ICSR - Individual case safety report; n - amount of ICSRs

Table S3. Reported seriousness of the health outcomes for individual case safety reports including medication errors "Inappropriate schedule of product administration" and "Incorrect dose administered."

	Inappropriate schedule of product administration	Incorrect dose administered
ICSRs, n (proportion)	**52,646 (100%)**	**32,379 (100%)**
At least 1 serious health outcome reported in ICSR n (proportion)	21,743 (41.3%)	15,978 (49.3%)
No health outcome reported, n (proportion)	30,903 (58.7%)	16,401 (50.7%)
Type of seriousness, n (proportion)		
Disabling / Incapacitating	951 (1.8%)	391 (1.2%)
Congenital Anomaly / Birth Defect	11 (<1%)	5 (<1%)
Other medically important condition, unspecified	16,407 (31.2%)	11,299 (34.9%)
Caused or prolonged hospitalisation	8,012 (15.2%)	6,044 (18.7%)
Death	1,281 (2.4%)	962 (3%)
Life threatening	591 (1.1%)	665 (2.1%)

ICSR - Individual case safety report; n - amount of ICSRs.

Table S4. List of drugs not mapped to a code from the Anatomical Therapeutic Chemical classification system in the entire EudraVigilance database.

UNMAPPED DRUG	COUNT
METHOTREXATE	96244
LEVONORGESTREL	94739
ACETYLSALICYLIC ACID	92196
PREDNISONE	47404
IBUPROFEN	47357
DICLOFENAC	45709
BEVACIZUMAB	44498
TACROLIMUS	41753
FENTANYL	38860
NOT RECODED	38114
LEVOFLOXACIN	38113
DEXAMETHASONE	37520
PREDNISOLONE	37170
CICLOSPORIN	36246
CIPROFLOXACIN	32961
HUMAN NORMAL IMMUNOGLOBULIN	32487
ISOTRETINOIN	31169
METHYLPREDNISOLONE	25401
INSULIN HUMAN	24853
CELECOXIB	23688
HEPARIN	21807
NAPROXEN	21481
EVEROLIMUS	21119
VANCOMYCIN	18872
MOXIFLOXACIN	18297
INFLUENZA VACCINE	18294
RUXOLITINIB	16875
IRON	15469
BUPRENORPHINE	15354
AZITHROMYCIN	15147
METRONIDAZOLE	14574
ETHANOL	14014
LITHIUM	12833
KETOPROFEN	12806
TERBINAFINE	12490
CLINDAMYCIN	12196
PNEUMOCOCCAL VACCINE	12188
SODIUM CHLORIDE	11568

Table S4. List of drugs not mapped to a code from the Anatomical Therapeutic Chemical classification system in the entire EudraVigilance database. (*continued*)

UNMAPPED DRUG	COUNT
AFLIBERCEPT	10619
DIPHENHYDRAMINE	10595
MEDROXYPROGESTERONE	10427
DOXYCYCLINE	9840
LIDOCAINE	9698
AMPHOTERICIN B	9455
BUDESONIDE	9262
FLUCONAZOLE	8649
CEFUROXIME	8420
ACICLOVIR	8339
FLUTICASONE	8282
DILTIAZEM	7969
HYDROCORTISONE	6982
PHLEUM PRATENSE	6860
BETAMETHASONE	6652
MINOXIDIL	6634
FINASTERIDE	6520
MEDROXYPROGESTERONE ACETATE, ESTROGENS CONJUGATED	6296
COCAINE	6055
OFLOXACIN	6026
SIROLIMUS	5948
PROMETHAZINE	5903
GENTAMICIN	5683
MISOPROSTOL	5530
GLUCOSE	5236
TRIAMCINOLONE	5137
EPINEPHRINE	5135
MINOCYCLINE	5104
SECALE CEREALE	5089
HEPATITIS A (INACTIVATED) AND HEPATITIS B (RDNA) VACCINE (ADSORBED)	4993
ERYTHROMYCIN	4831
CLONIDINE	4802
CHLORHEXIDINE	4643
MOMETASONE	4580
NIMESULIDE	4556
ULIPRISTAL	4481
TOBRAMYCIN	4407
COVID-19 VACCINE	4385

Table S4. List of drugs not mapped to a code from the Anatomical Therapeutic Chemical classification system in the entire EudraVigilance database. (*continued*)

UNMAPPED DRUG	COUNT
POTASSIUM CHLORIDE	4279
INDOMETACIN	4154
CANNABIS	4149
GLYCERYL TRINITRATE	4134
RABIES VACCINE	3931
CORYLUS AVELLANA L., BETULA PENDULA ROTH., ALNUS GLUTINOSA L.	3824
LOLIUM PERENNE	3734
TETANUS VACCINES	3666
CALCIUM CARBONATE	3607
ACETYLCYSTEINE	3599
KETOROLAC	3599
BECLOMETASONE	3593
IMIPENEM	3549
GANCICLOVIR	3277
CLADRIBINE	3257
POLYSACCHARIDE IRON COMPLEX	3246
IPRATROPIUM	3240
ISOSORBIDE	3219
APOMORPHINE	3138
ETHINYLESTRADIOL, GESTODENE	3134
EPINEPHRINE, LIDOCAINE	3103
AMIKACIN	3088
HYALURONIC ACID	3028
ASCORBIC ACID	2937
CORTISONE	2878
CLOTRIMAZOLE	2809
MINERALS NOS, VITAMINS NOS	2747
IVERMECTIN	2746
PIROXICAM	2610
CABERGOLINE	2479
TRETINOIN	2434
FORMOTEROL	2431
BENZYLPENICILLIN	2415
ETHINYLESTRADIOL, NORGESTIMATE	2337
SORBITAN TRIOLEATE, POLYSORBATE 80, SODIUM CITRATE, CITRIC ACID ANHYDROUS, B/MASSACHUSETTS/2/2012-LIKE STRAIN USED B/MASSACHUSETTS/2/2012 WILD TYPE, A/TEXAS/50/2012 (H3N2) – DERIVED STRAIN USED (NYMC X-223), SQUALENE, A/CALIFORNIA/7/2009 (H1N1)PDM09-DERIVED STRAIN USED (NYMC X-181)	2330

Table S4. List of drugs not mapped to a code from the Anatomical Therapeutic Chemical classification system in the entire EudraVigilance database. (*continued*)

UNMAPPED DRUG	COUNT
ALPROSTADIL	2226
TIMOLOL	2224
IMMUNGLOBULIN	2208
EPTACOG ALFA (ACTIVATED)	2158
MICONAZOLE	2107
ATROPINE	2066
DIPHENHYDRAMINE, PARACETAMOL	2058
FLURBIPROFEN	2039
INSULIN HUMAN, INSULIN INJECTION SOLUBLE	2019
KETOCONAZOLE	1998
PLACEBO	1970
BROMOCRIPTINE	1962
CALCIUM	1939
VITAMINS NOS	1913
BRIMONIDINE	1879
DEXPANTHENOL	1849
TYPHOID POLYSACCHARIDE VACCINE	1848
ROFLUMILAST	1797
AMPICILLIN	1796
CAFFEINE	1789
CICLESONIDE	1771
MESNA	1756
FUSIDIC ACID	1736
SODIUM FERRIC GLUCONATE COMPLEX	1712
PHENYLEPHRINE	1711
POVIDONE, IODINATED	1661
MAGNESIUM SULFATE	1639
NORETHISTERONE	1622
OXYMETAZOLINE	1604
TENOFOVIR	1549
CAPSAICIN	1449
RED BLOOD CELLS	1395
ALGELDRATE, N. MENINGITIDIS GROUP C (STRAIN C11) POLYSACCHARIDE (DE-O-ACETYLATED) CONJUGATED TO TETANUS TOXOID ADSORBED ON ALUMINUM HYDROXIDE	1389
	1384
TRIGLYCERIDES MEDIUM CHAIN, SOYA OIL	1330
MANNITOL	1308
DAPSONE	1279

Table S4. List of drugs not mapped to a code from the Anatomical Therapeutic Chemical classification system in the entire EudraVigilance database. (*continued*)

UNMAPPED DRUG	COUNT
SODIUM HYDROGEN CARBONATE	1260
GADOLINIUM	1251
CALCITRIOL	1229
NYSTATIN	1207
TRYPSIN, AMYLASE, CHYMOTRYPSIN, LIPASE, PAPAIN, PANCREAS POWDER, BROMELAINS, RUTOSIDE TRIHYDRATE	1190
PANCREATIN, TRYPSIN, AMYLASE, CHYMOTRYPSIN, LIPASE, BROMELAINS, RUTOSIDE TRIHYDRATE	1181
SODIUM PHOSPHATE	1178
ALUMINIUM PHOSPHATE, HAEMOPHILUS INFLUENZAE TYPE B POLYRIBOSYLRIBITOL PHOSPHATE CONJUGATED TO MENINGOCOCCAL PROTEIN ADSORBED ON AMORPHOUS ALUMINIUM HYDROXYPHOSPHATE SULFATE, DIPHTHERIA TOXOID ADSORBED ON ALUMINIUM PHOSPHATE, TETANUS TOXOID ADSORBED ON ALUMINIUM PHOSPHATE, BORDETELLA PERTUSSIS TOXOID ADSORBED ON ALUMINIUM PHOSPHATE, BORDETELLA PERTUSSIS FILAMENTOUS HAEMAGGLUTININ ADSORBED ON ALUMINIUM PHOSPHATE, BORDETELLA PERTUSSIS PERTACTIN ADSORBED ON ALUMINIUM PHOSPHATE, BORDETELLA PERTUSSIS FIMBRIAE TYPE 2 ADSORBED ON ALUMINIUM PHOSPHATE, BORDETELLA PERTUSSIS FIMBRIAE TYPE 3 ADSORBED ON ALUMINIUM PHOSPHATE, HEPATITIS B SURFACE ANTIGEN (RDNA) ADSORBED ON AMORPHOUS ALUMINIUM HYDROXYPHOSPHATE SULPHATE [PRODUCED IN S. CEREVISIAE BY RDNA], POLIOVIRUS (INACTIVATED) TYPE 1 (MAHONEY STRAIN) PRODUCED ON VERO CELLS, POLIOVIRUS (INACTIVATED) TYPE 2 (MEF-1 STRAIN) PRODUCED ON VERO CELLS, POLIOVIRUS (INACTIVATED) TYPE 3 (SAUKETT STRAIN) PRODUCED ON VERO CELLS, AMORPHOUS ALUMINIUM HYDROXYPHOSPHA	1172
THIOPENTAL	1169
TETRACYCLINE	1166
IRON, ION (FE3+)	1162
DRONABINOL, CANNABIDIOL	1133
GLYCEROL, TRIGLYCERIDES MEDIUM CHAIN, LECITHIN, SOYA OIL	1121
BILASTINE	1109
DOXIFLURIDINE	1101
POTASSIUM, SODIUM	1090
GRANULOCYTE COLONY-STIMULATING FACTOR	1083
MAGNESIUM	1074
PARACETAMOL, CAFFEINE, OPIUM, PREPARED	1068
ETHINYLESTRADIOL, NORETHISTERONE	1065
SALICYLIC ACID	1039
HYDROXOCOBALAMIN	1023

Table S4. List of drugs not mapped to a code from the Anatomical Therapeutic Chemical classification system in the entire EudraVigilance database. (*continued*)

UNMAPPED DRUG	COUNT
PARACETAMOL, BELLADONNA DRY EXTRACT, CAFFEINE, OPIUM	1019
AZELASTINE	1012
MICRONISED PURIFIED FLAVONOIC FRACTION	1006



Chapter 5

Macrolide prescribing and pre-emptive electrocardiograms in asthma, COPD, ACO, and general population: a drug-utilization study

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ABSTRACT

Background

Macrolides are used in patients with chronic respiratory conditions to prevent exacerbations. However, due to their QT interval prolonging effect, an electrocardiogram (ECG) assessment prior to long-term treatment is recommended.

Objectives

To evaluate the incidence of macrolides use (azithromycin, clarithromycin, erythromycin) in individuals with asthma, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap (ACO), and to assess the frequency of ECGs performed prior to long-term macrolide prescribing.

Methods

We utilized data from the Dutch Integrated Primary Care Information (IPCI) database, and Spanish Information System for Research in Primary Care (SIDIAP), between 2006–2022. The study population consisted of individuals diagnosed with asthma, COPD, and ACO with ≥365 days follow-up after diagnosis. Incidence was analyzed by type of macrolide, database, year and prescribing-duration (short-, medium-, long-term [<30, 30–179, ≥180 days]).

Results

SIDIAP included 224,783 individuals with asthma, 167,524 with COPD, and 34,475 with ACO, while IPCI included 66,383 with asthma, 26,805 with COPD, and 7,250 with ACO. The incidence of short-term use per 100,000 person-years (PYs) was 3,500-6,700 for azithromycin, 1,300-2,100 for clarithromycin and 200-300 for erythromycin. The incidence of medium- and long-term use was less than <1,100/100,000 PYs. Incidence rates were higher in SIDIAP, females, and 60–79 year-olds. Medium- and long-term use was 2–4 fold higher in COPD and ACO than asthma, and increased over time. ECGs were assessed in less than 1% of long-term macrolide users.

Conclusion

Long-term macrolide users were on the rise among COPD- and ACO individuals, however ECG monitoring was rare, raising concerns given guideline recommendations.

INTRODUCTION

Since the publication of the 2008 randomized controlled trial (RCT) study results by Seemungal *et al.* [173] and the 2011 RCT study results by Albert *et al.* [174], evidence has been emerging of benefits when initiating long-term macrolide therapy in populations with uncontrolled asthma and chronic obstructive pulmonary disease (COPD). Such benefits include reduced frequency of exacerbations, fewer lower respiratory tract infections, and an improvement in quality of life [175–179]. In addition to the antimicrobial effect, macrolides (in particular azithromycin) exhibit anti-inflammatory/immunomodulatory properties with airway epithelial barrier-promoting actions [180].

The 2024 report of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) includes recommendations for prescribing azithromycin for non-smoking individuals with COPD experiencing persistent exacerbations, despite treatment with long-acting β2 agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS), or those with a blood eosinophil count below 100 cells/μL [181]. The 2024 report of the Global Initiative for Asthma (GINA) suggests that a three times per week azithromycin therapy for at least 6 months could be considered for adults with persistent symptomatic asthma despite a treatment regimen with high-dose ICS and LABA [182]. While no official recommendations are available for children, evidence has been emerging of beneficial effects from macrolide therapy in children with chronic airway diseases, especially when used as a long-term low-dose azithromycin schedule [183].

Despite the potential benefits of long-term macrolide therapy, there are concerns about potential adverse drug reactions. Several drug safety communications were released by the United States of America's (USA) Food and Drug Administration (FDA) between 2011 and 2013, discussing safety issues of azithromycin relating to drug-induced heart-rate corrected QT (QTc) interval prolongation and torsade de pointes [184]. In their guidelines, GOLD warns for a prolongation of the QTc interval [181], while the GINA and the British Thoracic Society (BTS) recommend evaluating an electrocardiogram (ECG) before long-term azithromycin therapy is initiated [182,185]. Most recently, a meta-analysis found that administration of macrolides increases the risk of ventricular arrhythmia and sudden cardiac death [186], but results are conflicting as another study claims that there is no risk for adverse cardiac events when adjusting for patient characteristics [187].

So far, there is limited data on the real-world use of macrolides. Only two Canadian studies highlighted an increase since 2009 in the prevalence of long-term (i.e. ≥90 days) macrolide use in elderly with COPD and an increase in the prescribing of macrolides in elderly with either asthma or COPD [188,189]. There is also a lack of real-world evidence on the frequency of ECGs performed prior to initiation of long-term macrolides. A published audit report from a university hospital in the United Kingdom (UK) concluded that macrolides

were frequently prescribed to individuals with a high risk for QTc prolongation [190]; macrolide therapy was initiated in ten patients (14%) with a QTc ≥ 440ms and in one patient (1%) with no ECG. Overall, ECGs procedures were done in 71 (83%) patients.

The primary objective of this research was to assess the incidence of new-use of prescribed short-, medium-, and long-term macrolide therapy in individuals with asthma, COPD, and asthma-COPD overlap (ACO). The secondary objective was to assess the frequency of a registered ECG-procedure before long-term macrolide therapy.

METHODS

Databases and study design

The databases utilized in this study were the Dutch Integrated Primary Care Information (IPCI) database and the Spanish Information System for Research in Primary Care (SIDIAP, in Spanish: Sistema d'informació per al Desenvolupament de la Investigació en Atenció Primària). The databases were mapped to the format of the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [191], enabling the utilization of standardized analytical pipelines [192]. The IPCI and SIDIAP data resource profiles may be read elsewhere in detail [193,194]. Data from SIDIAP was additionally linked to hospital discharge data through the Data Analytics Program for Research and Innovation in Health (PADRIS, in Catalan: Programa d'analítica de dades per a la recerca i la innovació en salut). We used a retrospective cohort study design and the study period was from 1st of January 2006 to 31st of December 2022.

Definitions for drugs, co-morbidities, and ECG

Based on RxNorm codes, the standard vocabulary in the OMOP-CDM, respiratory drugs were defined as short- and long acting beta agonists (SABA and LABA), short- and long acting muscarinic antagonists (SAMA and LAMA), ICS, methylxanthines, leukotriene receptor antagonists (LTRA), phosphodiesterase type 5 inhibitors (PDE5i), cromones, and any combination of the afore mentioned drugs.

Macrolides were defined as a prescription of an oral formulation of azithromycin, clarithromycin, or erythromycin. A comorbidity of cardiovascular diseases, obesity, pneumonia, diabetes mellitus (DM), and gastroesophageal reflux disease was based on the presence of disease codes (i.e. conceptIDs) from the Systematized Nomenclature of Medicine (SNOMED) in the patient's medical history. ECG measurement was assessed via the presence of conceptIDs for ECG registration in the patient's medical file (see data processing and analysis procedures).

The JavaScript Object Notation (JSON) files representing concept sets for all the mentioned drugs and the clinical concepts of ECG, cardiovascular diseases, obesity, pneumonia, DM, and GERD are publicly available in the GitHub repository [195] and were created and reviewed using the Observational Health Data Sciences and Informatics' (OHDSI) ATLAS tool [196]. A concept set is a collection of standardized codes from medical vocabularies representing a clinical concept [197]. More information on standardized vocabularies leveraged within the OHDSI collaborative may be read elsewhere [56].

Definitions of asthma, COPD, ACO, and the general population

Several chronic respiratory diseases were defined based on the presence of disease codes and use of respiratory drugs (which may be viewed in the GitHub repository [195]).

i) Asthma was defined as individuals with (1) a disease code of asthma and (2) having at least 2 prescriptions of any respiratory drugs registered within 365 days after index date (i.e. date of first diagnosis of asthma within the database). Patients with a disease code for COPD were excluded.
ii) COPD was defined as (1) individuals with a disease code of COPD, (2) being aged 40 years or older, and (3) having at least 2 prescriptions of any respiratory drugs registered within 365 days after the index date (i.e. date of first diagnosis of COPD within the database). Patients with a disease code for asthma were excluded.
iii) ACO was defined as (1) individuals with a disease code for both asthma and COPD, (2) being aged 40 years or older, and (3) having at least 2 prescriptions of respiratory drugs registered within 365 days after the index date (i.e. date of a COPD diagnosis in individuals after the first asthma diagnosis or date of asthma diagnosis in individuals after the first COPD diagnosis).

Use of macrolides was also assessed in the general population which consisted of individuals without asthma or COPD and with at least 365 days of follow-up time, with the index date being the moment of first observation within the database.

COHORT INCLUSION CRITERIA

All individuals entering a cohort were required to have a follow-up time of at least 365 days. Every individual was able to re-enter a cohort after exiting the cohort if inclusion criteria were fulfilled. The cohorts were created in ATLAS version 2.13 [196].

Follow-up

In patients with asthma, COPD, or ACO, follow-up started from the index date and ended 365 days after the last day of supply from the last observed respiratory drug prescription or at the date representing the end of data availability (e.g. due to death or leaving the primary

care practice, whichever occurred first in time). For patients not diagnosed with asthma, COPD or ACO, follow-up ended at the end of data availability.

Exposure to macrolides

Exposure to macrolides was defined as patients having at least one prescription of any macrolide during follow-up. Individual prescriptions were combined into one prescription if the window between the end date of the previous prescription and start of next prescription was less than 7 days. Duration was defined as short-, medium-, and long-term, being respectively a duration of <30 days, 30 to 179 days, and ≥180 days.

Data processing and analysis procedures

All statistical analyses were performed using R Statistical Software [198] within the RStudio interface [199]. Multiple R-packages developed within the Data Analysis and Real World Interrogation Network (DARWIN EU®) were utilized to facilitate data processing and analysis [200]. The incidence rate of macrolide use was defined as the number of new users of macrolides divided by the number of person-years (PY) within the different cohorts of interest (asthma, COPD, ACO and the general population). A requirement of incident use was that no record of a macrolide prescription should be observed up to 365 days prior to the next identified record of macrolide use. The incidence rate was presented per 100,000 PY.

Baseline characteristics were assessed at time of first prescribed macrolide during follow-up. History of comorbidities such as cardiovascular diseases, obesity, pneumonia, DM, and GERD was assessed any time prior to the first macrolide drug exposure. Registration of an ECG measurement was assessed 7 days, 14 days, 30 days, 60 days, and any time before, as well as any time after the first macrolide drug exposure. For privacy reasons; results were masked if the count for a given outcome was less than 5. A full overview of all R-packages used for this study may be found when opening the R-project in a personal environment or by observing the lock file [195].

RESULTS

Cohort counts

For the SIDIAP database, the number of individuals present in the cohorts was as follows; 224,783 for asthma, 167,524 for COPD, 34,475 for ACO, and 6,654,579 for the general population. For the IPCI database, it was as follows: 66,383 for asthma, 26,805 for COPD, 7,250 for ACO, and 1,962,337 for the general population.

Baseline characteristics of first-time macrolide users

Baseline characteristics of individuals with newly prescribed macrolides following the start of follow-up are displayed in Table 1A and 1B. Of notice, the number of individuals being treated with macrolides of a medium- and long-term duration was small, especially for long-term use in IPCI (46 incident users for patients with asthma, 96 for COPD, 24 for ACO and 115 in the general population).

The median age at time of first macrolide prescribing ranged from 67-74 years for the COPD and ACO cohorts in both databases. In the asthma cohorts, the median age was predominantly between 40-66 years in both databases, except for the asthma cohort of medium-term macrolide users in SIDIAP, where the median age was 16 years. In the general population, the median age ranged between 32-57 years, except for the medium-term macrolide use cohort in SIDIAP having a median age of 12 years. In both IPCI and SIDIAP, the proportion of females exposed to macrolides was higher in the asthma, ACO, and general population cohort compared to the COPD cohorts.

There was a low prevalence of GERD and DM in SIDIAP (≤1%) and IPCI (<1-8%) over all cohorts. Obesity was more frequently registered in SIDIAP (7-39%) than in IPCI (<1-7%). Cardiovascular diseases were more prevalent in COPD and ACO cohorts in SIDIAP (75-82%) than in IPCI (54-66%). Cardiovascular diseases were in general less prevalent among individuals in the asthma cohorts (23-52%) and in the general population cohorts (14-30%). Prevalence patterns for pneumonia were similar in both databases; being the least common in the general population cohorts (IPCI, 7-21%; SIDIAP, 7-14%), followed by higher prevalences in the asthma cohorts (IPCI, 17-33%; SIDIAP, 17-32%), COPD cohorts (IPCI, 28-36%; SIDIAP, 27-47%), and ACO cohorts (IPCI, 32-47%; SIDIAP, 29-47%).

Table 1A. Baseline characteristics of individuals in SIDIAP upon the moment of first macrolide prescription after cohort entry. Short-, medium-, and long-term macrolide use periods resemble respectively a duration of <30 days, 30–179 days, and ≥180 days.

			Cohort (total individuals, including non-macrolide users), macrolide use period											
Variable	Category	Unit of measure	Asthma (224,783)			COPD (167,524)			ACO (34,475)			General population (6,654,579)		
			S	M	L	S	M	L	S	M	L	S	M	L
Macrolide users, total	-	N	66,466	3,952	1,409	45,356	6,199	4,460	12,150	1,656	1,125	1,449,119	38,898	10,418
Age	-	Median (IQR)	40 (18-60)	16 (5-59)	52 (22-68)	74 (65-81)	75 (68-81)	74 (67-80)	73 (62-81)	74 (65-81)	74 (64-81)	41 (24-59)	12 (4-50)	48 (28-66)
Sex	Female	N%	43,600 (66)	2,418 (61)	999 (71)	12,221 (27)	1,310 (21)	896 (20)	7,582 (62)	1,014 (61)	682 (61)	848,915 (59)	22,347 (57)	6,351 (61)
	Male	N%	22,866 (34)	1,534 (39)	410 (29)	33,135 (73)	4,889 (79)	3,564 (80)	4,568 (38)	642 (39)	443 (39)	600,204 (41)	16,551 (43)	4,067 (39)
History of comorbidities any time prior cohort entry	Cardiovascular diseases	N%	16,944 (25)	968 (24)	503 (36)	33,821 (75)	5,018 (81)	3,566 (80)	9,271 (76)	1,351 (82)	905 (80)	288,821 (20)	6,065 (16)	2,375 (23)
	Pneumonia	N%	11,298 (17)	1,258 (32)	448 (32)	12,215 (27)	2,927 (47)	2,098 (47)	3,536 (29)	717 (43)	534 (47)	95,259 (7)	5,448 (14)	1,460 (14)
	Obesity	N%	13,088 (20)	609 (15)	289 (21)	12,843 (28)	1,641 (26)	1,107 (25)	4,693 (39)	645 (39)	421 (37)	161,436 (11)	2,731 (7)	856 (8)
	GERD	N%	102 (<1)	11 (<1)	7 (<1)	203 (<1)	43 (1)	21 (<1)	83 (1)	13 (1)	10 (1)	1,237 (<1)	52 (<1)	29 (<1)
	DM	N%	53 (<1)	5 (<1)	<5 (NA)	60 (<1)	21 (<1)	14 (<1)	22 (<1)	6 (<1)	<5 (NA)	580 (<1)	13 (<1)	5 (<1)

ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; DM - Diabetes Mellitus; GERD - Gastroesophageal reflux disease; IQR - Interquartile range; L - Long term; M - Medium term; N - Count; NA - Not available, S - Short term; SIDIAP - Spanish Information System for Research in Primary Care.

Table 1B. Baseline characteristics of individuals in IPCI upon the moment of first macrolide prescription after cohort entry. Short-, medium-, and long-term macrolide use periods resemble respectively a duration of <30 days, 30–179 days, and ≥180 days.

			Cohort (total individuals, including non-macrolide users), macrolide use period											
Variable	Category	Unit of measure	Asthma (66,383)			COPD (26,805)			ACO (7,250)			General population (1,962,337)		
			S	M	L	S	M	L	S	M	L	Short	Medium	Long
Macrolide users, total	-	N	11,194	831	46	6,118	1,194	96	1,787	313	24	195,835	5,038	115
Age	-	Median (IQR)	42 (19-59)	56 (39-67)	66 (52-78)	71 (63-78)	71 (64-77)	72 (68-80)	67 (58-76)	68 (61-76)	68 (63-75)	38 (20-57)	32 (18-57)	57 (21-70)
Sex	Female	N%	7,125 (64)	557 (67)	32 (70)	3,168 (52)	573 (48)	43 (45)	1,143 (64)	198 (63)	16 (67)	112,586 (57)	2,827 (56)	67 (58)
	Male	N%	4,069 (36)	274 (33)	14 (30)	2,950 (48)	621 (52)	53 (55)	644 (36)	115 (37)	8 (33)	83,249 (43)	2,211 (44)	48 (42)
History of comorbidities any time prior cohort entry	Cardiovascular diseases	N%	2,586 (23)	281 (34)	24 (52)	3,343 (55)	660 (55)	63 (66)	1,029 (58)	194 (62)	13 (54)	27,461 (14)	698 (14)	34 (30)
	Pneumonia	N%	1,864 (17)	209 (25)	15 (33)	1,692 (28)	427 (36)	33 (34)	571 (32)	146 (47)	9 (38)	13,577 (7)	546 (11)	24 (21)
	Obesity	N%	440 (4)	41 (5)	<5 (NA)	128 (2)	20 (2)	<5 (NA)	115 (6)	23 (7)	<5 (NA)	2,769 (1)	67 (1)	<5 (NA)
	GERD	N%	164 (1)	16 (2)	<5 (NA)	124 (2)	16 (1)	<5 (NA)	59 (3)	14 (4)	<5 (NA)	1,355 (1)	35 (1)	<5 (NA)
	DM	N%	117 (1)	13 (2)	<5 (NA)	201 (3)	30 (3)	<5 (NA)	92 (5)	25 (8)	<5 (NA)	1,551 (1)	34 (1)	<5 (NA)

ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; DM - Diabetes Mellitus; GERD - Gastroesophageal reflux disease; IPCI - Integrated Primary Care Information; IQR - Interquartile range; L - Long term; M - Medium term; N - Count; NA - Not available, S - Short term.

Incidence rates of macrolide use

The incidence of any macrolide use in asthma was between 20-6,200/100,000 PYs, in COPD 80-6,300/100,000 PYs and in ACO 70-7,300/100,000 PYs (Figure 1 series). When exploring results by type of macrolide in asthma, COPD, and ACO, azithromycin had the highest incidence in each time window within both IPCI and SIDIAP, followed by clarithromycin and erythromycin. Short-term azithromycin user estimates ranged from 3,500-6,700/100,000 PYs, for short-term clarithromycin users it was 1,300-2,100/100,000 PYs, and for short-term erythromycin users it was 200-300/100,000 PYs (Figure 1A). Medium- and long-term user estimates (Figures 1B and 1C) for all macrolides were below 1,100/100,000 PYs in asthma, COPD, and ACO. In both databases, the incidence rate of medium and long-term macrolide prescribing was 2- to 4-fold higher in patients with COPD and ACO compared to patients with asthma. Incidence rates were higher for females than males (Figure 1 series) and this was most profound for short-term use of macrolides (Figure 1A), especially for azithromycin. In the general population, the incidence of macrolide use was the highest for short-term users (2,100-2,500/100,000 PYs), followed by medium- and long-term users (<15/100,000 PYs) as seen in Figure 1 series.

Incidence trends during the study period

In IPCI, short-term use of all macrolides decreased over time, while in SIDIAP an increase was observed for azithromycin (Figure 2A). In both databases a trend in increased incidence was observed up to 2019-2020 for medium- and long-term users for only azithromycin (Figures 2B and 2C). In the analyses of the long-term use window within IPCI (Figure 2C), estimates were only found for azithromycin starting from the second halve of the study period for the study cohorts, while the estimates within SIDIAP cohorts were found earlier in the study period. Trends were overall consistent on the level of macrolides irrespective of namely the asthma, COPD, and ACO cohorts.

ECG assessment before first macrolide prescription

As seen in Table 2, the registration of an ECG assessment up to 60 days prior to macrolide use initiation was very low in both databases (≤1% in both IPCI and SIDIAP) and slightly increased when using the complete history. ECGs were mainly assessed in individuals exposed to medium and long-term macrolide use (IPCI, 10-23%; SIDIAP, 7-23%). ECG procedure registration among individuals exposed to macrolides was much lower for asthma (8-10% for SIDIAP; 5-11% for IPCI) compared to COPD (16-18% for SIDIAP; 9-23% for IPCI) and ACO (in only SIDIAP, 19-23%).

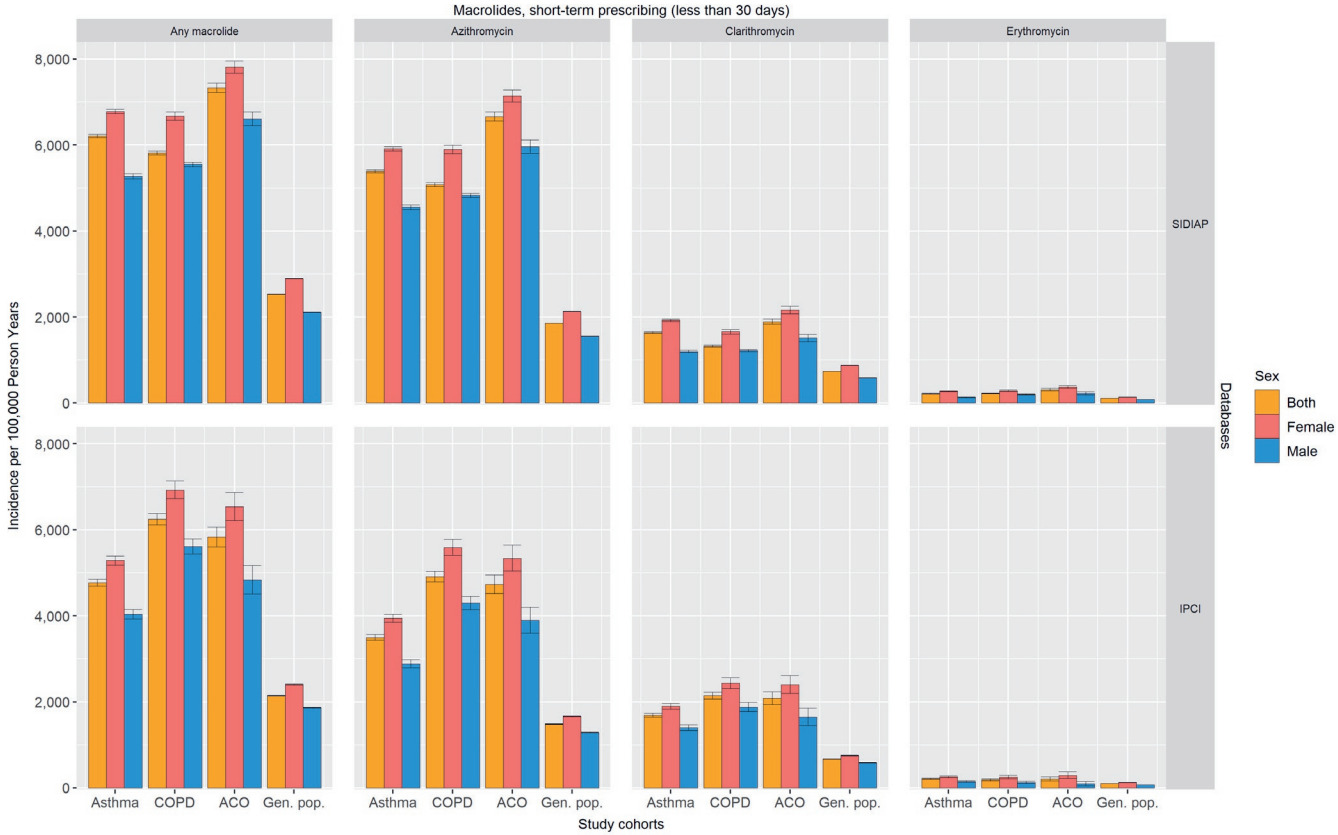

Figure 1A. Incidence rate for individuals with a new short term macrolide prescribing among study cohorts for females, males, and both sexes. ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; Gen. pop. - General population without asthma or COPD; IPCI - Integrated Primary Care Information; SIDIAP - Spanish Information System for Research in Primary Care.

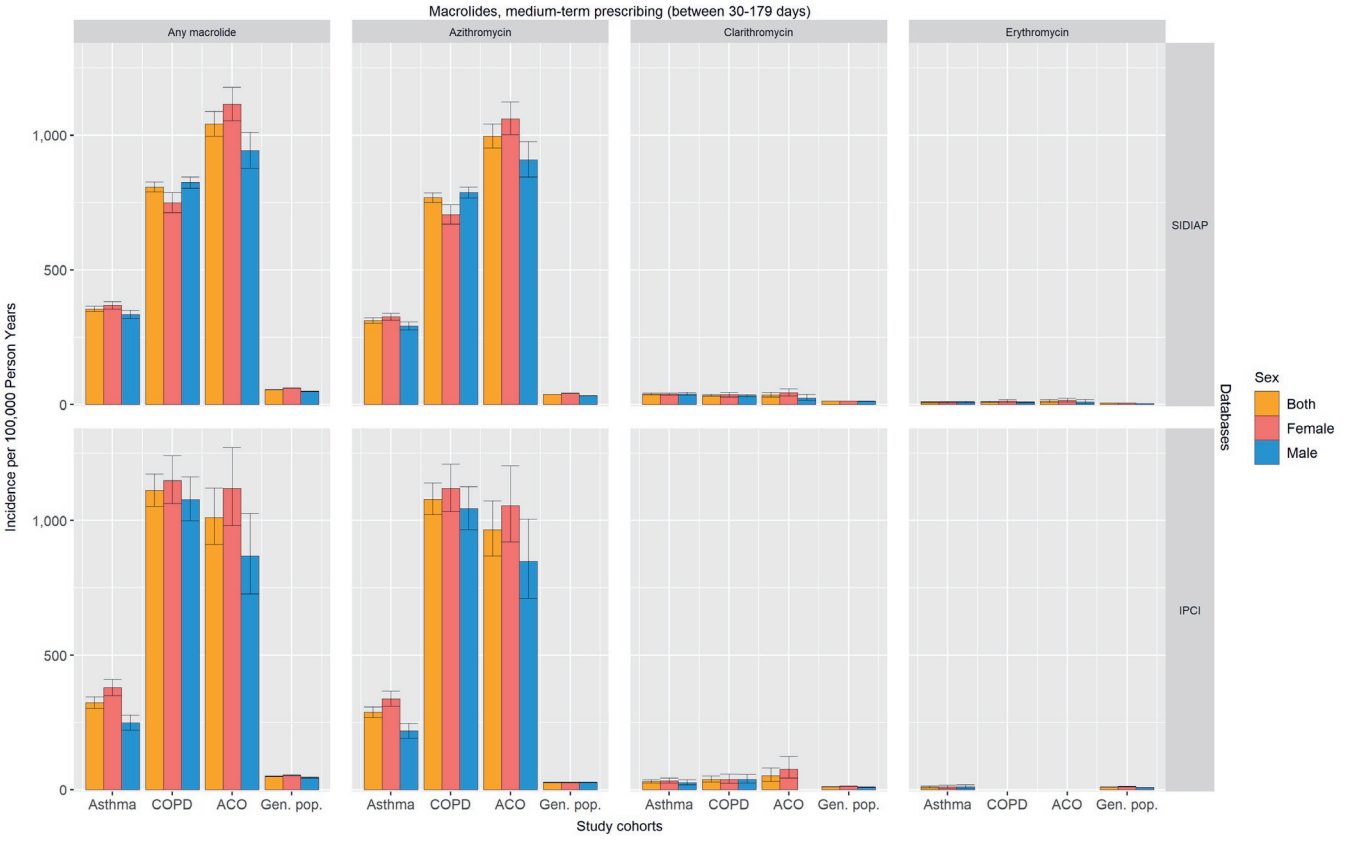

Figure 1B. Incidence rate for individuals with a new medium term macrolide prescribing among study cohorts for females, males, and both sexes. ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; Gen. pop. - General population without asthma or COPD; IPCI - Integrated Primary Care Information; SIDIAP - Spanish Information System for Research in Primary Care.

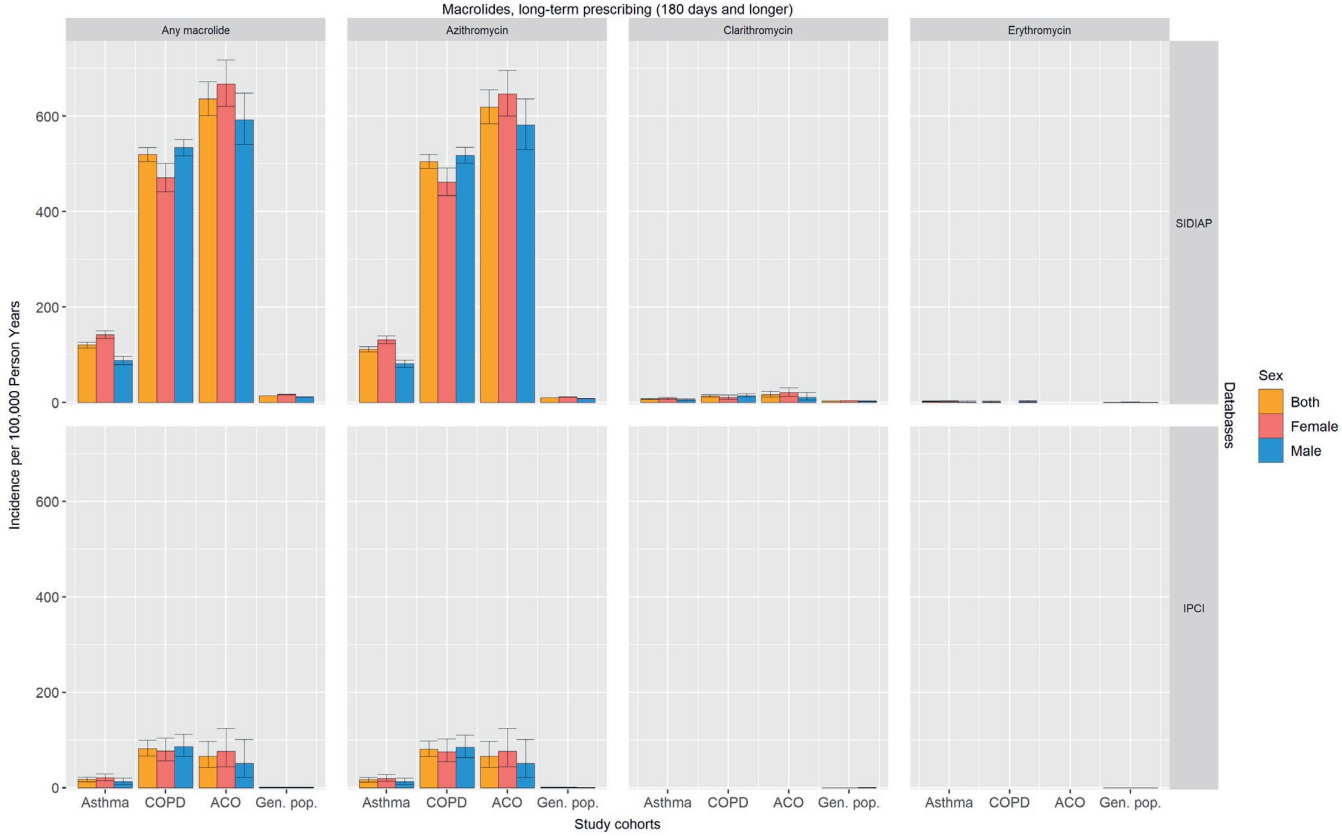

Figure 1C. Incidence rate for individuals with a new long term macrolide prescribing among study cohorts for females, males, and both sexes. ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; Gen. pop. - General population without asthma or COPD; IPCI - Integrated Primary Care Information; SIDIAP - Spanish Information System for Research in Primary Care.

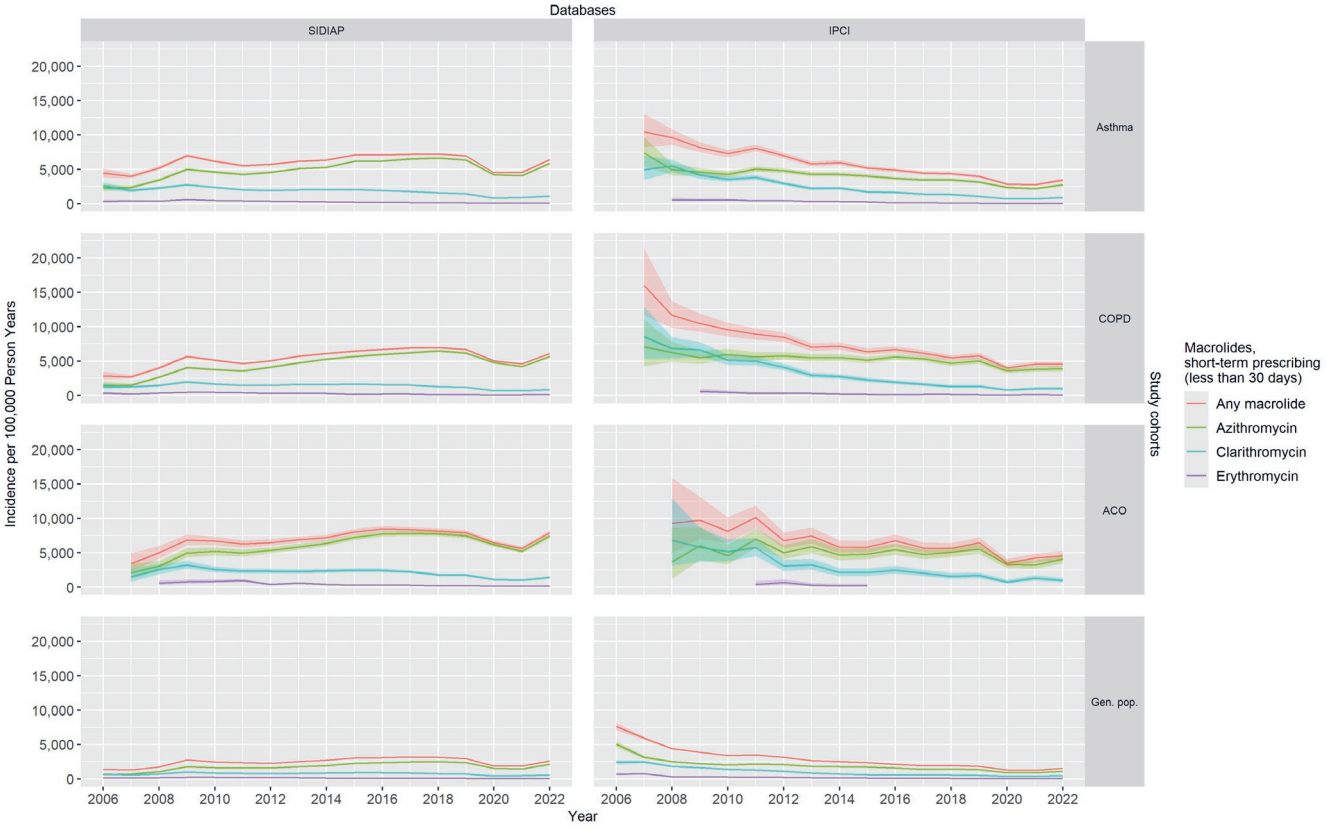

Figure 2A. Annual incidence rate for individuals with a new short term macrolide prescribing among study cohorts. ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; Gen. pop. - General population without asthma or COPD; IPCI - Integrated Primary Care Information; SIDIAP - Spanish Information System for Research in Primary Care.

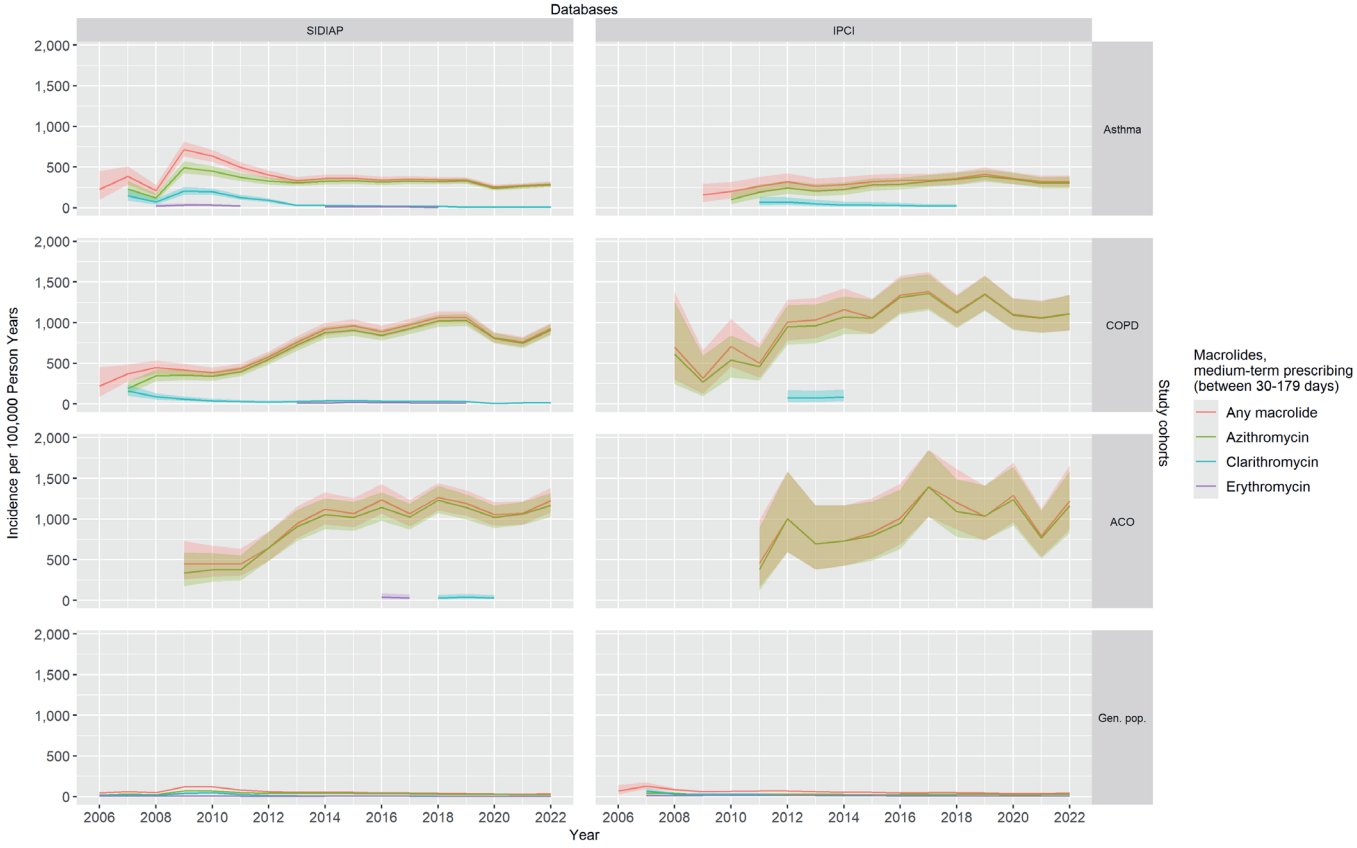

Figure 2B. Annual incidence rate for individuals with a new medium term macrolide prescribing among study cohorts. ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; Gen. pop. - General population without asthma or COPD; IPCI - Integrated Primary Care Information; SIDIAP - Spanish Information System for Research in Primary Care.

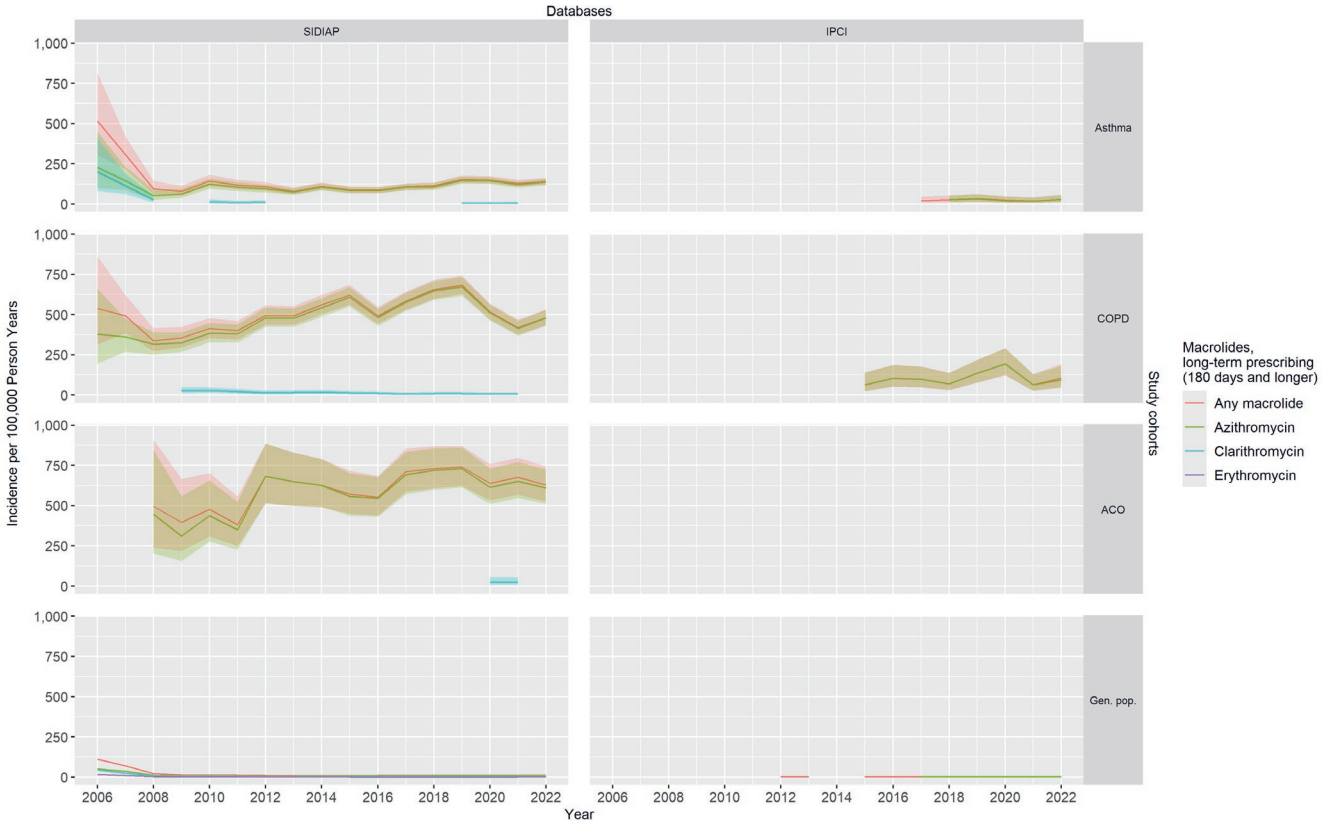

Figure 2C. Annual incidence rate for individuals with a new long term macrolide prescribing among study cohorts. ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; Gen. pop. - General population without asthma or COPD; IPCI - Integrated Primary Care Information; SIDIAP - Spanish Information System for Research in Primary Care.

Table 2. Presence of a registered electrocardiogram procedure upon the moment of first macrolide prescription after cohort entry. Short-, medium-, and long-term macrolide use periods resemble respectively a duration of <30 days, 30–179 days, and ≥180 days.

				Cohort, macrolide use period											
DB	**Variable**	**Category**	**Unit of measure**	**Asthma**			**COPD**			**ACO**			**General population**		
				S	M	L	S	M	L	S	M	L	S	M	L
SIDIAP	-	Individuals, total	N	66,466	3,9582	1,409	45,356	6,199	4,460	12,150	1,656	1,125	1,449,119	38,898	10,418
	Time window for ECG measure	7-0 days before	N%	127 (<1)	5 (<1)	<5 (NA)	195 (<1)	17 (<1)	7 (<1)	62 (1)	6 (<1)	<5 (NA)	2,147 (<1)	29 (<1)	9 (<1)
		14-0 days before	N%	155 (<1)	7 (<1)	<5 (NA)	246 (1)	27 (<1)	12 (<1)	81 (1)	6 (<1)	<5 (NA)	2,706 (<1)	34 (<1)	12 (<1)
		30-0 days before	N%	227 (<1)	12 (<1)	<5 (NA)	356 (1)	45 (1)	23 (1)	114 (1)	13 (1)	5 (<1)	3,964 (<1)	56 (<1)	20 (<1)
		60-0 days before	N%	345 (1)	19 (<1)	<5 (NA)	547 (1)	79 (1)	50 (1)	166 (1)	18 (1)	12 (1)	6,031 (<1)	90 (<1)	34 (<1)
		Any time before and after	N%	5,115 (8)	275 (7)	147 (10)	7,074 (16)	1,130 (18)	805 (18)	2,324 (19)	374 (23)	244 (22)	70,418 (5)	1,318 (3)	494 (5)
IPCI	-	Individuals, total	N	11,194	831	46	6,118	1,194	96	1,787	313	24	195,835	5,038	115
	Time window for ECG measure	7-0 days before	N%	12 (<1)	<5 (NA)	<5 (NA)	15 (<1)	<5 (NA)	<5 (NA)	<5 (NA)	<5 (NA)	<5 (NA)	170 (<1)	<5 (NA)	<5 (NA)
		14-0 days before	N%	14 (<1)	<5 (NA)	<5 (NA)	18 (<1)	<5 (NA)	<5 (NA)	<5 (NA)	<5 (NA)	<5 (NA)	222 (<1)	<5 (NA)	<5 (NA)
		30-0 days before	N%	24 (<1)	<5 (NA)	<5 (NA)	29 (<1)	5 (<1)	<5 (NA)	<5 (NA)	<5 (NA)	<5 (NA)	336 (<1)	6 (<1)	<5 (NA)
		60-0 days before	N%	47 (<1)	<5 (NA)	<5 (NA)	41 (1)	7 (1)	<5 (NA)	6 (<1)	<5 (NA)	<5 (NA)	540 (<1)	10 (<1)	<5 (NA)
		Any time before and after	N%	534 (5)	88 (11)	<5 (NA)	533 (9)	142 (12)	22 (23)	134 (7)	30 (10)	<5 (NA)	6,075 (3)	180 (4)	<5 (NA)

ACO - Asthma-COPD overlap; COPD - Chronic Obstructive Pulmonary Disease; DB - Database; ECG - Electrocardiogram; IPCI - Integrated Primary Care Information; L - Long term; M - Medium term; N - Count; NA - Not available, S - Short term; SIDIAP - Spanish Information System for Research in Primary Care.

DISCUSSION

Summary of main findings

In this study we reported incidence rates of macrolide use in individuals with chronic respiratory conditions and in the general population. Short-term macrolides use in SIDIAP ranged between 200-5,400/100,000 PY in individuals with asthma, 200-5,800/100,000 PY in individuals with COPD, 300-7,300/100,000 PY in individuals with ACO and 100-2,500/100,000 PY in the general population. For IPCI, results were comparable, namely: 200-4,800/100,000 PY in individuals with asthma, 200-6,300/100,000 PY in individuals with COPD, 200-5,800/100,000 PY in individuals with ACO and 100-2,100/100,000 PY in the general population. Incidence rates of medium- or long-term use of macrolides were much lower and almost absent in the general population. Macrolide use mainly consisted of azithromycin, especially for medium- or long-term use of macrolides. Incidence rates of macrolide prescribing were higher for females in the general population and in the population of individuals with respiratory conditions. Over time, the incidence rates of short-term use increased for SIDIAP while decreasing for IPCI. The incidence rates of medium and long-term use increased throughout time, mostly for COPD and ACO cohorts and particularly in SIDIAP. ECG recording was infrequently observed in both databases with slightly higher occurrences for medium-term and long-term users.

General macrolide use

It comes as no surprise that incidence estimates were higher for azithromycin compared to erythromycin and clarithromycin, because it has more favorable pharmacokinetic- and pharmacodynamic properties translating into less drug-drug interactions, convenient dosing regimens, improved patient adherence, higher antimicrobial efficacy, and a better safety profile [201–204]. A favoring for azithromycin over clarithromycin may be observed by the diverging trends in estimates for these drugs between 2008 and 2010, while erythromycin estimates were by far the lowest among the studied macrolides. Research on trends for different macrolides is rare, but in a Japanese study a trend was also observed in which use of multiple macrolides, including azithromycin, were slightly on the rise between 2013 and 2018, while use of clarithromycin was slightly on the decline [205]. The trend of decreasing estimates between the year 2019 and 2021 was most probably due to the coronavirus disease 2019 (COVID-19) pandemic as seen in other studies on antibiotic prescribing in primary care [206–212]. Overall, the estimates from the Spanish SIDIAP database were higher than from the Dutch IPCI database, which corresponds with international research highlighting a higher consumption rate of antibiotics in Spain compared to The Netherlands [213]. In the next years, it is likely that the incidence rates for azithromycin use will decrease as the European Medicines Agency (EMA) has recently recommended not longer to use azithromycin for the prevention of exacerbations forthcoming from eosinophilic and non-eosinophilic asthma because of concerns for antimicrobial resistance [214].

ECG

Despite recommendations to perform ECGs before initialization of long-term macrolide therapy, very few to no individuals in the cohorts seemed to have a registered ECG procedure before their first long-term macrolide prescription. One of the reasons might be that ECG assessment (prior to long-term macrolide prescribing) is done by the specialist and that this information is unavailable in IPCI, which is a primary care database. However, it should be noted that it is not uncommon in the Netherlands for general practitioners (GPs) to perform ECGs, and it can be at an average rate of 14 ECGs per month for those who willingly perform it in primary care [215,216]. For SIDIAP, the linkage with secondary data only included hospital discharge information. As a result, ECG assessments were available exclusively from primary care records, which may have contributed to the low number of recorded ECG procedures.

Short-, medium, and long-term users

As expected, incidence rates were the highest for the short-term (<30 days) users of oral macrolides as usual treatment duration of oral azithromycin (3-5 days), clarithromycin (7-14 days), and erythromycin (5-15 days) is relatively short in case of bacterial infections [217–220]. Medium- and long-term users among individuals with asthma, COPD and ACO was less common, although medium- and long-term prescribing could have been initiated for the purpose of exacerbation management. Our results were also in line with the Canadian study by Yan *et al.* which highlighted an increase in macrolide use for a duration of 90 days and longer in people with COPD between the years 2004 and 2018 [188]. Increase in new medium- and long-term users might have been propelled by the 2008 publication of Seemungal *et al.* [173] and the 2011 publication of Albert *et al.* [174] which showed reduced COPD exacerbations for individuals on a 12-month therapy of respectively erythromycin and azithromycin.

Sex

New-users of macrolides was the highest in females which corresponds with previous findings on macrolide-specific prescribing [205,212,221,222] and overall antibiotic prescribing [221–230]. This might be due to more frequent visits by females to the general practitioner combined with higher rates of inappropriate and overly cautious prescribing, and even possibly due to differences in genetic background [231,221,228].

Asthma, COPD, and ACO

Overall, the incidence of new macrolide users in both IPCI and SIDIAP was higher in COPD and ACO, compared to asthma, most prominently for the medium- and long-term users. GINA guidelines state that azithromycin can be considered in adult patients with symptomatic asthma despite high use of ICS with LABA, thus in the subset of severe asthma. Also, it needs to be considered that COPD and ACO populations are considerably more different than asthma populations, as people with asthma tend to be younger, smoke

less, have fewer comorbidities, higher income, higher education levels, and exercise more [232,233].

Research Strengths

To our knowledge, this is the first study on the incidence of new-macrolide users in populations with asthma, COPD, and ACO, forthcoming from two different countries, while going more in-depth on various findings based on multiple time windows, calendar years, and sex. The large cohort sizes enabled research on sub-groups and obtaining estimates with relatively small confidence intervals. A high level of generalizability was present by the fact that IPCI and SIDIAP are representative for respectively the Dutch and Spanish population. The fact that these databases were standardized to the OMOP-CDM facilitates the use of standardized analytical packages, reproducibility, and shareability.

Research Limitations

There were several limitations present in this study. Both the IPCI and SIDIAP database contained only primary care prescription data. This means that prescriptions which are more commonly initiated in secondary care would not be observed, and that therefore population-wide macrolide prescribing and actual use might be underestimated. Likewise, performing ECG procedures is a common practice in secondary care, therefore an underestimation of ECG procedures is likely explaining why the prevalence of ECS assessment (prior to medium- or long-term azithromycin use) is low. As the analyses were performed on observational data and estimates were based on prescriptions, this might contribute to an overestimation of actual dispensing and consumption of macrolides. Disease misclassification may have occurred, as disease-based cohort entry was determined by the presence of a disease code and prescribed medication for respiratory diseases, rather than a manually validated diagnosis.

Conclusion

This is the first drug-utilization study describing the incidence patterns of new macrolide users in individuals with asthma, COPD, ACO, and the general population. Over time, short-term macrolide users were in decline in IPCI, but medium- and long-term users were on the rise in both IPCI and SIDIAP. While prolonged macrolide use was occurring more frequently throughout time, ECG procedures were infrequently registered before the first long-term macrolide prescription, which may trigger some concerns given the guidelines recommending such a procedure beforehand.

DECLARATIONS

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Ethics Approval

This project was approved by the IPCI Review Board and the Clinical Research Ethics Committee of the IDIAPJGol (project code: 24/090-EOm).

Conflict of interest

The research group from the Department of Medical Informatics received unconditional research grants from Chiesi, UCB, Amgen, Johnson and Johnson, and the European Medicines Agency (EMA), none of which relate to the content of this manuscript. Furthermore, the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability data and materials

Patient-level data from the IPCI and SIDIAP databases are accessible only to authorized users on authorized computers at the respective sites. Data sharing is restricted to aggregated forms, as presented in this study. Detailed methodologies and code are available in the GitHub repository cited in this work. For further inquiries, please contact the corresponding author.

Author contributions

VP: Conceptualization, Formal Analysis, Methodology, Software, Visualization, Writing–original draft, Writing–review and editing, Methodology, Visualization. HL: Formal Analysis, Software, Visualization, Writing–review and editing, CB: Software, Writing–review and editing, APC: Software, Writing–review and editing, ILS: Writing–review and editing, TDS: Resources, Writing–review and editing PR: Supervision, Writing–review and editing. KV: Conceptualization, Supervision, Writing–review and editing.

6

Chapter 6

Parasitic infections related to anti-type 2 immunity monoclonal antibodies: a disproportionality analysis in the Food and Drug Administration's Adverse Event Reporting System (FAERS)

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ABSTRACT

Introduction

Monoclonal antibodies (mAbs) targeting immunoglobulin E (IgE) [omalizumab], type 2 (T2) cytokine interleukin (IL) 5 [mepolizumab, reslizumab], IL-4 Receptor(R) α [dupilumab], and IL-5R [benralizumab], improve quality of life in patients with T2-driven inflammatory diseases. However, there is a concern for an increased risk of helminth infections. The aim was to explore safety signals of parasitic infections for omalizumab, mepolizumab, reslizumab, dupilumab, and benralizumab.

Methods

Spontaneous reports were used from the Food and Drug Administration's Adverse Event Reporting System (FAERS) database from 2004-2021. Parasitic infections were defined as any type of parasitic infection term obtained from the Standardised Medical Dictionary for Regulatory Activities® (MedDRA®). Safety signal strength was assessed by the Reporting Odds Ratio (ROR).

Results

15,502,908 reports were eligible for analysis. Amongst 175,888 reports for omalizumab, mepolizumab, reslizumab, dupilumab and benralizumab, there were 79 reports on parasitic infections. Median age was 55 years (interquartile range 24-63 years) and 59.5% were female. Indications were known in 26 (32.9%) reports; 14 (53.8%) biologicals were reportedly prescribed for asthma, 8 (30.7%) for various types of dermatitis, and 2 (7.6%) for urticaria. A safety signal was observed for each biological, except for reslizumab (due to lack of power), with the strongest signal attributed to benralizumab (ROR = 15.7, 95% Confidence Interval: 8.4 - 29.3).

Conclusion

Parasitic infections were disproportionately reported for mAbs targeting IgE, T2 cytokines, or T2 cytokine receptors. While the number of adverse event reports on parasitic infections in the database was relatively low, resulting safety signals were disproportionate and warrant further investigation.

INTRODUCTION

The discovery of human immunoglobulin E (IgE) in 1968 [234] and an increased understanding of type 2 (T2) inflammatory pathways since the 1990s contributed to the development of today's monoclonal antibodies (mAbs) targeted at T2 inflammation driven diseases [235]. Within asthma there is an endotype that is broadly characterized by T2 inflammation, namely T2 asthma [236]. T2 asthma demands a different treatment strategy than non-T2 asthma. Besides T2 asthma, also chronic urticaria, chronic rhinosinusitis with nasal polyps (CRSwNP), and atopic dermatitis are characterized by T2 inflammation [237,238]. While increased blood eosinophils are a biomarker for T2 asthma, a differential diagnosis is extensive and includes CRSwNP, vasculitis, and parasitic disease [239]. These eosinophils contribute to innate immune responses against helminths (i.e. multicellular parasitic worms) through phagocytosis, release of cytotoxic proteins and formation of extracellular traps [240].

The availability of biologicals has aided patients with severe asthma in reducing exacerbations and oral corticosteroid use, while improving lung function and quality of life, especially in patients with T2 asthma [241]. The IgE-binding mAb omalizumab was approved in 2002 for the treatment of moderate-to-severe allergic asthma among adults and adolescents by the Therapeutic Goods Administration in Australia [242]. After that, more mAbs targeting T2 asthma were approved, namely mepolizumab, reslizumab, benralizumab, and dupilumab [243]. Dupilumab was primarily registered for the treatment of moderate-to-severe atopic dermatitis in 2017 [244], for the treatment of asthma in 2018, and for the treatment of CRSwNP in 2019 [245]. Omalizumab was additionally registered for the treatment of chronic urticaria in 2014 [246]. Clinical trials have shown that these biologicals contribute to disease control of T2 inflammatory diseases, especially in patients with T2 asthma [238,247]. While the effectiveness of these biologicals in real life has been demonstrated, further evaluation of the long-term safety of biologicals is needed as safety profiling studies are limited [248]. In the clinical trials safety profiles were similar for patients in the intervention group and placebo group, with a low number of serious adverse events (AEs) [249–251]. More recently post-marketing studies confirm the low incidence of serious AEs in patients receiving anti-T2 biologicals, while identifying previously unknown risks [252–254]. Anaphylaxis signals have been described for omalizumab, benralizumab, reslizumab, and mepolizumab [255]. Dupilumab has been linked with eye disorders, especially in patients with atopic dermatitis [256].

In recent years, concerns were expressed for a hypothesized increased risk of parasitic infections among patients using biologicals affecting the T2 immune response [257]. Such biologicals are dupilumab, omalizumab, mepolizumab, benralizumab, and reslizumab. Omalizumab binds to free IgE, inhibiting further binding of IgE to high-affinity IgE receptors on mast cells and basophils [248], while IgE is considered an important part of the multi-component T2 immune response towards parasitic infections [258,259]. Dupilumab

binds to interleukin (IL-) 4 receptor α, which inhibits IL-4 and IL-13 signaling [248], while both cytokines contribute to the elimination of parasites through increased mucus production and eosinophilic mucosal inflammation in the gut [260,261]. Benralizumab binds to IL-5Rα, resulting into depletion of eosinophils in the blood and mucosal tissues via antibody-dependent cell-mediated cytotoxicity [248], and might thus interfere with the eosinophil-mediated killing and expulsion of gastro-intestinal helminths [261]. Reslizumab and mepolizumab bind to circulating interleukin IL-5 [248], likewise an important cytokine contributing to eosinophilic differentiation and activation [261,262].

In current clinical studies and routine practice, reporting of parasitic infections is based on spontaneous reporting, rather than systematic anamnestic or biochemical screening. Especially in endemic regions, routine screening for parasitic infections may be useful. So far, no studies were performed on the Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) investigating the risk of parasitic infections among patients using biologicals affecting the T2 immune response. Therefore, the objective of this study was to determine if parasitic infections are disproportionately reported for biologicals affecting the T2 immune response.

METHODOLOGY

Data source

For this study, we used publicly available quarterly data files from FAERS covering the period 2004-2021 [77,78]. FAERS data represents data from spontaneous reports on (product quality complaints resulting in) AEs and medication errors in relation to medication (excluding vaccines) and medical devices [46]. The FDA receives reports from healthcare professionals, consumers, manufacturers, and lawyers. The FDA's MedWatch Online Voluntary Reporting Form is freely available to the worldwide public and facilitates sending in a report [76]. Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities® (MedDRA®) are used as a standardized coding practice for the reported events in a received report.

Data processing

Data processing of the quarterly files was performed by the Adverse Event Open Learning through Universal Standardization (AEOLUS) system [80]. AEOLUS performs standardization of the FAERS data, case deduplication, and disproportionality analyses as described in further detail by Banda *et al.* [55]. The algorithm removes any duplicate cases based on exact matches on the combined demographic fields, list of drugs and list of outcomes (FAERS reactions). Additionally, the FDA and manufacturers provide a list of suggested cases to be deleted within each batch of quarterly datafiles since the first quartile of 2019 for various purposes, including combining cases. The original AEOLUS scripts were adapted for

downloading and processing data up to the final quarter of 2021. Mapping of drug names to the Anatomical Therapeutic Chemical (ATC) coding system was performed by the locally developed AIOLI system [81]. Only drugs mapped to an ATC code and marked as primary suspect within a FAERS report were included in the analysis. All age units in the data were converted to years. The age variable was marked as invalid in case of a negative value, no indicated age unit, or missing age.

Case definition and selection process

All the selected FAERS reports from the FAERS database as described previously were processed. The reported AE of interest was a parasitic infection, which was defined as any PT falling under the MedDRA® High Level Group Term (HLGT) "Helminthic Disorders" or a PT related to parasitic infections noted under High Level Term (HLT) "Infections – Not elsewhere classified (NEC)" according to MedDRA® version 24.1. All these PTs are listed in Supplementary Table S1. Descriptive statistics and disproportionality results were presented for reports stating a parasitic infection and one of the following mAbs marked as the primary drug suspect: dupilumab (ATC: D11AH05), omalizumab (ATC: R03DX05), mepolizumab (ATC: R03DX09), benralizumab (ATC: R03DX10), and reslizumab (ATC: R03DX08).

Disproportionality analyses

Signals of disproportionate reporting (SDRs) were produced by AEOLUS and expressed as Reporting Odds Ratio's (RORs) with a 95% confidence interval (CI). The ROR and 95% CI were calculated according to equations (1) and (2). Letters A, B, C and D in equations (1) and (2) represent drug-event combinations (DECs) as specified in Table 1.

$$ROR = \frac{A/C}{B/D} \tag{1}$$

$$95\%\ CI\ for\ ROR = e^{ln(ROR) \pm 1.96\sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}} \tag{2}$$

Table 1. Overview of report counts based on various drug-event combinations (DECs) expressed by the letters A, B, C and D, including variations on counts C and D, represented by the dagger (†) and double dagger (‡), for the purpose of various disproportionality analyses as previously represented by equations (1) and (2) in the manuscript. The found fixed A and B counts for every biologic of interest were used in every analyses, while the C and D counts were different per analysis.

	Parasitic infection	**Other events**	**Target Analysis**
A biologic of interest	A	B	All analyses
All other drugs	C	D	Primary analysis
All other drugs, excluding ATC group P drugs	C †	D †	1st secondary analysis
All other biologics of interest	C ‡	D ‡	2nd secondary analysis

ATC - Anatomical Therapeutic Chemical classification; group P - Antiparasitic products, insecticides and repellents.

A SDR was considered disproportionate if the lower boundary of the 95% CI was greater than 1 and the drug-event count was at least 3, in accordance to guidelines from the European Medicines Agency (EMA) [85]. Three disproportionality analyses were performed as described in Table 1: i) using DECs over the entire FAERS database, ii) using DECs over the entire FAERS database excluding drugs under ATC group P [antiparasitic products, insecticides, and repellents] and iii) using DECs of only dupilumab, omalizumab, mepolizumab, benralizumab, and reslizumab. Descriptive statistics were performed on the reports relating to parasitic infections and users of the mAb therapies of interest.

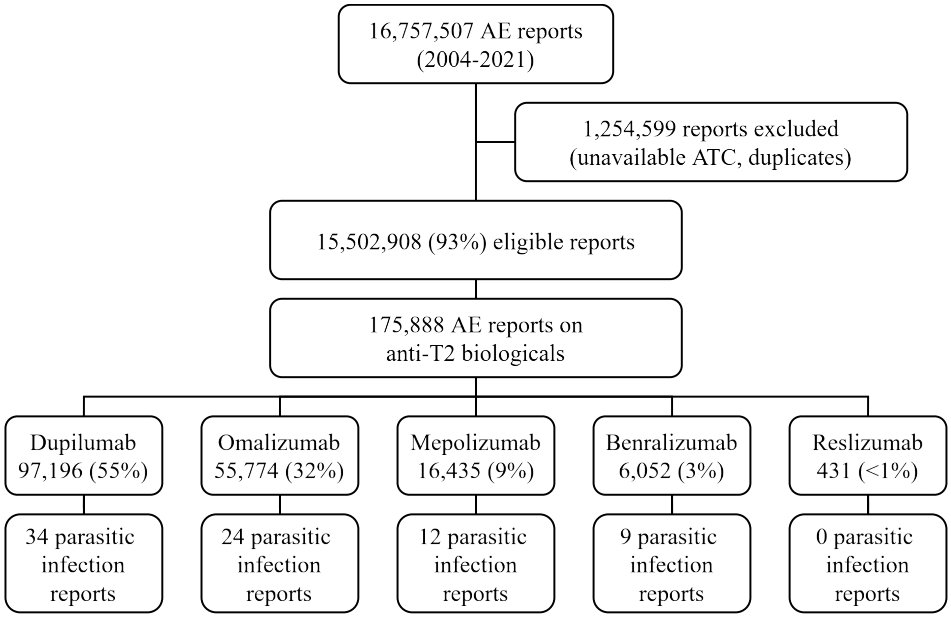

Figure 1. Overview of the data extraction process. AE - Adverse Event; ATC - Anatomical Therapeutic Chemical classification; T2 - Type 2.

RESULTS

Primary analysis

The FAERS database contains 16,757,507 AE reports from 2004-2021. The data extraction process is displayed with a flowchart (Figure 1). A total of 15,502,908 (93%) reports were eligible for the primary disproportionality analysis based on the availability of an ATC code for the primary drug suspect. Among the 175,888 AE reports concerning anti-T2 immunity biologicals in FAERS, 97,196 (55%) were on dupilumab, followed by 55,774 (32%) for omalizumab, 16,435 (9%) for mepolizumab, 6,052 (3%) for benralizumab, and 431 (<1%) for reslizumab. For these biologicals, 79 reports on parasitic infections were found within FAERS, mentioning 81 PTs related to parasitic infections. The following report characteristics are displayed in Table 2. Reported median age within the 79 reports was 55 years with an

interquartile range of 24-63 years. Most of the reports indicated sex (47 [59.5%] individuals were female). The reports were mostly submitted by consumers, accounting for 44 (55.7%) reports, followed by 25 (32.9%) submitted by physicians. Most reports originated from the United states of America (USA), being 58 (73.4%). Indications were mentioned in 26 reports; 14 (53.8%) biologicals were reportedly prescribed for asthma, 5 (19.2%) for atopic dermatitis and 2 (7.7%) for dermatitis. The following indications were reported only once: "chronic spontaneous urticaria", "eosinophil count increased", "nasal polyps", "neurodermatitis", and "urticaria chronic". FAERS case numbers and data on case level for these reports can be found in Supplementary Table S2.

Table 2. Characteristics of reports related to the monoclonal antibodies of interest with a mention of parasitic infection.

Total reports of interest	79
Median Age, in years (IQR)	55 (24-63)
	Count (proportion)
Sex	
Female	47 (59.5 %)
Male	18 (22.8 %)
Unknown	14 (17.7 %)
Reporter type	
Consumer	44 (55.7%)
Physician	26 (32.9%)
Pharmacist	1 (1.3%)
Other health-professional	5 (6.3%)
Unknown	3 (3.8%)
Reporter country	
United States of America	58 (73.4%)
15 other countries, each contributing <5%	21 (26.6%)
Indication	
Asthma	14 (17.7 %)
Dermatitis Atopic	5 (6.3 %)
Dermatitis	2 (2.5 %)
Chronic Spontaneous Urticaria	1 (1.3 %)
Eosinophil Count Increased	1 (1.3 %)
Nasal Polyps	1 (1.3 %)
Neurodermatitis	1 (1.3 %)
Urticaria Chronic	1 (1.3 %)
Unknown	53 (67.1 %)

IQR - Interquartile range.

Health outcomes varied per mAb of interest (Figure 2). Omalizumab reports had proportionally the most reported health outcomes and the least missing outcomes. The most commonly reported outcome was "other serious (important medical event, unspecified)", accounting for 16 (61.5%) of the omalizumab reports. The highest proportion for no health outcome reported was for benralizumab, being 6 (66.7%) reports. Death has been reported in 1 (7.7%) report for mepolizumab and 1 (3.8%) in omalizumab. The "life-threatening" health outcome was reported in 2 (7.7%) reports of omalizumab and 1 (2.6%) report of dupilumab. Available raw data on start date therapy, end date therapy, and time of event were provided in supplementary Table S3.

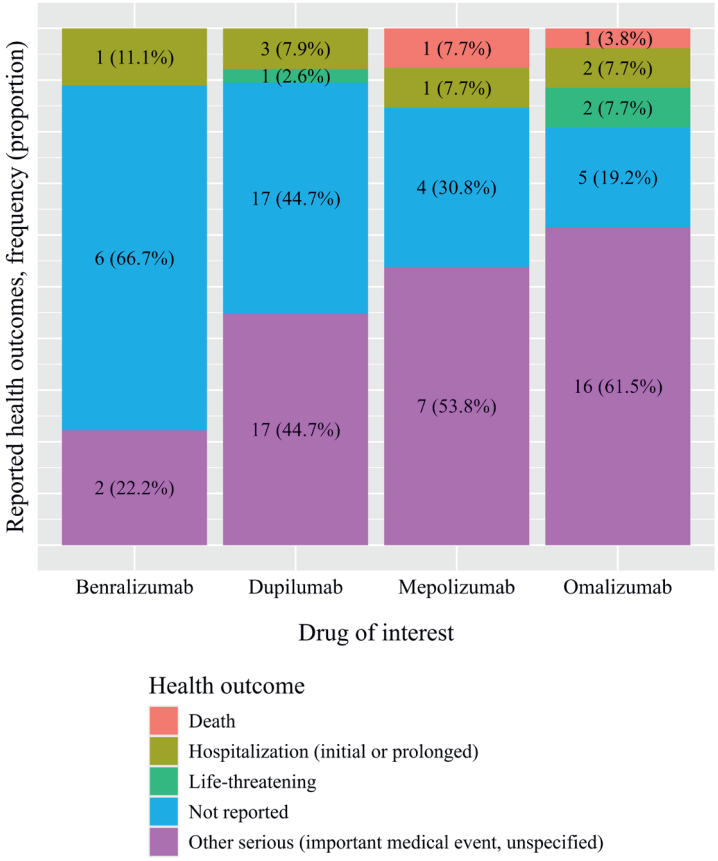

Figure 2. Reported health outcomes for benralizumab, dupilumab, mepolizumab, and omalizumab, expressed in absolute numbers and proportions per drug.

Parasitic infections were found in 34 (43%) reports for dupilumab, followed by 24 (30.4%) reports for omalizumab, 9 (11.4%) for benralizumab, and 12 (15.2%) for mepolizumab. No parasitic infections were reported for reslizumab. The specific parasitic infections for each biological can be found in supplementary Table S2. Benralizumab showed the strongest SDR for the primary analysis (Figure 3), with a ROR of 15.7 (95% CI: 8.4-29.3). The second strongest SDR was for mepolizumab, showing a ROR of 5.9 (95% CI: 3.4-10.4). The SDRs for omalizumab and dupilumab were similar, with RORs of 3.9 (95% CI: 2.6-5.8) and 4 (95% CI: 2.8-5.6), respectively. For reslizumab no ROR could be calculated in any analysis because there were no AE reports on parasitic infections for this biological.

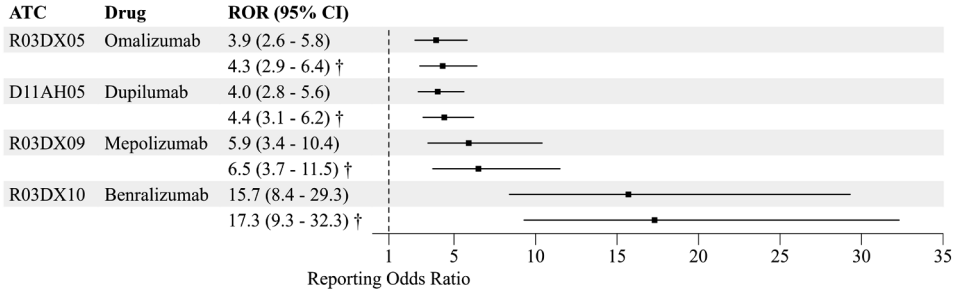

Figure 3. Signals of disproportionate reporting for biologics of interest compared to other drugs concerning parasitic infections. Results are shown of the primary analysis utilizing the entire database and of the 1st secondary analysis. No signal could be produced for reslizumab due to lack of power. ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio. †Results from the 1st secondary analysis utilizing the entire database, excluding drugs under Anatomical Therapeutic Chemical classification group Antiparasitic products, insecticides and repellents [see methods for detailed description].

Secondary sensitivity analyses

In the 1st secondary analysis (Figure 3, results marked by a dagger [†]), we excluded 30,748 AE reports concerning drugs under ATC level 5 group P [Antiparasitic products, insecticides and repellents], to minimize the risk of bias (e.g. due to "reverse causation"). In this secondary analysis, the SDRs for the biologicals of interest were similar to those in the primary analyses, however with a slight increase in ROR for all biologicals. In the 2nd secondary analysis, we tested the disproportionality on parasitic infections only within the group of selected biologicals (Figure 4). Parasitic infections were disproportionately reported for benralizumab compared to the other biologicals of interest. The ROR for benralizumab was 3.8 (95% CI: 2-7.4), while the RORs for dupilumab, omalizumab and mepolizumab were not signifying disproportionality. Details of various DECs are illustrated in Supplementary Table S4-S6 in the Online Repository.

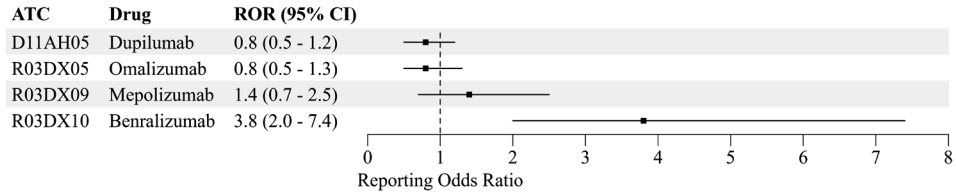

Figure 4. Signals of disproportionate reporting within the group of biologics of interest concerning parasitic infections. Results are shown of the 2nd secondary analysis utilizing reports only from dupilumab, omalizumab, mepolizumab, benralizumab and reslizumab [see methods for detailed description]. No signal could be produced for reslizumab due to lack of power. ATC - Anatomical Therapeutic Chemical classification; CI - Confidence interval; ROR - Reporting odds ratio.

DISCUSSION

Even though a limited amount of AE case reports on parasitic infections were retrieved from the FAERS database, we demonstrated SDRs for parasitic infections associated with anti-IgE omalizumab and anti-T2 cytokine (receptor) antibodies dupilumab, mepolizumab, and benralizumab. In addition, we discovered that within the group of these biologicals parasitic infections were disproportionately reported for benralizumab. Given the mechanism of action of benralizumab [binding to IL-5R on eosinophils and basophils, and consequently depleting eosinophils in the blood and mucosal tissues such as the gastro-intestinal tract through antibody-dependent, cell-mediated toxicity][248], it could be reasoned why proportionally more AE reports on parasitic infections were found in FAERS for benralizumab compared to the other biologicals. These SDRs should be taken seriously since a major clinical impact has been reported in the case reports, including death, life-threatening situations, hospitalizations, and other serious (unspecified) medical events.

For reslizumab no AE reports were found on parasitic infections within FAERS, which could be attributed to a general low reporting rate for this biological and most probably due to lack of power. Indeed, spontaneous reports for the other biologicals were roughly a 12-16-fold more often received by the FDA than for reslizumab. The lower reporting rate for reslizumab might be due to a low number of patients receiving the drug because reslizumab has to be administered intravenously in the hospital. In contrast, other biologicals can be self-administered subcutaneously (e.g. at home), making treatment with reslizumab less practical and potentially more costly within the healthcare system [263]. Excluding drugs from the ATC drug group P in the 1st secondary analysis showed a slight increase in disproportionality for all the biologicals of interest, indicating a confounding effect.

Notably, 50 out of 79 parasitic infections were unspecified, raising concerns on the validity of the submitted reports. The parasitic infections might have been reported by individuals, such

as consumers or even healthcare workers, with no experience in the diagnosis of parasitic infections. On the other hand, sufficient information might have been provided by an experienced or treating healthcare professional to the reporter of the AE. The validity of the start date of treatment, end date of treatment, and event date (i.e. date of parasitic infection) should be carefully interpreted, as in most cases these data elements were not reported, and in some cases the parasitic infection was reported before the start date of the mAb treatment. The latter would be unlikely as only primary drug suspects for the reported events were selected for analysis. Recently, a correspondence article by Lifar *et al.* has been published describing a disproportionality analysis of parasitic infections among omalizumab, mepolizumab, benralizumab and dupilumab within the VigiBase using a case/noncase design in which the control group was represented by the disease concept "asthma" in combination with at the time approved inhalation therapies [264]. Lifar *et al.* showed that only benralizumab among the biologicals of interest was disproportionately reported for parasitic infections compared to the control group. In comparison, our study showed disproportionality for all biologicals of interest, except for reslizumab, while utilizing the entire FAERS database representing a broader range of patients and medication.

While theoretically it can be expected that patients using these biologicals would be at an increased risk for parasitic infections, literature is relatively scarce on the topic, and evidence on the increased risk is weak. A 2007 clinical trial performed in Brazil reported that 50% (34 of 68) of the omalizumab arm experienced at least 1 intestinal helminth infection, compared to 41% (28 of 69) of the placebo arm [265]. The odds ratio (OR) was 1.47 with a 95% CI of 0.74-2.95. The OR was 2.2 (95% CI: 0.94-5.15) after adjusting for study visit, baseline infection status, sex, and age. In a 2013 omalizumab study in Turkey with 19 participants having severe asthma, 1 case of giardiasis was reported [266]. An observational Italian study between 2007 and 2016 in which 91 patients received omalizumab did not report any parasitic infections [267]. A 2021 clinical trial showed that 7 out of 271 (2.6%) children with uncontrolled moderate-to-severe asthma in the dupilumab arm experienced a non-severe parasitic infection compared to 0 out of 134 subjects in the placebo arm [268]. A 2019 pooled analysis on infections in 1841 atopic dermatitis patients using dupilumab showed that no parasitic infections were reported [269]. In a review from 2019 by Tan *et al.* no cases of parasitic infections were reported in clinical trials assessing dupilumab, benralizumab, reslizumab, and mepolizumab in patients with severe asthma [257]. A more recent 2021 review by Dragonieri and Carpagnano highlighted additional studies for mepolizumab and reslizumab, however, did not find reported cases with parasitic infections [270]. In all of the summary of product characteristics (SmPCs) of the studied biologicals, it is recognized that IgE and eosinophils are involved in the immunological response for parasitic infections, hence some caution should be considered when individuals at high risk of parasitic infection are treated with the discussed biologicals [271–275].

Besides the well-known shortcomings of randomized clinical trials (RCTs) compared to observational studies [276], RCTs involving the discussed biologicals often excluded patients with a (history of) parasitic infection or a recent (or planned) visit to a country with prevalent parasitic infections [260,269,277–280]. A 2022 open-label extension study on the safety and efficacy of dupilumab also excluded individuals which were suspected or at high risk of parasitic infections [281]. Therefore, more real world studies on this topic should be performed to gain deeper understanding on the effect of anti-T2 immunity biologicals on parasitic infections.

Limitations and strengths

While the FAERS database contains a rich dataset which is publicly available, it is subject to underreporting and selective reporting of cases [127], potentially leading to biased results. Unmeasured and unknown confounders related to the population of the select mAb users and the population which contracted parasitic infections while being on any kind of drug therapy might have biased the results. To the best of our knowledge, there are no (strong) confounders theorized in literature which should be taken into account to produce less biased results. Potential confounding effect was addressed by excluding reports where the primary drug suspect was related to ATC group P. If the seriousness of a parasitic infection is low, then it might not be reported, as previous research among physicians showed that AEs are most probably reported in case of being a serious unknown AE of an established drug or new drug, or a serious known Adverse Drug Reaction (ADR) attributed to a new drug [282]. Even though most of the biologicals showed disproportionate reporting for parasitic infections, further root cause analysis is necessary to conclude if these biologicals were truly causative for the parasitic infections. Pharmacovigilance studies are based on spontaneous reports which allow for the calculation of RORs, however event rates cannot be calculated as these would require data on the total number of patients exposed to these biologicals. A major limitation of spontaneous reporting is indeed that causation does not have to be proven. Due to a relatively low reporting of reslizumab cases, a SDR could not be calculated. Besides underreporting, in-depth analysis of these data are hampered by missing data for the available reports, and the scarcity of demographic and clinical metadata for these cases. While dupilumab is on the market since 2002, the public FAERS database has only been made available since 2004, potentially missing more cases of parasitic infections on dupilumab. It should be noted that this is the first study, with a thoroughly described analysis and in-depth case details, performed on a spontaneous reporting system on the disproportionate reporting of parasitic infections associated with biologicals targeting IgE, T2 cytokines, or T2 cytokine receptors, opening up further discussions on the safety profile of these biologicals and motivating additional studies on the proposed association.

CONCLUSION

Parasitic infections were disproportionately reported for mAbs targeting IgE, T2 cytokines, or T2 cytokine receptors. While the number of AE reports on parasitic infections in the FAERS database was relatively low, the resulting safety signals were disproportionate and warrant further investigation.

DECLARATIONS

Data availability statement

The publicly available datasets can be found here: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. Further inquiries can be directed to the corresponding author.

Author contributions

VP, GB, and KV contributed to the conception and design of the study; Software and input components were provided by RP, JK, EM, and MW; Analysis and data visualization was performed by VP. The first draft of the manuscript was written by VP, GB, SR and KV; Supervision for this work was provided by KV and PR; All authors reviewed previous versions of the manuscript; All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The research group from the Department of Medical Informatics receives/received unconditional research grants from Chiesi, GlaxoSmithKline (GSK), UCB, and Amgen, Johnson and Johnson, and the European Medicines Agency, none of which relate to the content of this manuscript. GB received payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Merck Sharp & Dohme (MSD), Novartis, and Sanofi, none of which relate to the content of this manuscript. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIALS

Table S1. Preferred terms from the Medical Dictionary for Regulatory Activities®, version 24.1, representing parasitic infections under the high level group term "Helminthic disorders" and "Infections - pathogen unspecified". NEC - Not elsewhere classified.

Code	Preferred Term	High Level Term
10069517	Angiostrongylus infection	Nematode infections
10002533	Anisakiasis	Nematode infections
10060967	Arthritis helminthic	Helminthic infections NEC
10003442	Ascariasis	Nematode infections
10065200	Biliary tract infection helminthic	Helminthic infections NEC
10007187	Capillariasis	Nematode infections
10061039	Cestode infection	Cestode infections
10009344	Clonorchiasis	Trematode infections
10059547	Cutaneous larva migrans	Nematode infections
10065199	Cystitis helminthic	Helminthic infections NEC
10080485	Dicrocoeliasis	Trematode infections
10013029	Diphyllobothriasis	Cestode infections
10080486	Dipylidiasis	Cestode infections
10080290	Dirofilariasis	Nematode infections
10080496	Disseminated strongyloidiasis	Nematode infections
10013618	Dracunculiasis	Nematode infections
10014096	Echinococciasis	Cestode infections
10065327	Endocarditis helminthic	Helminthic infections NEC
10014881	Enterobiasis	Nematode infections
10065204	Enterocolitis helminthic	Helminthic infections NEC
10065180	Eye infection helminthic	Helminthic infections NEC
10016234	Fascioliasis	Trematode infections
10016235	Fasciolopsiasis	Trematode infections
10016674	Filariasis	Nematode infections
10016675	Filariasis lymphatic	Nematode infections
10065207	Gastritis helminthic	Helminthic infections NEC
10065223	Genital infection helminthic	Helminthic infections NEC
10018490	Gnathostomiasis	Nematode infections
10061201	Helminthic infection	Helminthic infections NEC
10019659	Hepatic echinococciasis	Cestode infections
10065216	Hepatic infection helminthic	Helminthic infections NEC
10020017	Heterophyiasis	Trematode infections
10020376	Hookworm infection	Nematode infections
10020546	Hymenolepiasis	Cestode infections

Table S1. Preferred terms from the Medical Dictionary for Regulatory Activities®, version 24.1, representing parasitic infections under the high level group term "Helminthic disorders" and "Infections - pathogen unspecified". NEC - Not elsewhere classified. (*continued*)

Code	Preferred Term	High Level Term
10021857	Infection parasitic	Infections NEC
10065210	Lymphadenitis helminthic	Helminthic infections NEC
10065171	Meningoencephalitis helminthic	Helminthic infections NEC
10027436	Metagonimiasis	Trematode infections
10065219	Myocarditis helminthic	Helminthic infections NEC
10062701	Nematodiasis	Nematode infections
10058443	Neurocysticercosis	Cestode infections
10030314	Onchocerciasis	Nematode infections
10084319	Onchodermatitis	Nematode infections
10030897	Opisthorchiasis	Trematode infections
10065329	Oral helminthic infection	Helminthic infections NEC
10065189	Pancreatitis helminthic	Helminthic infections NEC
10033794	Paragonimiasis	Trematode infections
10069588	Parasitic encephalitis	Infections NEC
10067720	Parasitic gastroenteritis	Infections NEC
10056704	Parasitic esophagitis	Infections NEC
10078883	Parasitic pneumonia	Infections NEC
10065221	Pericarditis helminthic	Helminthic infections NEC
10065326	Peritonitis helminthic	Helminthic infections NEC
10065246	Pneumonia helminthic	Helminthic infections NEC
10037374	Pulmonary echinococciasis	Cestode infections
10078264	Renal echinococciasis	Cestode infections
10039603	Schistosomiasis	Trematode infections
10039605	Schistosomiasis bladder	Trematode infections
10039606	Schistosomiasis cutaneous	Trematode infections
10039610	Schistosomiasis liver	Trematode infections
10065172	Skin infection helminthic	Helminthic infections NEC
10065193	Splenic infection helminthic	Helminthic infections NEC
10042254	Strongyloidiasis	Nematode infections
10080487	Syngamiasis	Nematode infections
10043095	Taeniasis	Cestode infections
10043720	Thyroid echinococciasis	Cestode infections
10044269	Toxocariasis	Nematode infections
10061859	Trematode infection	Trematode infections
10044608	Trichiniasis	Nematode infections
10044627	Trichostrongyliasis	Nematode infections

Table S1. Preferred terms from the Medical Dictionary for Regulatory Activities®, version 24.1, representing parasitic infections under the high level group term "Helminthic disorders" and "Infections - pathogen unspecified". NEC - Not elsewhere classified. (*continued*)

Code	Preferred Term	High Level Term
10044630	Trichuriasis	Nematode infections
10065258	Tropical eosinophilia	Nematode infections
10065186	Upper respiratory tract infection helminthic	Helminthic infections NEC
10065328	Vulvovaginitis helminthic	Helminthic infections NEC
10065243	Wound infection helminthic	Helminthic infections NEC

Table S2. Reference numbers for case reports describing the use of (i) omalizumab, dupilumab, mepolizumab, benralizumab or reslizumab and (ii) describing a parasitic infection, accompanied by a description of indication, type of parasitic infection and year with quarter. †From the legacy adverse event reporting system database.

Report id	Drug	Indication	Parasitic Infection	Report year	Quarter	Reporter	Country
6412861†	Omalizumab	Unknown	Infection Parasitic	2009	Q4	Other health-professional	United States
6422338†	Omalizumab	Unknown	Infection Parasitic	2009	Q4	Physician	United States
7456124†	Omalizumab	Asthma	Taeniasis	2011	Q2	Physician	Italy
7831160†	Omalizumab	Asthma	Helminthic Infection	2011	Q4	Physician	United Kingdom
88868233	Omalizumab	Asthma	Hepatic echinococciasis	2013	Q2	Other health-professional	Unknown
112279541	Omalizumab	Unknown	Infection parasitic	2015	Q2	Other health-professional	United States
116713721	Omalizumab	Unknown	Infection parasitic	2015	Q4	Consumer	United States
120462742	Omalizumab	Unknown	Infection parasitic	2016	Q1	Physician	United States
127270233	Omalizumab	Unknown	Infection parasitic	2017	Q2	Other health-professional	United States
128327562	Mepolizumab	Unknown	Infection parasitic	2016	Q4	Consumer	United States
130536502	Omalizumab	Unknown	Infection parasitic	2017	Q1	Physician	Canada
133047542	Omalizumab	Urticaria Chronic	Diphyllobothriasis	2017	Q2	Physician	Denmark
135297952	Omalizumab	Asthma	Enterobiasis	2017	Q2	Physician	United States
135384151	Omalizumab	Asthma	Strongyloidiasis	2017	Q2	Physician	Spain
135833931	Omalizumab	Unknown	Infection parasitic	2017	Q2	Consumer	Netherlands
135951192	Omalizumab	Chronic Spontaneous Urticaria	Opisthorchiasis	2017	Q3	Physician	Russian Federation
152438235	Dupilumab	Unknown	Infection parasitic	2018	Q4	Physician	United States
153768121	Omalizumab	Unknown	Infection parasitic	2018	Q3	Consumer	United States
154171474	Benralizumab	Unknown	Infection parasitic	2019	Q2	Physician	United States
155437031	Mepolizumab	Unknown	Strongyloidiasis	2018	Q4	Other health-professional	Australia
155446756	Omalizumab	Asthma	Arthritis helminthic	2019	Q3	Consumer	Brazil
156369229	Dupilumab	Dermatitis Atopic	Helminthic infection	2020	Q3	Consumer	United States
159035971	Benralizumab	Asthma	Enterobiasis	2019	Q1	Physician	United States

Table S2. Reference numbers for case reports describing the use of (i) omalizumab, dupilumab, mepolizumab, benralizumab or reslizumab and (ii) describing a parasitic infection, accompanied by a description of indication, type of parasitic infection and year with quarter. †From the legacy adverse event reporting system database. (*continued*)

Report id	Drug	Indication	Parasitic Infection	Report year	Quarter	Reporter	Country
159198241	Omalizumab	Unknown	Infection parasitic	2019	Q1	Physician	United States
159279334	Benralizumab	Asthma	Infection parasitic	2019	Q2	Unknown	United States
159279334	Benralizumab	Asthma	Strongyloidiasis	2019	Q2	Unknown	United States
159385621	Omalizumab	Unknown	Infection parasitic	2019	Q1	Consumer	United States
159385621	Omalizumab	Unknown	Enterobiasis	2019	Q1	Consumer	United States
159389361	Omalizumab	Unknown	Enterobiasis	2019	Q1	Consumer	United States
160665231	Mepolizumab	Unknown	Infection parasitic	2019	Q1	Consumer	Canada
160926871	Benralizumab	Unknown	Infection parasitic	2019	Q1	Consumer	United States
161733721	Benralizumab	Asthma	Helminthic infection	2019	Q2	Physician	United States
162228012	Mepolizumab	Unknown	Enterobiasis	2019	Q2	Consumer	United States
162231351	Dupilumab	Unknown	Infection parasitic	2019	Q2	Physician	United States
163153155	Dupilumab	Asthma	Enterobiasis	2020	Q2	Consumer	United States
164557632	Mepolizumab	Asthma	Helminthic infection	2019	Q3	Consumer	United States
164821131	Dupilumab	Unknown	Infection parasitic	2019	Q2	Consumer	United States
165259972	Mepolizumab	Unknown	Infection parasitic	2019	Q4	Consumer	United States
165380635	Dupilumab	Dermatitis Atopic	Helminthic infection	2020	Q4	Consumer	United States
165871631	Dupilumab	Unknown	Infection parasitic	2019	Q3	Consumer	United States
166135231	Omalizumab	Unknown	Infection parasitic	2019	Q3	Physician	Peru
166854971	Dupilumab	Unknown	Infection parasitic	2019	Q3	Consumer	United States
168228951	Mepolizumab	Unknown	Parasitic gastroenteritis	2019	Q3	Consumer	Slovakia
169536901	Dupilumab	Asthma	Helminthic infection	2019	Q4	Consumer	United States
169750711	Dupilumab	Unknown	Infection parasitic	2019	Q4	Consumer	United States
170932051	Mepolizumab	Unknown	Strongyloidiasis	2019	Q4	Consumer	United States

Table S2. Reference numbers for case reports describing the use of (i) omalizumab, dupilumab, mepolizumab, benralizumab or reslizumab and (ii) describing a parasitic infection, accompanied by a description of indication, type of parasitic infection and year with quarter. †From the legacy adverse event reporting system database. (*continued*)

Report id	Drug	Indication	Parasitic Infection	Report year	Quarter	Reporter	Country
173246732	Omalizumab	Asthma	Enterobiasis	2020	Q4	Consumer	Canada
175066951	Omalizumab	Unknown	Infection parasitic	2020	Q1	Consumer	United States
175440962	Omalizumab	Unknown	Parasitic gastroenteritis	2020	Q2	Physician	Uruguay
176897311	Dupilumab	Unknown	Helminthic infection	2020	Q2	Consumer	United States
177316141	Benralizumab	Eosinophil Count Increased	Enterobiasis	2020	Q2	Consumer	United States
178661361	Dupilumab	Unknown	Cestode infection	2020	Q2	Pharmacist	Germany
178773361	Benralizumab	Asthma	Trichuriasis	2020	Q2	Physician	United States
181342151	Mepolizumab	Unknown	Helminthic infection	2020	Q3	Consumer	United Kingdom
181359671	Mepolizumab	Unknown	Helminthic infection	2020	Q3	Consumer	United Kingdom
182472141	Mepolizumab	Unknown	Infection parasitic	2020	Q3	Consumer	United States
182565491	Dupilumab	Dermatitis	Enterobiasis	2020	Q3	Consumer	United States
182811391	Dupilumab	Unknown	Infection parasitic	2020	Q3	Unknown	United States
183252511	Benralizumab	Unknown	Helminthic infection	2020	Q3	Unknown	United States
183524341	Dupilumab	Unknown	Helminthic infection	2020	Q4	Consumer	United States
184553801	Dupilumab	Unknown	Infection parasitic	2020	Q4	Consumer	United States
187547381	Dupilumab	Unknown	Parasitic gastroenteritis	2021	Q1	Consumer	United States
188900731	Dupilumab	Unknown	Infection parasitic	2021	Q1	Consumer	United States
189987444	Dupilumab	Dermatitis	Enterobiasis	2021	Q4	Physician	United States
190275381	Dupilumab	Unknown	Helminthic infection	2021	Q1	Physician	United States
190772101	Dupilumab	Unknown	Enterobiasis	2021	Q1	Consumer	United States
191667251	Dupilumab	Neurodermatitis	Helminthic infection	2021	Q2	Consumer	Germany

Table S2. Reference numbers for case reports describing the use of (i) omalizumab, dupilumab, mepolizumab, benralizumab or reslizumab and (ii) describing a parasitic infection, accompanied by a description of indication, type of parasitic infection and year with quarter. †From the legacy adverse event reporting system database. (*continued*)

Report id	Drug	Indication	Parasitic Infection	Report year	Quarter	Reporter	Country
192436002	Dupilumab	Unknown	Infection parasitic	2021	Q3	Consumer	United States
192538592	Dupilumab	Nasal Polyps	Nematodiasis	2021	Q3	Consumer	United States
194491684	Dupilumab	Dermatitis Atopic	Helminthic infection	2021	Q4	Physician	United States
194749502	Dupilumab	Unknown	Infection parasitic	2021	Q3	Consumer	United States
195031201	Benralizumab	Unknown	Echinococciasis	2021	Q3	Physician	Germany
195420921	Dupilumab	Unknown	Infection parasitic	2021	Q3	Consumer	United States
196135061	Mepolizumab	Unknown	Parasitic pneumonia	2021	Q3	Consumer	Austria
196159612	Dupilumab	Unknown	Infection parasitic	2021	Q3	Consumer	United States
197404401	Dupilumab	Unknown	Infection parasitic	2021	Q3	Consumer	United States
199016991	Dupilumab	Unknown	Infection parasitic	2021	Q3	Consumer	United States
199162231	Dupilumab	Unknown	Infection parasitic	2021	Q4	Physician	United States
199611801	Dupilumab	Dermatitis Atopic	Helminthic infection	2021	Q4	Physician	United States
201822031	Dupilumab	Unknown	Enterobiasis	2021	Q4	Physician	United States
201925381	Dupilumab	Dermatitis Atopic	Helminthic infection	2021	Q4	Physician	United States

Table S3. Raw data on the occurrence of the parasitic infection, start/end date of the therapy, and calculated time of onset based on available data. Dates are expressed in the format YYYYMMDD (year, month, day). †From the legacy adverse event reporting system database.

Report id	Drug	Date of parasitic infection	Start date of therapy	End date of therapy	Time to onset (days)
6412861†	Omalizumab				
6422338†	Omalizumab				
7456124†	Omalizumab	20110406	20110330		-24
7831160†	Omalizumab	20110522	20110413		9
88868233	Omalizumab				
112279541	Omalizumab				
116713721	Omalizumab				
120462742	Omalizumab				
127270233	Omalizumab	20160329	20160329	20160824	0
128327562	Mepolizumab	20160930	2016		
130536502	Omalizumab	20161214	20160809		5
133047542	Omalizumab	20160601	20160111		-10
135297952	Omalizumab	200910	200909		
135384151	Omalizumab	20150526	20130730		-4
135833931	Omalizumab				
135951192	Omalizumab	201705	201705		
152438235	Dupilumab	20180227	20161220	20161220	7
153768121	Omalizumab				
154171474	Benralizumab	20180512	20180411		1
155437031	Mepolizumab				
155446756	Omalizumab	20180812	20180912		0
156369229	Dupilumab	201901	20181115		
159035971	Benralizumab				
159198241	Omalizumab				

Table S3. Raw data on the occurrence of the parasitic infection, start/end date of the therapy, and calculated time of onset based on available data. Dates are expressed in the format YYYYMMDD (year, month, day). †From the legacy adverse event reporting system database. (*continued*)

Report id	Drug	Date of parasitic infection	Start date of therapy	End date of therapy	Time to onset (days)
159279334	Benralizumab	201812	2018		
159385621	Omalizumab	20181114	201807		
159389361	Omalizumab				
160665231	Mepolizumab				
160926871	Benralizumab				
161733721	Benralizumab				
162228012	Mepolizumab				
162231351	Dupilumab				
163153155	Dupilumab	20190426	20190426	20190426	0
164557632	Mepolizumab	201812	20160113		
164821131	Dupilumab	201905	20170501		
165259972	Mepolizumab				
165380635	Dupilumab	2020	20190322	20201029	
165871631	Dupilumab		20190610		
166135231	Omalizumab	2016	201511	20160407	
166854971	Dupilumab	20190704			
168228951	Mepolizumab	201908			
169536901	Dupilumab				
169750711	Dupilumab	2019	2019		
170932051	Mepolizumab				
173246732	Omalizumab	20180227	20180227		0
175066951	Omalizumab				
175440962	Omalizumab	20200220	201906		
176897311	Dupilumab	202003	20200220		

Table S3. Raw data on the occurrence of the parasitic infection, start/end date of the therapy, and calculated time of onset based on available data. Dates are expressed in the format YYYYMMDD (year, month, day). †From the legacy adverse event reporting system database. (*continued*)

Report id	Drug	Date of parasitic infection	Start date of therapy	End date of therapy	Time to onset (days)
177316141	Benralizumab		202001		
178661361	Dupilumab				
178773361	Benralizumab		20200129		
181342151	Mepolizumab				
181359671	Mepolizumab				
182472141	Mepolizumab	2020			
182565491	Dupilumab	2020	202004		
182811391	Dupilumab				
183252511	Benralizumab	2020	20200824		
183524341	Dupilumab	2020	202007		
184553801	Dupilumab		20190919		
187547381	Dupilumab		20190606		
188900731	Dupilumab		20201210		
189987444	Dupilumab	20210212	20210212		0
190275381	Dupilumab				
190772101	Dupilumab	20210325			
191667251	Dupilumab		2021		
192436002	Dupilumab	20210503	20180731		-28
192538592	Dupilumab	20210406	20200211	20210408	-5
194491684	Dupilumab		20210525	20211005	
194749502	Dupilumab	2020	2020		
195031201	Benralizumab				
195420921	Dupilumab	20210222	202011		
196135061	Mepolizumab				

Table S3. Raw data on the occurrence of the parasitic infection, start/end date of the therapy, and calculated time of onset based on available data. Dates are expressed in the format YYYYMMDD (year, month, day). †From the legacy adverse event reporting system database. (*continued*)

Report id	Drug	Date of parasitic infection	Start date of therapy	End date of therapy	Time to onset (days)
196159612	Dupilumab				
197404401	Dupilumab		202004		
199016991	Dupilumab	20210927	20201212		15
199162231	Dupilumab	20210901	202012		
199611801	Dupilumab	20190101	20191101	20191101	0
201822031	Dupilumab		20210216		
201925381	Dupilumab	20210101	20210525	20210525	-24

Table S4. Primary disproportionality analysis, in which "other-drug" represents all other drugs in FAERS. "Event" represents a parasitic infection. Counts A, B, C, and D correspond with counts as presented in Table 1.

Drug	ATC	Drug-event count (A)	Drug-other event count (B)	Other drug-event count (C)	Other drug-other event count (D)	ROR (95% CI)
Omalizumab	R03DX05	25	149,272	1,597	37,368,549	3.9 (2.6 - 5.8)
Dupilumab	D11AH05	34	201,181	1,588	37,316,640	4.0 (2.8 - 5.6)
Mepolizumab	R03DX09	12	47,270	1,610	37,470,551	5.9 (3.4 - 10.4)
Benralizumab	R03DX10	10	14,807	1,612	37,503,014	15.7 (8.4 - 29.3)
Reslizumab	R03DX08	0	997	1,622	37,516,824	NA

ATC - Anatomical Therapeutic Chemical classification; NA - Not Applicable; ROR - Reporting odds ratio; CI - Confidence Interval.

Table S5. 1st secondary disproportionality analysis, in which "other-drug" represents all other drugs in FAERS, excluding all drugs under ATC level 5 code P. "Event" represents a parasitic infection. Counts A,B,C† and D† correspond with counts as presented in manuscript Table 1.

Drug	ATC	Drug-event count (A)	Drug-other event count (B)	Other drug-event count (C†)	Other drug-other event count (D†)	ROR (95% CI)
Omalizumab	R03DX05	25	149,272	1,443	37,267,467	4.3 (2.9 - 6.4)
Dupilumab	D11AH05	34	201,181	1,434	37,215,558	4.4 (3.1 - 6.2)
Mepolizumab	R03DX09	12	47,270	1,456	37,369,469	6.5 (3.7 - 11.5)
Benralizumab	R03DX10	10	14,807	1,458	37,401,932	17.3 (9.3 - 32.3)
Reslizumab	R03DX08	0	997	1,468	37,415,742	NA

ATC - Anatomical Therapeutic Chemical classification; NA - Not Applicable; ATC code P - Antiparasitic products, insecticides and repellents; ROR - Reporting odds ratio; CI - Confidence Interval.

Table S6. 2nd secondary disproportionality analysis, in which "other-drug" represents the other biologics in this table. "Event" represents a parasitic infection. Counts A,B,C‡ and D‡ correspond with counts as presented in manuscript Table 1.

Drug	ATC	Drug-event count (A)	Drug-other event count (B)	Other drug-event count (C‡)	Other drug-other event count (D‡)	ROR (95% CI)
Dupilumab	D11AH05	34	201,181	47	212,346	0.8 (0.5 - 1.2)
Omalizumab	R03DX05	25	149,272	56	264,255	0.8 (0.5 - 1.3)
Mepolizumab	R03DX09	12	47,270	69	366,257	1.4 (0.7 - 2.5)
Benralizumab	R03DX10	10	14,807	71	398,720	3.8 (2.0 - 7.4)
Reslizumab	R03DX08	0	997	81	412,530	NA

ATC - Anatomical Therapeutic Chemical classification; NA - Not Applicable; ROR - Reporting odds ratio; CI - 95% Confidence Interval.

7

Chapter 7

General Discussion

RECAPITATION OF OBJECTIVE AND MAIN FINDINGS

The main objective of this thesis was to research medication errors (MEs) and adverse drug events (ADEs) through a series of approaches applied to spontaneous reporting systems (SRSs) and electronic health records (EHRs). The first fundamental step in that process was achieved in **Chapter 2**, where we developed and validated the Aioli software system that is capable of standardizing drug names and mapping these to Anatomical Therapeutic Chemical (ATC) classification codes, which served us in **Chapters 3**, **4**, and **6**. **Chapter 3** offered an updated characterization of almost 500,000 ME reports and identified more than 400 signals of disproportionately reporting (SDRs) from the United States of America (USA) Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database, of which some drug-ME-combinations (DMECs) were new. In **Chapter 4** we explored sex and age-group stratified SDRs in relation to MEs within the European's Medicines Agency (EMA) EudraVigilance database and found important variations in SDR-magnitude between age-groups, while many SDRs were not previously described in published literature. In **Chapter 5** we found that for both the Spanish and Dutch primary care population with chronic lung diseases, medium- and long-term macrolide prescribing, especially for azithromycin, was becoming more prevalent throughout time. In addition, we identified that ECG assessments were rarely registered although presence of arrhythmia should be excluded before initiation of long-term macrolide therapy. In **Chapter 6** we reported a signal on the association between parasitic infections and use of type 2 immunity monoclonal antibodies based on spontaneous reports from the FAERS database.

The value of Aioli and the ongoing challenges

The developed Aioli software system as described in **Chapter 2** has proven its value by being applied to both the FAERS database (**Chapters 3** and **6**) and the EudraVigilance database (**Chapter 4**). Without Aioli it would have been a challenge to aggregate data based on ATC codes and facilitate our analyses. For example, in **Chapter 6** , to control for confounding by indication, it was important to exclude drugs from the ATC group *Antiparasitic products, insecticides and repellents,* which would not have been possible without having the ATC codes. In parallel, it has to be recognized that the performance of Aioli directly impacts the outcomes of **Chapters 3**, **4**, and **6**. One of the main issues that influenced Aioli's performance was that not all (drug) substances could be mapped to an ATC code due to a substance having multiple ATC code options (such as *calcium*). Besides these issues forthcoming from missingness of data or the simple unavailability of mapping, the ATC coding system remains a dynamic system and is subject to updates of ATC codes [283]. On top of that, new substances enter the market every single year, and new ATC codes need to be assigned, which requires that systems such as Aioli need to be updated regularly.

Principals of disproportionality and signal detection

The essence of disproportionality is that a specific occurrence is more profoundly present than other occurrences within a given context. In our studies (**Chapter 3, 4, and 6**) we specifically studied occurrences expressed as DMEC or DEC. Calculating the reporting odds ratio's (RORs) with their 95% confidence intervals (95% CI) gave us numeric values to compare which represented to an extent a measure of disproportionality. The principle of disproportionality was used to identify MEs for specific drugs being reported more often than any other event compared to other DMECs and DECs within the same database. Based on the criteria of disproportionality, an occurrence may be then identified as a signal which is by the World Health Organization (WHO) defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" [284]. By definition, a signal is not conclusive and requires more investigation before it may be established whether the signal represents a drug-related problem which needs to be addressed by the different stakeholders. The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for prioritizing and assessing such signals as authorized by the European Union (EU). After PRAC's evaluation of a signal, the PRAC may provide recommendations such as additional monitoring, analysis within EudraVigilance or other data sources, need for additional data from marketing authorization holders (MAHs) or post-authorisation safety studies to be conducted by MAHs. Regulatory actions may be recommended such as updating the product information, the risk management plan, a referral procedure (i.e. scientific assessment by the EMA) or safety restrictions [285]. Figure 1 depicts an overview of all the steps performed in the context of signal management and how different stakeholders are involved. In **Chapter 3**, **4**, and **6** we performed our disproportionality analyses ending up with measures expressed as SDRs.

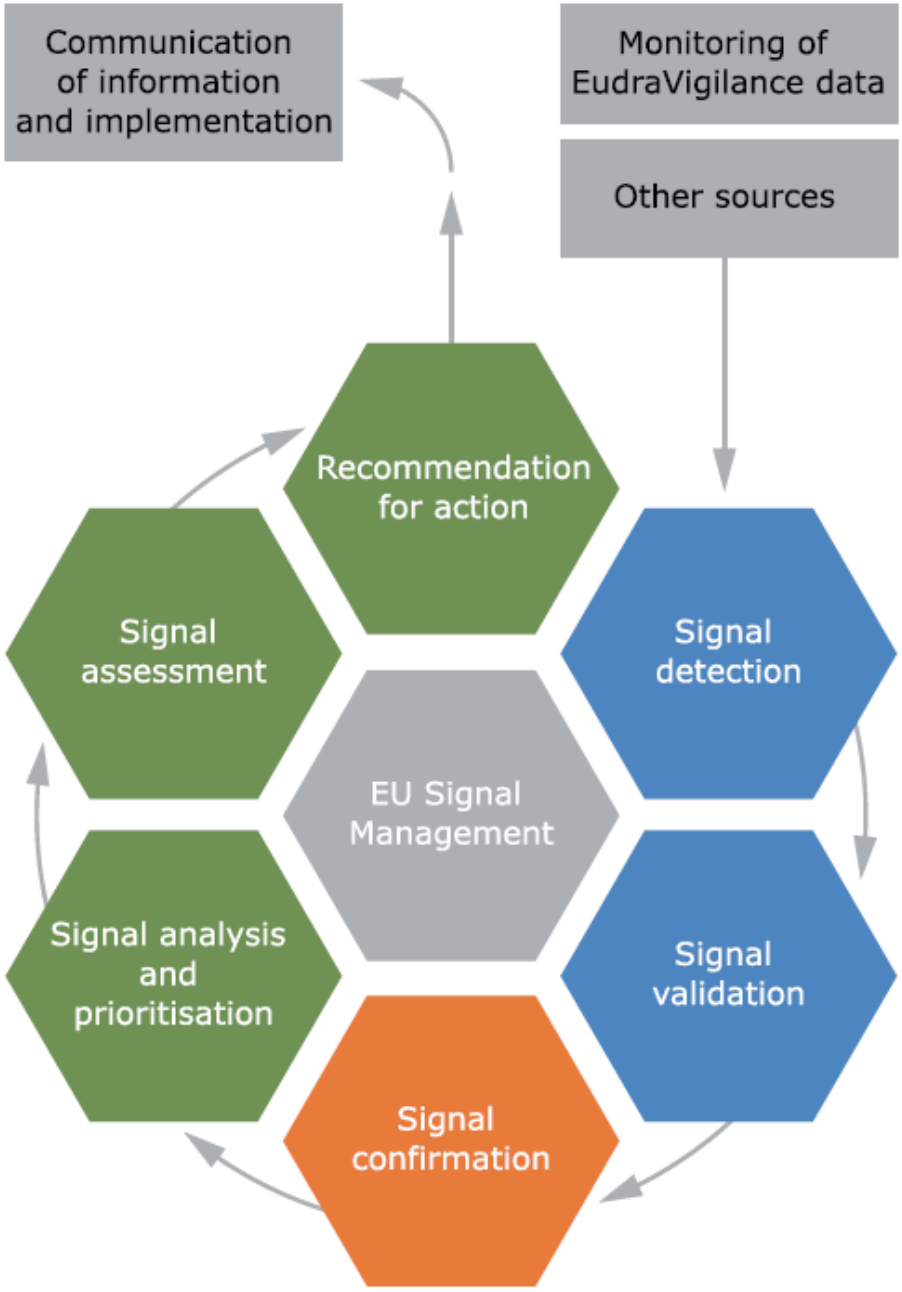

Figure 1. Overview of signal management as governed by European Union law with all stakeholders. EMA - European Medicines Agency; EU - European Union; MAH - Marketing Authorisation Holder; MS - Member State; Rapp - Rapporteur/Designated member of committee; PRAC - Pharmacovigilance Risk Assessment Committee. From *Potts J, Genov G, Segec A, Raine J, Straus S, Arlett P. Improving the safety of medicines in the European Union: From signals to action. Clin Pharmacol Ther. 2020;107(3):521-9. doi:10.1002/cpt.1678. Licensed under CC BY-NC-ND* [286].

Patterns and gaps in spontaneously reported medication errors

The FAERS and EudraVigilance database as SRSs have their differences and similarities when it comes to reported ME characteristics, generated SDRs, and missingness of data. The main differences were found in the harm severity co-reported with MEs, where in EudraVigilance 37% of MEs was co-reported with harm, whereas in FAERS, this proportion was much higher namely 60%. The reporters in EudraVigilance consisted for almost 40% of consumers, which was in FAERS almost 60%, while a small proportion consisted of lawyers (<3%) in both SRSs, and the rest accounted for healthcare professionals. There was somewhat an overlap in findings regarding the most frequently reported drugs in relation to MEs and SDRs (for adalimumab, salbutamol, insulin glargine, insulin lispro, and paracetamol), but there were also many differences in findings across the SRSs. The difference in these findings might boil down to the differences in reporting country of origin as for FAERS, almost 80% of ME reports originate from the USA, while in EudraVigilance this is less than 40%. This big difference may trickle down to differences in reporting behaviors, drug availability, quality of healthcare, healthcare consumption, and general healthcare culture. Other factors that might explain the differences in findings might be due to different study periods used for the databases, EudraVigilance in containing reports on vaccines (which are in the USA mostly submitted to the Vaccine Adverse Event Reporting System [VAERS] rather than FAERS), and differences in completeness of reports (influencing ATC mapping).

While the differences in results were prominent, similarities were likewise found. Most reports were on females, accounting for 55%, while males accounted for 33-35%, and the rest of the reports did not specify the sex of the subject. The most reported type of MEs in both SRSs were *inappropriate schedule of product administration*, *incorrect dose administered*, *wrong technique in product usage process*, *accidental overdose*, and *medication error* as such. Since the inception of both databases, ME reporting has been on the rise, and in EudraVigilance a big reporting influx was observed for 2021, connected to the 2021 worldwide mass vaccination against the Coronavirus disease 2019 (COVID-19) [287]. In absolute terms, most ME reports represented adults and elderly in both FAERS (**Chapter 3**) and EudraVigilance (**Chapter 4**), but more SDRs were reported for individuals up to the age group of 17 years (**Chapter 4**), and most reports were characterized by the use of a single drug (69-80%).

Similarities between FAERS and EudraVigilance were also found regarding missingness of data. Age was the most frequently unreported or invalid input variable (30-40%) followed by sex (9-12%). This is a major obstacle when specific subpopulations are of interest for analysis, but also for acquiring a full epidemiological picture. In the future, it might be of interest to evaluate and test methodologies for imputing missing data points in SRSs.

High frequency occurrences versus disproportionality

Chapter 4 touched upon the topic of prioritization of findings based on either disproportionality measures or even something simple as report counts. On one hand, a benefit of focusing on the highest report counts for a DEC or DMEC is that one can understand where the most reduction in MEs could be achieved. On the other hand, swift regulatory actions based on early low counts might be needed upon a drug entering the market that beforehand unknowingly has a tendency to cause harmful side-effects when administered to the *real world* populations that are larger and more different than the ones tested upon for drug-safety and -efficacy in randomized clinical trials in a controlled setting. Taking into account the viewpoint of patients, it is the most favorable for them to be as less as possible exposed to any kind of MEs, but especially the ones which may cause harm or even death and invalidity. A patient must be able to trust the drug treatment process, otherwise the trust in the healthcare system will be challenged. While disproportionality measures offer interesting insights, it is key to remember that SDRs can be strongly biased or masked based on reporting behaviors and analytical methodology, but also if a SDR is found, it still requires an assessment on the causal link within the DMEC. This additional work is preceded by ongoing challenges on how to prioritize further investigation on SDRs, as we have seen that alone in FAERS (**Chapter 3**) hundreds of signals were identified, and that some SDRs from EudraVigilance (**Chapter 4**) were already known, but plentiful were unknown or not publicly acknowledged. For now, it seems that prioritization of signals for healthcare authorities such as the EMA is based on multiple factors such as severity, frequency of adverse event, population vulnerability, treatment discontinuation consequences, regulatory intervention expectations, and likeliness of adverse event occurrence in similar substance class [288]. However, all these actions seem to require a manual approach, while limited research is done on how to automatically prioritize SDRs [289], and the way of prioritization may be different for various stakeholders. Better methods are needed to reduce false positives and utilize resources efficiently. Pharmacovigilance for ensuring drug safety

Chapter 5 and **6** showed different approaches in research and how they contribute to drug safety. **Chapter 5** highlights the emerging trend in increased medium- and long-term azithromycin prescribing, while (the registration of) ECG procedures is rarely done beforehand by healthcare professionals, despite patients being at risk of adverse cardiac events given the warnings for these drugs. It may prompt further investigation on the appropriateness of prescribing and the reasons for the low amount of ECG (registered) procedures before prescribing.

While in **Chapter 6** the SDR for the DEC type 2 immunity monoclonal antibodies and parasitic infections is a signal rather than a finding of causality, it may prompt stakeholders to further assess this signal, and based on recent [290] and future findings, it may change the way the drugs are utilized given patients' susceptibility to parasitic infections.

Opportunities for drug safety research

There is a plethora of ways to do research on drug safety in observational databases, whether it is in databases which present standardized ME and adverse event terms (**Chapters 3** and **4**), or by detecting emerging events determined by a specific (non-)occurrence of an event (**Chapters 5** and **6**). Besides performing absolute case counts and generating SDRs, detecting a ME can be also as simple as finding that a drug was used within inappropriate age categories (**Chapter 4**), but it can be also as complex as querying for drug-drug interaction (DDI) and establishing if the identified DDI was a well-thought-over pharmacotherapeutic decision or a mistake given the existence of a more appropriate combination of other drugs. Identification of MEs might also be performed on unstructured data such as manually written clinical texts in EHRs. Even though these types of systems are not designed to collect MEs and ADEs, they may offer important insights in MEs otherwise not detected or reported elsewhere. Preliminary findings from our in-house Dutch Integrated Primary Care Information (IPCI) EHR database showed that it was possible to manually identify - within clinical texts - inhaler-related MEs among asthma patients that routinely visit the general practice (GP) nurse for their check-ups (schematic methodology presented in Figure 2). Hundred clinical texts fields from IPCI asthma patients who structurally visited the nurse-practitioner to check-up on their asthma-status were randomly selected. Two researchers first annotated 20 texts entries together as a practice sessions and next, 80 randomly selected texts were independently annotated. Annotation and reaching consensus was primarily focused on whether a ME was identified and the type of ME. For 17 out of 80 texts there were disagreements for which we reached consensus, and the interrater agreement was expressed with a $\kappa = 0.378$, reflecting a fair agreement, but also the difficulty in recognizing MEs. MEs were identified in 25% of these free text entries and most of these MEs seemed in control of the patient based on the clinical texts. Most of the MEs were found in patients that were already classified as insufficiently adhering to the prescribed pharmacotherapy as structurally registered by the GP nurse. The types of MEs that were identified were related to e.g. *inappropriate dosing (schedule), incorrect inhalation technique, and forgetting medication* (especially when on vacation). Most of these MEs were found to be harmless based on the available information in the clinical text, partially due to the GP nurses performing (and registering in the EHRs) corrective actions to prevent further escalation of the identified MEs. Focusing on the clinical texts from the routine visits of asthma-patients for their check-up aided in achieving a relatively high rate in finding MEs, while going through many clinical texts from IPCI (including the ones of spontaneous visits to the GP office) was cumbersome, realizing the general difficulty in identifying MEs in a pile of clinical texts. While some efforts have already been made to contribute to automated detection of MEs in free text [291–293], much progress has yet to be made to make these approaches robust and applicable to larger text datasets from a given database of another language. There is room for improvement by also implementing specific ME registration options in software used by healthcare professionals in both primary and secondary care. Also, a standardized way of reporting MEs to a central database would be beneficial and offer national and local insights as demonstrated by

the National Reporting and Learning System (NRLS) implemented since 2003 in England and Wales [294].

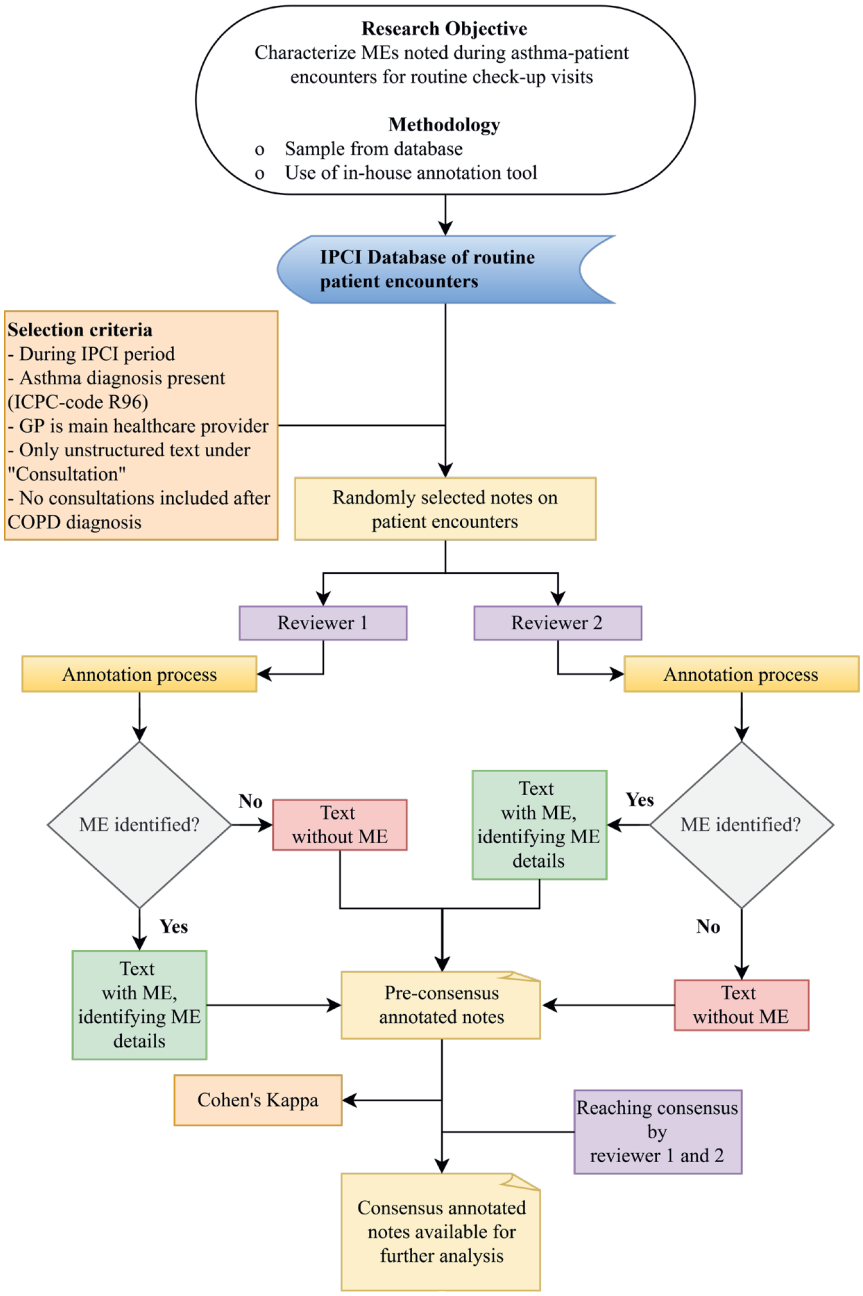

Figure 2. Schematic overview on preliminary research on medication errors in IPCI clinical texts within the population of asthma patients routinely visiting the general practice. COPD - Chronic Obstructive Pulmonary Disease; GP - General Practitioner; ICPC - International Classification of Primary Care; IPCI - Integrated Primary Care Information; ME - Medication Error.

Thesis Strengths and Limitations

The strengths of this thesis are embodied in a variety of approaches based on SRSs and primary care databases. Within the studies utilizing SRSs we presented results stratified for many populations providing more insights on populations at risk for MEs, which was not done before. We developed our own drug standardization software which facilitated our research and may benefit other researchers in the future. Preliminary results have been shared of an attempt to identify MEs in clinical texts of EHRs, highlighting insights upon which may be built for future research. Primary care databases mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) in combination with the use of Darwin EU® software packages facilitated multi-database research representing findings on macrolide use and ECG assessment for Dutch and Spanish primary care. We shad a broad light within the thesis on the topic of MEs and other related topics in pharmacovigilance using. While interesting results were produced, they need to be interpreted with care due to the inherent shortcomings of observational data and retrospective research. It has to be noted that much more research opportunities are available to further portray the broad topic of MEs. Primary and secondary healthcare databases offer a richness in both structured and unstructured data but are difficult to utilize due to the vast amount of data available and the complexity of identifying a wide variety of MEs themselves, necessitating carefully thought out methodologies for different types of MEs as they occur in different settings and are not always actively or spontaneously reported.

Improving research on Medication Errors using electronic health care records

Currently there are 3 main ways of data gathering which are of interest for research on MEs; Data from SRSs, data from existing EHRs, and prospectively gathering of data in various healthcare settings. In all of these domains there are opportunities to improve identification of MEs. Due to their designs and way of data gathering, in SRSs there is most to gain in data imputation and in the way the data is analyzed, in the sense that more novel and complex methodologies may be utilized beyond the scope of this thesis. In EHRs much may be gained through automatic detection of MEs either based on clinical texts, structured data or even utilizing them both. While healthcare systems already rely on many rule-based algorithms, not all types of MEs might be detected, although Large Language Models (LLMs) may be of assistance in identifying MEs in free clinical text.

Efforts may be made in gathering data on MEs in prospective ways, although this type of research may be costly and lengthy but may also offer appropriate incidence values on a select type of MEs. An example of this type of research is the prospective monitoring of MEs in hospitals. Indeed, many hospitals already have their own way of internally registering ME-which is of value to allows to improve local healthcare procedures (as it is even established by law in The Netherlands [295]). Ideally, this data could be centralized (for instance at a national level) to have this data centralized and gathered in a standardized way for improved analyses and broader overview of MEs.

Final thoughts on medication errors

While a ME seems broadly yet clearly defined by the regulatory health authorities as introduced in **Chapter 1**, various complexities may arise when assessing MEs using (retrospective) observational data. With new insights and knowledge gained throughout time, what is considered a ME today, might not have been considered a ME yesterday (e.g. valproate became strictly contraindicated throughout time towards pregnant- or potentially childbearing women) [296]. Also, guidelines in the past may have dictated approaches which are nowadays considered obsolete (e.g. standalone use of short-acting beta agonists for asthmatic patients was allowed in the past, but nowadays it is recommended to be combined with inhalation corticosteroids) [297]. Additionally, when applying knowledge of today to data from the past, the knowledge and setting of that time has to be taken into consideration, which is important when performing retrospective research. A remaining caveat of ME research is that despite best research efforts giving estimates based on available data and providing a magnitude of the ME problem (**Chapter 1**), it will remain unclear what the actual incidence is on any population level due to a wide range of reasons for not reporting MEs or MEs simply passing by unnoticed. This is especially the case for SRSs, while less of a case when data is collected prospectively. As long as (near-) MEs are not reported or noticed and context is missing, a proper full overview of the epidemiology of MEs will be far from complete.

Conclusion

Many insights were provided on the characteristics of MEs, and potential focus points on safety signals were highlighted to further investigate MEs and ADEs in order to understand and prevent them in the future. Through our research we also showed how our software facilitated ME and ADE research on not fully standardized databases such as SRSs. We also showed the added value of performing research on standardized observational databases from primary care. Much improvements can still be made in the area of standardization of drug names, mapping to ATC codes, and maintaining self-developed software, while opportunities may be found in resolving data missingness, lack of data registration, and analysis on unstructured clinical text data from EHRs with novel methodologies such as LLM.

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Appendices

SUMMARY, IN ENGLISH

In this thesis, we applied various approaches to create an epidemiological overview of medication errors (MEs) and to study select adverse drug events (ADEs). There was a knowledge gap in regards to previously unknown MEs characteristics, undiscovered safety signals, and lack of data standardization of spontaneous reporting systems (SRSs). Unstandardized datasets from SRSs were standardized with in-house developed software in an effort to make analyses possible. Observational data from SRSs and electronic health records (EHRs) was used to provide more insight on MEs and safety signals.

Chapter 1 provides a brief history on ME research showing the lack of it in the 20th century and a surge of it at the beginning of the 21st century. *To Err Is Human: Building a Safer Health System* was a pivotal publication that shed light on medical errors occurring in the United States of America (USA) healthcare system and advocated for drastic actions and improvements. Much has moved in the area of ME research and implementations following this publication, but despite global efforts on various fronts of drug safety research, more research was needed on drug safety and MEs for the sake of patient safety. SRSs are the main type of databases which store received spontaneously reported ADEs in suspicion of being related to the intended drug therapy, but also contain reports on MEs, offering research opportunities in the field of pharmacovigilance. Besides opportunities, also challenges arise when utilizing SRSs, such as a lack of standardized drug names. This pushed us to not just merely develop and validate a methodology that tackles the lack of standardization, but to also consider standardized databases from EHRs to perform drug safety research.

In **Chapter 2**, we described how the Aioli software system was developed for the purpose of standardizing manually supplied drug names to normalized drug names from the RxNorm terminology based on Food and Drug Administration's Adverse Event Reporting System (FAERS) data. RxNorm drug names were also mapped to the corresponding Anatomical Therapeutic Chemical (ATC) classification system codes. Aioli managed to map 94% of the unstandardized drug names to RxNorm drug names. The RxNorm mappings were for 92% correct. The proportion of RxNorm drug names mapped correctly to an ATC code was 94%. The Aioli software system was considered suitable to be applied for further SRS data standardization purposes.

In **Chapter 3**, we performed a characterization of ME reports and a disproportionality analysis based on the FAERS data from 2004 to 2020. The entire FAERS database consisted of a nearly 15 million reports. Almost 500,000 (3%) reports were found to be ME-related. These reports were characterized as following: median reported age of 57 years (interquartile range: 37-70 years), one third being associated with a serious health outcome, mostly submitted by consumers (59%), mostly associated with females (55%), most often associated with the drug class *antineoplastic and immunomodulating agents* (25%), and most frequently associated with

the ME *incorrect dose administered* (9%). The disproportionality analysis generated more than 400 signals of disproportionate reporting (SDRs), of which adalimumab was most frequently reported with MEs with a reporting odds ratio (ROR) of 1.22 (95% Confidence Interval [CI]: 1.22-1.24).

In **Chapter 4,** we characterized MEs from the EudraVigilance database reported between 2002 and 2021, and we explored sex- and age-group stratified differences in SDRs in relation to MEs. More than 9.5 million reports were processed, of which 267,000 (2.8%) were related to MEs. There reports were characterized as following: reported median age of 50 years (interquartile range: 26-68 years), most (60%) were associated with a serious health outcome, mostly submitted by healthcare professionals (58%), mostly associated with females (55%), and most frequently resembled by the ME *inappropriate schedule of product administration* (17.5%). The disproportionality analysis generated more than 800 SDRs. While SDRs for males and females of the same drug-ME combination (DMEC) were of similar magnitude, prominent differences were observed for SDRs between age-groups. The ROR for the vaccine against human papillomavirus (ATC code: J07BM01) ranged from 1.5 to 47.0 for the age groups between 2 months and 85 years. Acetylsalicylic acid (ATC code: B01AC06), the vaccine against rotavirus (ATC code: J07BH02), and nicotine (ATC code: N07BA01) showed also prominent differences in SDR between age-groups. SDRs were generated for many disease-modifying antirheumatic drugs (DMARDS), most frequently associated with the ME *contraindicated product administered*, and were not previously discussed in published literature on the topic of MEs. Other SDRs not yet reported in literature were found for several other vaccines, but also oxycodone, rivaroxaban, risperidone, and this may prompt further investigation by stakeholders in the future.

In **Chapter 5**, we investigated the new-user incidence of short- (<30 days), medium- (30-179 days), and long-term (≥180 days) prescribed macrolides such as azithromycin, clarithromycin and erythromycin, amongst individuals with asthma, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap syndrome (ACOS). Additionally, we investigated whether electrocardiogram (ECG) procedures were registered before long-term macrolide prescribing. We utilized the Dutch Integrated Primary Care Information (IPCI) database and the Spanish *Sistema d'informació per al Desenvolupament de la Investigació en Atenció Primària* (SIDIAP, the Information System for Research in Primary Care) database, both mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM), and gathered data from 2006 to 2022. The incidence of short-term users per 100,000 person-years (PYs) for azithromycin was 3,500-6,700**,** clarithromycin 1,300-2,100**,** and erythromycin 200-300. Medium- and long-term users accounted for <1,100/100,000 PYs. Incidence was higher in SIDIAP, females, and individuals 60–79-year-olds. Medium- and long-term user estimates were 2–4 fold higher in COPD and ACO than in asthma. Over time, new short-term users increased in SIDIAP and declined in IPCI, while new medium- and long-term users increased in both. The proportion of individuals where ECG

was assessed was ≤1%. This low proportion of ECGs in individuals initiating medium- and long-term macrolide use is a concerning trend and requires further investigation to understand the full scope of safety practices and outcomes.

In **Chapter 6**, we assessed the adverse drug event of parasitic infections among individuals using type 2 immunity monoclonal antibodies. This assessment was done by performing a disproportionality analysis within the FAERS database between 2004 and 2021. There were almost 180,000 reports in total submitted for type 2 immunity monoclonal antibodies of interest, which were omalizumab, mepolizumab, reslizumab, dupilumab, and benralizumab. A mere 79 reports were related to parasitic infections. After adjusted analysis, benralizumab showed the strongest SDR with a ROR of 17.3 (95%CI: 9.3-32.3), followed by mepolizumab (ROR=6.5, 95%CI: 3.7-11.5), dupilumab (ROR=4.4, 95%CI: 3.1-6.2), and omalizumab (ROR=4.3, 95%CI: 2.9-6.4). No reports on parasitic infections were submitted for reslizumab. While disproportionate reporting was established for this drug-event combination (DEC), further investigation is necessary to confirm the causal link within this DEC and the magnitude of risk.

In **Chapter 7** we discuss all of our findings based on all thesis chapters. This thesis has contributed to extensive characterization of MEs from observational data and unveiled potentially new safety signals to be further investigated. We conclude that while we managed to fill the knowledge gap to some extent in the field of MEs and ADEs, improvements can still be made by addressing standardization and mapping of drug names, data missingness, lack of data registration, and analysis on unstructured clinical text data from EHRs with novel methodologies such as LLM.

SUMMARY, IN DUTCH (SAMENVATTING, IN HET NEDERLANDS)

In dit proefschrift pasten we verschillende benaderingen toe om een epidemiologisch overzicht van medicatiefouten te creëren en om selecte *adverse drug events* (ADEs, *ongewenste voorvallen bij geneesmiddelgebruik*) te onderzoeken. Er was een kenniskloof met betrekking tot voorheen onbekende medicatiefout karakteristieken, onontdekte veiligheidssignalen en een gebrek aan standaardisatie van *spontaneous reporting systems* (SRSs, *systemen voor het spontaan melden van ongewenste voorvallen bij geneesmiddelgebruik*). Ongestandaardiseerde datasets van deze systemen werden gestandaardiseerd met in-huis ontwikkelde software om analyses mogelijk te maken. Observationele data van SRSs en elektronische patiëntendossiers werden gebruikt om meer inzicht te geven in medicatiefouten en veiligheidssignalen.

Hoofdstuk 1 weergeeft een korte geschiedenis over medicatiefoutenonderzoek en het gebrek ervan in de 20ste eeuw, maar ook een toename ervan aan het begin van de 21e eeuw. *To Err Is Human: Building a Safer Health System* (*Fouten maken is menselijk: Het opbouwen van een veiliger gezondheidssysteem*) was een cruciale publicatie die licht wierp op medische fouten die zich voordeden in de Amerikaanse gezondheidszorgsysteem en pleitte voor drastische acties en verbeteringen. Er was na deze publicatie veel veranderd op het gebied van onderzoek en implementatie op het gebied van medicatiefouten, maar ondanks de wereldwijde inspanningen op verschillende fronten van geneesmiddelveiligheidsonderzoek, was er meer onderzoek nodig op het gebied van geneesmiddelveiligheid en medicatiefouten omwille van de patiëntveiligheid. SRSs zijn de belangrijkste type databases die spontaan gemelde ADEs bevatten in verdenking van verband met het beoogde geneesmiddelgebruik, maar bevatten ook rapporten over medicatiefouten; dit biedt onderzoeksmogelijkheden aan op het gebied van farmacovigilantie. Naast kansen zijn er ook uitdagingen bij het gebruik van SRSs, zoals een gebrek aan gestandaardiseerde medicatienamen. Dit zette ons ertoe aan om niet alleen een methodologie te ontwikkelen en te valideren die het gebrek aan standaardisatie aanpakt, maar ook om gestandaardiseerde databases die patiëntendossiers bevatten ook te overwegen om geneesmiddelveiligheidsonderzoek uit te voeren.

In **Hoofdstuk 2** beschreven we hoe het Aioli software systeem werd ontwikkeld met het oog op het standaardiseren van handmatig ingevoerde medicatienamen naar genormaliseerde namen vanuit de RxNorm terminologie gebaseerd op data uit de *Food and Drug Administration's Adverse Event Reporting System* (FAERS, *de Amerikaanse SRS*). RxNorm medicatienamen werden ook gekoppeld aan corresponderende codes vanuit de Anatomische Therapeutische Chemische (ATC) classificatie systeem. Aioli slaagde erin om 94% van de niet-gestandaardiseerde namen om te zetten naar RxNorm medicatienamen. Deze RxNorm omzettingen waren voor 92% correct. Het aandeel van RxNorm medicatienamen dat een correcte ATC-code toegewezen kreeg was 94%. Het Aioli-softwaresysteem werd geschikt geacht voor verdere standaardisatiedoeleinden binnen SRSs.

In **Hoofdstuk 3** hebben we een karakterisering op medicatiefoutmeldingen uitgevoerd en een disproportionaliteitsanalyse uitgevoerd op data uit FAERS van 2004 tot 2020. De volledige FAERS database bestond uit bijna 15 miljoen rapporten. Bijna 500,000 (3%) meldingen bleken gerelateerd te zijn aan medicatiefouten. De karakteristieken van deze meldingen waren als volgt: een gerapporteerde mediane leeftijd van 57 jaar (interkwartielafstand: 37-70 jaar), één-derde werd geassocieerd met een ernstig gezondheidsuitkomst, meestal ingediend door consumenten (59%), het vaakst geassocieerd met vrouwen (55%), grotendeels geassocieerd met antineoplastische en immunomodulerende geneesmiddelen (25%), en het meest geassocieerd met de medicatiefout *onjuiste toegediende dosis* (9%). De disproportionaliteitsanalyse genereerde meer dan 400 *signals of disproportionate reporting* (SDRs, *signalen van disproportioneel rapporteren*), waarvan adalimumab het meest werd gerapporteerd in combinatie met medicatiefouten gerepresenteerd door een *reporting odds ratio* (ROR, *kansverhoudsingratio voor rapporteren*) van 1.22 (95% *Confidence Interval* [CI, *betrouwbaarheidsinterval*]: 1.22-1.24).

In **Hoofdstuk 4** karakteriseerden we medicatiefouten uit de EudraVigilance database die tussen 2002 en 2021 werd gerapporteerd, en we onderzochten verschillen tussen geslachts- en leeftijdsgroep-gestratificeerde SDRs in relatie tot medicatiefouten. Meer dan 9,5 miljoen meldingen werden verwerkt, waarvan 267,000 (2,8%) gerelateerd waren aan medicatiefouten. De karakteristieken van deze meldingen waren als volgt: een gerapporteerde mediane leeftijd van 50 jaar (interkwartielafstand: 26-68 jaar), de meeste meldingen (60%) werden geassocieerd met een ernstig gezondheidsuitkomst, meestal ingediend door zorgverleners (58%), vaakst geassocieerd met vrouwen (55%), en het vaakst geassocieerd met de medicatiefout *ongepaste schema voor producttoediening* (17,5%). De disproportionaliteitsanalyse heeft meer dan 800 SDRs opgeleverd. Hoewel SDRs voor mannen en vrouwen met dezelfde *drug-medication error combination* (DMEC, *geneesmiddel-medicatiefout combinatie*) van vergelijkbare orde van grootte waren, werden opvallende verschillen geobserveerd voor SDRs van verschillende leeftijdsgroepen. De ROR voor het vaccin tegen het humaan papillomavirus (ATC-code: J07BM01) varieerde van 1.5 tot 47.0 voor de leeftijdsgroepen tussen 2 maanden en 85 jaar. Acetylsalicylzuur (ATC-code: B01AC06), het vaccin tegen de rotavirus (ATC-code: J07BH02) en nicotine (ATC-code: N07BA01) toonden ook opvallende verschillen in SDRs tussen leeftijdsgroepen. SDRs werden gegenereerd voor veel *disease-modifying antirheumatic drugs* (DMARDS, *ziekteverloop beïnvloedende geneesmiddelen tegen reuma*), het vaakst geassocieerd met de medicatiefout *gecontra-indiceerd product toegediend*, en werden niet eerder besproken in gepubliceerde literatuur in de context van medicatiefouten. Andere SDRs die nog niet zijn vermeld in de literatuur werden gevonden voor verschillende andere vaccins, maar ook oxycodone, rivaroxaban en risperidon; dit kan belanghebbenden motiveren om verder onderzoek hiernaar te verrichten in de toekomst.

In **Hoofdstuk 5** onderzochten we de incidentie van kort- (<30 dagen), middellang- (30-179 dagen) en lange termijn (≥180 dagen) gebruik van macroliden zoals azitromycine, claritromycine en erytromycine, bij personen met astma, *chronic obstructive pulmonary disease* (COPD, *chronische obstructieve longziekte*) en astma-COPD-overlap (ACO). Daarnaast onderzochten we of elektrocardiogram (ECG) procedures werden geregistreerd vooraf voorschrijven van lange termijn macroliden. We hebben gebruik gemaakt van de *Integrated Primary Care Information* (IPCI, *geïntegreerde primaire zorg informatie*) database en de Spaanse *Sistema d'informació per al Desenvolupament de la Investigació en Atenció Primària* (SIDIAP, *informatiesysteem voor onderzoek in primaire zorg*) database, beide omgezet naar het *Observational Medical Outcomes Partnership Common Data Model* (OMOP CDM, *observationeel medisch uitkomstenpartnerschap gemeenschappelijk datamodel*). We hebben databasegegevens verzameld van het jaar 2006 tot 2022. De incidentie van korte termijngebruikers per 100,000 *person years* (PYs, *persoonsjaren*) voor azitromycine was 3,500-6,700, claritromycine 1,300-2,100 en erytromycine 200-300. Incidentie van middel- en lange termijn gebruikers was <1,100/100,000 PYs. De incidentie was hoger in SIDIAP, vrouwen en personen tussen de 60 en 79 jaar. De middellange- en lange incidentie was 2 tot 4 keer hoger bij mensen met COPD en ACO in vergelijking met astma. In verloop van tijd namen de nieuwe korte termijngebruikers toe in SIDIAP en daalden zij in IPCI, terwijl de nieuwe middellange- en lange termijn gebruikers in beide databases toenamen. Het percentage personen waarbij ECGs werden geregistreerd was ≤1%. Dit lage percentage ECGs bij personen die middellange- en lange termijn macroliden gebruiken is een zorgwekkende ontwikkeling en vereist nader onderzoek om de volledige reikwijdte van veiligheidsprocedures en uitkomsten te begrijpen.

In **Hoofdstuk 6** hebben we de ADE van het oplopen van parasitaire infecties in verband met het gebruik van type 2-immuniteit monoklonale antilichamen onderzocht. Deze beoordeling werd uitgevoerd door middel van een disproportionaliteitsanalyse in de FAERS-database tussen 2004 en 2021. Er werden in totaal bijna 180,000 meldingen ingediend voor type 2-immuniteit monoklonale antilichamen, zoals omalizumab, mepolizumab, reslizumab, dupilumab en benralizumab. Slechts 79 meldingen waren gerelateerd aan parasitaire infecties. Na een aangepaste analyse toonde benralizumab de sterkste SDR met een ROR van 17.3 (95%CI: 9.3-32.3), gevolgd door mepolizumab (ROR=6.5, 95%CI: 3.7-11.5), dupilumab (ROR=4.4, 95%CI: 3.1-6.2) en omalizumab (ROR=4.3, 95%CI: 2.9-6.4). Er waren geen meldingen ingediend van parasitaire infecties voor reslizumab. Hoewel voor deze *drug-event combination* (DEC, *geneesmiddel-gebeurtenis combinatie*) disproportionele rapportage werd vastgesteld, is verder onderzoek noodzakelijk om het causale verband binnen deze DEC te bevestigen en de omvang van het risico te bepalen.

In **Hoofdstuk 7** bespreken we al onze bevindingen op basis van alle thesis hoofdstukken. Dit proefschrift heeft bijgedragen tot een uitgebreide karakterisering van medicatiefouten op basis van observationele data en mogelijk nieuwe veiligheidssignalen onthuld die verder onderzocht zouden kunnen worden. We concluderen dat hoewel we erin geslaagd zijn om de kenniskloof tot op zekere hoogte op het gebied van medicatiefouten en ADEs op te vullen, er toch ruimte voor verbetering is op het gebied van standaardisatie, het omzetten van drugsnamen, aanpak ontbrekende gegevens, tekort aan gegevensregistratie en analyse van ongestructureerde klinische tekstgegevens van elektronische patiëntendossiers met nieuwe methoden zoals *large language models* (LLMs, *grote taalmodellen*).

PHD PORTFOLIO

Presentations and attendance

ICPE, Berlin, Germany (2024)
Poster presentation - Medication Errors in EudraVigilance: Signals of Disproportionate Reporting Among Age Groups

OHDSI Europe Symposium, Rotterdam, The Netherlands (2024)

MedDRA User Group Meeting, Amsterdam, The Netherlands (2024)
Oral presentation - Use of MedDRA preferred terms in signal detection within the FDA's Adverse Event Reporting System database

ERS Congress, Milan, Italy (2023)
Poster presentation, delegated - Trends in outpatient azithromycin prescribing in respiratory diseases

Erasmus MC PhD day, Rotterdam, The Netherlands (2023)

Clinical & Health Sciences PhD Day, Rotterdam, The Netherlands (2023)

OHDSI Europe Symposium, Rotterdam, The Netherlands (2023)
Poster presentation - Contraception use in females with underlying conditions

ATS International Conference, Washington D.C., United States of America (2023)
Thematic poster session presentation, delegated - Parasitic infections related to anti-type 2 immunity monoclonal antibodies: a disproportionality analysis utilizing the Food and Drug Administration's Adverse Event Reporting System

OHDSI Europe Symposium, Rotterdam, The Netherlands (2022)
Poster presentation - Macrolide use among patients with asthma and chronic obstructive pulmonary disease: A drug-utilization and prediction study

OHDSI Global Symposium, Bethesda, United States of America (2022)
Poster presentation - Incidence analysis and prediction of potentially harmful drugs among asthma patients

ICPE, Copenhagen, Denmark (2022)
Poster presentation - Descriptive analysis of disproportionate medication errors and associated patient characteristics in the FDA's Adverse Event Reporting System

Erasmus MC PhD Day, Rotterdam, The Netherlands (2022)

Biomedical Science PhD day, Rotterdam, The Netherlands (2022)

MedDRA Coding of Medication Errors (Part 2) – Workshop Webinar (2022)

OHDSI Global Virtual Symposium, Rotterdam, The Netherlands (2021)

MedDRA Coding of Medication Errors - Workshop Webinar (2021)

European Industry MedDRA User Group Webinar (2021)

Career perspectives for junior epidemiologists, Rotterdam, The Netherlands (2021)

HIMSS21 & Health 2.0 European Health Conference, virtual (2021)

Joint HMA/EMA virtual workshop on artificial intelligence in medicines regulation (2021)

Digital PhD day (2021)

Online fall event for junior epidemiologists: Epidemiology of the future, Rotterdam, The Netherlands (2020)

Courses

Advances in Clinical Epidemiology [ESP77] (2023)
Netherlands Institute for Health Sciences, Erasmus Medical Center

Introduction to Bayesian Methods in Clinical Research [ESP68] (2022)
Netherlands Institute for Health Sciences, Erasmus Medical Center

Introduction to Data-analysis [ESP03] (2022)
Netherlands Institute for Health Sciences, Erasmus Medical Center

History of Epidemiologic Ideas [ESP53] (2022)
Netherlands Institute for Health Sciences, Erasmus Medical Center

Networking and Influencing Skills [LLS14] (2022)
Netherlands Institute for Health Sciences, Erasmus Medical Center

Getting you PhD done – with Outlook and OneNote (2021)
The Erasmus Postgraduate School

Scientific Integrity (2021)
Graduate school, Erasmus Medical Center

Teaching and Reviewing

Peer reviewing for international journals (2023-2025)
Pharmacoepidemiology & Drug Safety, Pharmacological Reports, Therapeutic advances in Drug Safety, Drug Safety

EU2P facilitator (2021 - 2024)
Virtual

Master thesis supervision for 7 Pharmacy students from the University of Ghent, Belgium (2021 - 2024)
Department of Medical Informatics, Erasmus Medical Center

Teaching assistant for Pharmaco-epidemiology and Drug Safety [EL012] (2022)
Erasmus Medical Center

Teaching assistant for Medicine students in Systematic Review Assignments (2021)
Erasmus Medical Center

LIST OF PUBLICATIONS

Included in this thesis

Parry RE, **Pera V**, Verhamme KMC, de Wilde M, van Mulligen EM, Kors JA. Aioli: Standardising Drugs in the FDA Adverse Event Reporting System (FAERS) to RxNorm and Anatomical Therapeutic Chemical (ATC) Codes. Pharmacoepidemiology and Drug Safety. 2025;34(9):e70216. https://doi.org/10.1002/pds.70216.

Pera V, van Vaerenbergh F, Kors JA, van Mulligen EM, Parry RE, de Wilde M, et al. Descriptive analysis on disproportionate medication errors and associated patient characteristics in the Food and Drug Administration's Adverse Event Reporting System. Pharmacoepidemiology and Drug Safety 2024;33:e5743. https://doi.org/10.1002/pds.5743.

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ABOUT THE AUTHOR



Victor was born in the city of Zadar (Croatia) in 1993, but soon after his birth he migrated with his family to the picturesque Capelle aan den IJssel (The Netherlands) where he grew up and completed his primary education at the public primary school *De Klim-op* in 2005. He finished his secondary education in 2011 at the *gymnasium* level of the public Catholic secondary school *Emmauscollege* in Rotterdam (The Netherlands). After that, he enjoyed his fruitful student period while obtaining his Bachelor of Science (2014) and Master of Science (2020) in Pharmacy from the University of Groningen (The Netherlands). His unsatiable hunger for knowledge pushed him to simultaneously complete a Master of Science degree (2020) in Medical Pharmaceutical Sciences with a specialization in the field of Pharmaco-Epidemiology at the University of Groningen. He wrote his final master thesis on the effectiveness of antibiotics for the treatment of Chronic Obstructive Pulmonary Disease (COPD) exacerbations by utilizing both the LifeLines and the IADB.nl database. In November 2020, Victor joined as a *philosophiae doctor* (Ph.D.) candidate in the Health Data Science group of the Medical Informatics department at the Erasmus University Medical Center in Rotterdam. He worked extensively with the Food and Drug Administration's Adverse Event Reporting System (FAERS), the European Medicines Agency's EudraVigilance, the Integrated Primary Case Information (IPCI) database, and utilized tools from the Observational Health Data Sciences and Informatics (OHDSI) collaborative and the Data Analysis and Real World Interrogation Network (DARWIN EU®) to work on databases mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM). Next to his day-to-day research activities, he also supervised Master of Science students enrolled in Ghent's (Belgium) Pharmacy program, both online and on-site for various projects. He was also a facilitator for the online European program in Pharmacovigilance and Pharmacoepidemiology (EU2P) and assisted at multiple university courses. Alongside his educational journey, Victor indulged in various long-term activities over the course of his life. About 20 years were spent on training the Japanese art of Judo (since 1999), eventually earning his First dan grade (*shodan*, black belt), and helping others earn their First and Second dan grade (*nidan*, black belt). Many events in his life accelerated a change in spare time activities, making Victor explore ice-skating (2017), salsa, bachata dancing (2019), calisthenics (2020), cardio-kickboxing (2022), Brazilian jiu-jitsu (2023), wakeboarding (2023), and snowboarding (2025). All we can say for now is that it is just a matter of time before Victor endeavors upon his next adventure.