Chapter

Prevalence and Significance of Antibiotic-Associated Adverse Reactions

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Abstract

The World Health Organization (WHO) defines Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects. The aim is to promote the safety and effective use of medicines through an early detection and evaluation of drug safety risks. The pharmacovigilance system is essentially based in spontaneous reports of Adverse Drug Reactions (ADR). ADR can be associated with severe outcomes and significant mortality, besides, most of them are deemed to be preventable events. Globally, antibiotics are among the most widely prescribed medications and their extensive use is linked to antibiotic-associated ADR. This chapter aims to summarize available epidemiological data concerning antibiotic use related ADR and analyze the reports received by the EudraVigilance system regarding the exclusive usage of antibiotics.

Keywords: Antibiotics, Adverse Drug Reactions, Pharmacovigilance System

1. Introduction

The history of antibiotics and its use can be dated back to the previous century [1]. According to the World Health Organization (WHO), antibiotics are "medicines used to prevent and treat bacterial infections" [2]. These powerful medicines are used to destroy specific bacteria, or to prevent their spread, thus not being suitable to treat, for instance, viral infections. Over the years, antibiotics have shown to effectively treat several previously life-threatening diseases caused by bacteria, being the first therapeutic approach in those clinical conditions [3, 4].

The appropriate use of antibiotics is safe, effective and has few adverse effects. However, when these medicines are improperly prescribed, bacterial resistance may arise. This problem, commonly known as antibiotic resistance (ABR), is one of the major public health threats of the 21st century worldwide [4, 5]. Globally, the annual predicted number of deaths caused by bacterial agents may increase from 700 thousand million deaths to 10 million by 2050, if no action is adopted [5]. A study based on data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) during 2015 estimated that, annually, around 670 thousand infections occur in the European Union (EU) due to antibiotic-resistant bacteria, with approximately 33 thousand people dying as a direct outcome of these types of infection [6]. The overall crude economic burden of ABR was estimated to be

at least 1.5 billion euros a year in the EU, the majority due to hospital costs [7]. Consequently, the fight against ABR stands as an extremely important public health target that should not be underestimated.

The appropriate use of antibiotics is essential to prevent ABR and reduce the risk of adverse reactions. Adverse drug reactions (ADR) are another public health problem, namely in terms of mortality, morbidity and healthcare costs, that requires maximum attention [8]. An ADR can be defined as "a noxious and unintended response to a medicinal product" [9], and can be caused by any drug class. Nevertheless, globally, antibiotics are among the leading drug classes responsible for the occurrence of ADR [10, 11].

Pharmacovigilance systems are essential to enhance patients' care and safety, being responsible for the monitoring of pre-market review and post-market surveillance processes. Moreover, they provide reliable and balanced information for an effective evaluation of the benefits and risks of available medical drugs [12].

The development of educational interventions to improve the awareness of health professionals, and the literacy of the population in general about the dangerous health implications of an inadequate antibiotics use is indispensable.

With this in mind, the aims of this chapter are:

- To review the major antibiotic classes discovered and their mechanisms of action;
- To discuss the relevance of an adequate antibiotic use and highlight the main barriers associated with the emergence of ABR;
- To describe the importance of establishing good pharmacovigilance practices;
- To summarize available epidemiological data concerning antibiotic use related ADR;
- To analyze the reports received by the EudraVigilance system regarding the exclusive usage of antibiotics.

2. Antibiotics

The global significance of antibiotics discovery in medical science is unquestionable. According to the Centers for Disease Control and Prevention (CDC), antibiotics can be described as "medicines that fight infections caused by bacteria in humans and animals, by either killing the bacteria or making it difficult for the bacteria to grow and multiply" [13]. Antibiotics can be of natural occurring origin or chemically synthesized, and have proven to be essential in fighting infectious diseases [14]. The discovery and development of these compounds has allowed the effective treatment of several bacterial infections, leading to an increased lifespan and to an improvement in the quality of life of millions of people [14].

Salvarsan, the first synthetic anti-infective drug reported, was synthesized and discovered by Paul Ehrlich, Alfred Bertheim and Sahachiro Hata in 1907. This antibiotic had its first clinical application in 1910 in syphilis treatment, and was shown to be highly effective and therapeutically safe, regardless of the side effects [1, 15, 16]. Afterwards, in 1932, Gerhard Domagk discovered Prontosil, a sulfonamide drug, which was further developed and commercially released in 1935 for public use by the pharmaceutical company Bayer. These were two of the first antibiotics of synthetic origin discovered [14–16]. On the other hand, penicillin

was the first naturally occurring antibiotic discovered in modern medicine, being observed in a petri dish in 1928 by Alexander Fleming. In 1941, Howard Florey, Norman Heatly and Ernst Chain pursued Fleming's studies and penicillin was finally produced in sufficient quantities to be used in clinical trials, allowing the treatment of uncountable soldiers during World War II. In 1945, the discovery of this unprecedent live-saving antibiotic led Fleming, Florey and Chain to won the Nobel prize [1, 14–16].

The discovery of these three antibacterial drug agents was remarkable and unveiled the future discovery, development and release of several new antibiotic classes during the so called "Golden Age" of antibiotics, a period between 1940s and middle 1960s [1, 15]. Interestingly, most of the antibiotics discovered during this era are still being currently used in the treatment of bacterial infections, once the pharmaceutical industry significantly reduced its investments in the production of new antibiotics due to the little benefit over existing treatments [3].

Antibiotics are classified in different classes. Some share similar chemical and pharmacological features and thus are used in the treatment of similar bacteria infections. These classes briefly comprise β-lactams, sulfonamides, aminoglycosides, tetracyclines, chloramphenicol, macrolides, glycopeptides, sulphonamides, ansamycins, polymyxins, quinolones, streptogramins, oxazolidinones and lipopeptides [16].

According to the Anatomical Therapeutic Chemical (ATC) Index 2020 from the WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health, antibiotics are categorized as antibacterials for systemic use – J01 therapeutic subgroup, belong to the anti-infectives for systemic use (J anatomical group) and consist of the 10 different pharmacological subgroups displayed in **Table 1** [17]. Additionally, antibiotics can also be categorized as bactericidal or bacteriostatic, based on their mechanism of action (**Table 1**). The general assumption within the society for many years was that bactericidal antibiotics (agents that eliminate bacteria by causing cell death) were more powerful and effective than bacteriostatic antibiotics (agents that inhibit bacterial growth and reproduction). However, it became relevant to assess if this belief was indeed true and verified at a clinical level for several bacterial infections [18]. Several studies included in a systematic literature review on the topic have shown that for many invasive bacterial infections, such as pneumonia, skin and soft tissue infection, intraabdominal, genital and nonendocarditis bloodstream infections, there was no significant clinical differences in outcomes nor in mortality. Therefore, one can assume that this classification seems to be irrelevant when applied to these types of clinical infections [18].

2.1 Main challenges with antibiotic use

The discovery of new antibiotics allowed to save countless lives and revolutionize the future of medicine concerning, for instance, transplantation, surgery and chemotherapy, by preventing and treating bacterial infections in these patients. This has led to a significant decline in mortality and morbidity, and to an extended expected lifespan worldwide [19].

After this remarkable era, only a couple of new antibiotic classes were discovered, and the ones that were in clinical use started to become less effective, due to the rise of an emerging and global health threat, the ABR [7, 19].

The development of ABR is created by specific modifications in bacteria, namely mutations or acquisition of resistant genes by horizontal gene-transfer, allowing them to proliferate and survive in the presence of an antibiotic concentration that used to be enough to either prevent the growth or completely eliminate these

J01: Antibacterials for systemic use				
ATC code	**Pharmacological subgroup**	**Examples of antibiotics**	**Type of agent**	**Mechanism of action**
J01A	Tetracyclines	• Demeclocycline • Doxycycline • Chlortetracycline • Lymecycline • Metacycline • Oxytetracycline • Tetracycline • Minocycline	Bacteriostatic	Bacterial protein biosynthesis inhibition (30-S ribosomal subunit targeting)
J01B	Amphenicols	• Chloramphenicol • Thiamphenicol • Combinations of Thiamphenicol	Bacteriostatic	Bacterial protein biosynthesis inhibition (50-S ribosomal subunit targeting)
J01C	β-Lactam Antibacterials – Penicillins	• Ampicillin • Amoxicillin • Benzylpenicillin • Flucloxacillin • Meticillin • Sulbactam • Combinations of penicillins	Bactericidal	Bacterial cell wall synthesis inhibition
J01D	Other β-Lactam Antibacterials	• Cephalosporins: Cefalexin, Cefoxitin, Cefotaxime, Cefepime • Monobactams: Aztreonam • Carbapenems: Meropenem • Other cephalosporins and penems: Ceftobiprole medocaril	Bactericidal	Bacterial cell wall synthesis inhibition
J01E	Sulfonamides and Trimethoprim	• Trimethoprim • Sulfanilamide • Sulfadiazine • Sulfadimethoxine • Combinations of Sulfonamides and Trimethoprim	Bacteriostatic	Folic acid synthesis inhibition
J01F	Macrolides, Lincosamides and Streptogramins	• Macrolides: Erythromycin, Azythromycin • Lincosamides: Clindamycin, Lincomycin • Streptogramins: Pristinamycin, Quinupristin/Dalfopristin	Bacteriostatic (Macrolides and Lincosamides) and Bactericidal (Streptogramins)	Bacterial protein biosynthesis inhibition (50-S ribosomal subunit targeting)

J01: Antibacterials for systemic use				
ATC code	**Pharmacological subgroup**	**Examples of antibiotics**	**Type of agent**	**Mechanism of action**
J01G	Aminoglycoside Antibacterials	• Streptomycins: Streptomycin, Streptoduocin • Other Aminoglycosides: Neomycin, Kanamycin, Gentamicin	Bactericidal	Bacterial protein biosynthesis inhibition (30-S ribosomal subunit targeting)
J01M	Quinolone Antibacterials	• Fluoroquinolones: Ciprofloxacin, Levofloxacin, Trovafloxacin • Other Quinolones: Nalidixic acid, Cinoxacin, Oxolinic acid	Bactericidal	Nucleic acid synthesis inhibition (inhibitors of DNA replication)
J01R	Combinations of Antibacterials	• Penicillins with other Antibacterials • Sulfonamides with other Antibacterials • Spiramycin and Metronidazole • Tetracycline and Oleandomycin • Ciprofloxacin and Ornidazole • Norfloxacin and Tinidazole	Bacteriostatic and Bactericidal	Multiple mechanisms inhibition
J01X	Other Antibacterials	• Glycopeptide Antibacterials: Vancomycin • Polymyxins: Colistin • Steroid Antibacterials: Fusidic acid • Imidazole Derivatives: Metronidazole • Nitrofuran Derivatives: Nitrofurantoin • Other Antibacterials: Fosfomycin	Bacteriostatic and Bactericidal	Multiple mechanisms inhibition

Table 1.
Classification of antibiotics based on the ATC index 2020.

microorganisms [4]. The ABR phenomenon brought serious health and financial consequences to the society, particularly the increased risk in compromising the healthcare sector, together with a global economic impact, because the pharmaceutical companies no longer perceived both antibiotic discovery and development as lucrative investments [19]. Over the past 25 years, several economic, regulatory, and scientific barriers arose and led to a significant decline in the production of new antibiotics, with only two new classes entering the market and being applied into clinical therapy. Instead of generating new drug classes chemically different from the existent ones, the pharmaceutical industry chose to modify the already

existent antibiotics, particularly the naturally-occurring antibiotics, and to alert for its judicious use, aiming to increase their treatment efficiency and combat bacterial resistance on the long run [14, 20].

The global prevalence of bacteria resistance to antibiotics has been progressively growing. The major facilitating drivers of ABR are the overuse and misuse of these drugs, both in human and veterinary medicine and agriculture, as well as the inappropriate prescription of antibiotic therapy by health professionals. Additionally, ABR can also be triggered by the excessive and unrestricted consumption of antibiotics easily available at low price and over the counter for self-medication, in countries that lack antibiotic regulations, or by the free online acquisition of these medicines in countries where antibiotics are strictly regulated [4, 5, 19].

When an antibiotic successfully reaches its target with a certain required concentration, it causes the death or growth inhibition of pathogens. The resistance mechanisms frequently used by bacteria can be developed by the modification of the antibiotic main target or by the reduction of the antibiotic quantity able to reach the target. There are four key molecular mechanisms involved in bacteria resistance [21]:

- Antibiotic modification or destruction – production of specific enzymes able to inhibit or destroy the drug through chemical alterations, thus preventing the antibiotic to interact with its target;

- Antibiotic uptake decrease and/or antibiotic extruding via efflux pumps – leads to a significant reduction in antibiotic's intracellular concentration, preventing it from achieving the target site;

- Target sites modification – either by protecting (antibiotic is unable to achieve its binding site) and/or modifying (the affinity between the drug and its target is reduced) the target site;

- Bacterial resistance development due to global cell adaptive procedures – bacteria are able to survive and protect the disruption of essential cellular mechanisms, by developing resistance inside the host environment.

2.2 Epidemiological data

A close link between excessive and inadequate antibiotic consumption and the associated ABR spread has been extensively reported in the literature as a public health hazard worldwide. Antibiotics overuse and misuse were shown to be two of the most critical ABR contributors [5, 19, 20].

The 2019 annual epidemiological report of antimicrobial consumption in the EU/European Economic Area (EEA) published by the ECDC disclosed that the average total consumption of antibacterials for systemic use (ATC group J01) from both primary care and hospital sectors in 2018 was of 19.4 defined daily doses (DDD) per 1000 inhabitants per day (ranging from 9.5 in the Netherlands to 34.1 in Greece). This surveillance report is based on antimicrobial consumption data reported by the 28 EU Member States, together with 2 EEA countries (namely, Iceland and Norway). Overall, a statistically significant decrease in the trend of antibiotics consumption over the 10-year period (2009–2019) was observed in the EU/EEA, with statistically significant differences (either a decrease or an increase) being noticed for particular countries. Apart from Slovakia, the antibiotic subgroup with the highest average consumption in all countries of the EU/EEA was β-lactam antibacterials – Penicillins (J01C) [22].

Approximately two-thirds of the world's population are living at the Asia Pacific region (APAC), one of the largest vulnerable regions to the serious problems posed by ABR. Countries belonging to the WHO South-East Asia region were acknowledged to display the greatest risk of ABR development and propagation comparing to all WHO regions [23]. The lack of a formal and efficient surveillance system, strictly dedicated to detecting and monitor human antibiotic consumption and resistance in APAC countries, makes it impossible to determine the overall burden and estimates of antibiotic use in this region. Nevertheless, there is a high demand for the adoption of successful strategies aiming to decrease the impact of this public health threat in Asia, as it is one of the most critical ABR epicenters worldwide [23].

Data on total antibiotic consumption in DDD per 1000 inhabitants per day are presented for 2 Asian and 1 African countries of the WHO Eastern Mediterranean Region, respectively the Islamic Republic of Iran with 38.8 (wholesalers data), and Jordan with 8.9 (import data, with the exception of locally produced medicines that would account for a significant fraction of the total antibiotic use), as well as Sudan with 35.3 (combined data from import and local manufacturers). The antibiotic subgroup most commonly used in Islamic Republic of Iran and Sudan was penicillin, respectively accounting for 33% and 41% of the total consumption, while in Jordan more than 50% of the antibiotics consumed were macrolides/lincosamides/streptogramins (J01F), followed by penicillins and other β-lactam antibacterials (J01D) [24].

The same data is also available for 6 countries of the WHO Western Pacific Region, including Brunei Darussalam with 5.9 DDD per 1000 inhabitants per day, Japan with 14.2, Mongolia with 64.4, New Zealand with 22.7, Philippines with 8.2 and the Republic of Korea with 27.7. However, Brunei Darussalam and New Zealand only provided partial data, either of the public health care or community sectors, respectively [24]. Overall, within this region, approximately 33 to 50% of the antibiotics used were penicillins. The most commonly consumed antibiotic subgroups in Brunei Darussalam, Japan, Mongolia, New Zealand, Philippines and Republic of Korea were, respectively, β-lactam antibacterials (70%), macrolides/lincosamides/streptogramins (32%) and other β-lactam antibacterials (32%), penicillins (33%), penicillins (44%), tetracyclines (J01A, 30%) and penicillins (30%) and other β-lactam antibacterials (33%) [24].

The WHO African Region only provided total antibiotic consumption data in DDD per 1000 inhabitants per day for 4 countries, specifically Burkina Faso with 13.8, Burundi with 4.4 (data restricted to the public sector), Côte d'Ivoire with 10.7 and, finally, the United Republic of Tanzania with 27.3 (data reports only from 2016). The pharmacological subgroup most commonly consumed in all these 4 countries was penicillin, accounting for about 40% of the total consumption in both Burkina Faso and Côte d'Ivoire, 78% in Burundi and 27% in United Republic of Tanzania [24].

The ABR threat greatly affects healthcare development, food production, and lifespan. To efficiently combat ABR, the 1st step is to prevent bacterial infections, the 2nd step is to restrict the resistant bacteria spread by improving an adequate antibiotic use and, finally, the 3rd step is to immediately interrupt the spread when the development has occurred [25].

According to the CDC's Antibiotic Resistance Threats in the United States (US) Report from 2019, which delivered the most recent national antibiotic resistance-associated burden estimates, there are still over 2.8 million infections occurring in the US per year, yielding more than 350 thousand deaths. Although estimates have improved, particularly the death rate which decreased by 18% when compared to the same report from 2013, the high number of ABR-associated infections still remains an important challenge [25]. Moreover, 2016 CDC estimates revealed that

approximately 30% of all antibiotics prescribed in the US, which corresponds to about 47 million prescriptions per year, are still being inadequately used to treat diseases that do not require antibiotics [26].

Since ABR is a natural and irreversible phenomenon, it is crucial that countries around the world start adopting rigorous measures to slow down and inhibit the spread of bacterial resistance. In response to the emerging global public health threat posed by ABR, a number of national and international actions and initiatives have been developed in recent years to address this issue [27]. In 2015, WHO adopted a global action plan with several interventions that included strengthening health systems and surveillance, reducing the unnecessary use of antibiotics, as well as the prevention and control of ABR in humans, animals, agriculture, and the environment, highlighting the need for an efficient, indispensable and global "OneHealth" approach [27–29]. According to the CDC, the "OneHealth" approach is a "collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment" [30]. Subsequently, on June 29th, 2017, the European Commission adopted a similar integrated action plan, consisting of a series of global, rigorous and high priority strategies and measures, designed to restrict the development and spread of ABR in humans and animals, based on the "OneHealth" perspective [31]. Antibiotic resistance is indeed a One Health challenge, where people's and animal's health are linked together with the environment, that must be rapidly curbed.

The pointless or inadequate antibiotics usage is frequently determined by the knowledge, attitudes and beliefs of all the involved stakeholders on this relevant topic. In order to fight this threat, a couple of initiatives have been adopted by many countries worldwide. These have shown to effectively impact ABR and comprise bacterial infection regulatory programs to limit the transmission of resistant microorganisms, antibiotic stewardship courses based on the adherence to awareness guidelines and approaches to increase the judicious antibiotic prescription, educational interventions among health professionals to improve prudent antibiotic prescription and vaccination programs [20, 29, 32–35].

3. Adverse drug reactions associated with antibiotics

Pharmacovigilance is very important for monitoring the safety profile of authorized drugs [12, 36]. The ADR remain a challenge in medicine use and are regarded as a critical public health concern due to their potential harmful life-threatening effects [37].

According to the European Directive 2010/84/EU, an *adverse reaction* is defined as a "response to a medicinal product which is noxious and unintended". Moreover, these reactions may arise from the use of the medicinal product within or outside the terms of the marketing authorization (such as off-label use, overdose, misuse, abuse) or from occupational exposure. On the other hand, the definition of an *adverse effect* is given by the EU Directive 2001/20/EC as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment". One can then conclude that while an adverse effect is not necessarily triggered by the drug, as it is only temporally correlated with the drug use, an ADR is a form of adverse effect both temporally and causally associated with the drug [38, 39].

The classical or traditional pharmacological classification of ADR primarily adopted was only differentiating dose-related and non-dose-related

reactions, respectively as type A and type B, being solely characterized by properties of the drug (its well-known pharmacology and dose dependent effects). Subsequently, other 4 types of reactions were further established to facilitate the inclusion of adverse reactions that did not belong to type A or type B. Therefore, the modern ADR classification currently includes 6 types of reactions [40].

In 2003, to improve the drawbacks and oversimplifications of the traditional approach, an alternative and more accurate classification system was proposed by Aronson and Ferner, as it had been noticed that some ADR still did not fit well into just one of the classes described above. This classification scheme is known as DoTS and operates by taking into account 3 major parameters: the Dose responsiveness of the drug, the Time course of the reaction and the relevant Susceptibility factors of the patient (including genetic, pathological and other biological differences). Although this 3-dimensional approach is more precise and comprehensive when considering the diagnosis and prevention of ADR, it is also more complex for daily use, which prevented its extensive use in the clinic [41].

Globally, ADR have shown to cause significant morbidity and mortality across diverse populations, either in hospitalized or ambulatory patients, with a significant economic burden to the healthcare system. Adverse reactions affect the quality of life of patients, their confidence in the healthcare system and can significantly increase hospitalizations and the hospital stay period [42, 43].

Over the years, several studies have reported that on average, ADR are responsible for 5–10% of the hospitalizations worldwide, with 80% being frequently considered predictable and possibly avoidable reactions (type A). Moreover, it has also been shown that approximately one fourth of the ambulatory patients in primary care centers can also suffer an ADR reported as serious in 13% of the cases [42].

Studies from the US have shown that ADR were observed in over 1.2 million hospital stays (about 3.1% of all hospital stays) in 2004. In US hospitals, the incidence of serious and fatal ADR was extremely high, with evaluations of 6.7% and 0.32% respectively, making ADR between the 4th and 6th leading cause of death. In 2012, a management consulting firm estimated a profit of USD 115 billion for the prevention of 35 million adverse drug events. In United Kingdom, ADR incidence among admitted patients was found to be 6.5%, with admissions costing up to £466 million annually or 0.62% of annual health budget [44]. Within the EU, in 2008 the European Commission estimated that around 5% of all hospital admissions were triggered by ADR, with 5% of hospitalized patients experiencing an ADR during their hospital stay. Additionally, approximately 197 thousand deaths per year took place in the EU due to ADR [43].

These findings were undoubtedly one of the starting points for the implementation of a new EU pharmacovigilance regulatory framework in 2012, to reduce the ADR burden [43]. Currently, countless countries around the world already have well-established, active and robust national pharmacovigilance systems to safeguard patient's wellbeing.

Some medicines have been especially involved in hospital admissions due to ADR, including antibiotics. Inpatients are given at least one antibiotic in about 50% of the cases, with roughly 20–30% of these being considered unnecessary and accounting for 20–50% of drug costs in hospitals [10, 45]. Additionally, a previous study has reported that although antibiotics use seems to lead to a small incidence of adverse events, its widespread consumption accounts for 23% of all adverse events documented [10]. Between 2000 and 2010, developing countries were the major contributors to the global rise in antibiotics use and, consequently, in the risk of acquiring associated ADR [11].

There is a lack of studies assessing the incidence of ADR due to antibiotic consumption in the hospital sector, during patient's admission, stay and after discharge, as well as its incidence across all antibiotic classes. Nevertheless, the available literature has shown the clear contribution of antibiotics to 19% of ADR in the emergency department in the US between 2004 and 2006 (with allergic reactions accounting for 79%), 8% linked to hospital admissions in Greece in 2005, 6% in Spain between 2001 and 2006, 5% in The Netherlands in 2003, and 11% in India between 2002 and 2009, together with 10% of hospital-acquired ADR in the US and 22% in South Africa [11].

There are several mechanisms explaining different ADR, and the most well-known include pharmacological causes, idiosyncrasies, hypersensitivity (allergic reactions), carcinogenesis and teratogenesis, direct toxicity, chronic exposure, drug-disease interaction and drug intolerance [46].

3.1 ADR analysis in Europe: EudraVigilance

EudraVigilance, the official EU pharmacovigilance database managing the collection and analysis of suspected ADR to authorized medical products in the EEA, was primarily launched in 2001, with a new format emerging in 2017. This new revised and enhanced version aimed to achieve an improved effective monitoring of the medicine safety, contributing to public health protection, and the communication of validated signals to the European Medicines Agency (EMA) and the national medicines regulatory authorities, in line with the legislative framework. By the end of 2017, submissions to EudraVigilance overcome the 12 million individual case safety reports (ICSR), referring to around 8 million individual cases, and making it one of the largest spontaneous reporting systems worldwide [47].

As previously mentioned, one of the drug classes most commonly prescribed and responsible for ADR, both in primary care and hospital sectors, are antibiotics. For Portugal, according to the data provided by the System of Information and Monitoring of the Portuguese National Health System (SIM@SNS) platform [48], developed by the shared services of the Health Ministry, the four antibacterials for systemic use mostly prescribed during the last couple of years (2018–2020) were: a combination of Amoxicillin and Clavulanic acid (**I**), Azithromycin (**II**), Amoxicillin (**III**) and Fosfomycin (**IV**) [49]. In particular, during the year of 2019, the total number of antibiotic packages prescribed within the public sector accounted for around 4.5 million, from which 1.27, 0.63, 0.52, and 0.35 million, respectively corresponded to I, II, III and IV. Data from 2018 revealed the same trend as 2019. Until August 2020, the only alteration observed was the increase in fosfomycin prescriptions over amoxicillin [49].

The individual safety reports stored at the VigiBase (for I) [50] and EudraVigilance (for II, III and IV) [51] databases at 14th November 2020 revealed that among all ADR reported, the most affected System Organ Classes (SOC) for each antibiotic were[1]:

I. Combination of Amoxicillin and Clavulanic Acid (ICSR total = 140942): Skin and subcutaneous tissue disorders – **50.5%**, Gastrointestinal disorders – **24.9%**, and General disorders and administration site conditions – **11.9%**. Within all ADR reported for this combination, 24.6% were considered serious ADR;

[1] The antibiotic-associated ADR reported data are displayed in different ways, as they were retrieved from two different databases, VigiBase (for I) and EudraVigilance (for II, III and IV).

II. Azithromycin (ICSR total = 13404): Gastrointestinal disorders – **26.2%** (of which 15.6% were serious), Skin and subcutaneous tissue disorders – **24.7%** (of which 17% were serious) and General disorders and administration site conditions – **24.5%** (of which 20.2% were serious);

III. Amoxicillin (ICSR total = 34427): Skin and subcutaneous tissue disorders – **56.2%** (of which 36% were serious), Gastrointestinal disorders – **18.4%** (of which 10.9% were serious) and General disorders and administration site conditions – **16.1%** (of which 11.8% were serious);

IV. Fosfomycin (ICSR total = 2483): Gastrointestinal disorders – **38.6%** (of which 10.1% were serious), Skin and subcutaneous tissue disorders – **24.8%** (of which 12.6% were serious) and General disorders and administration site conditions – **21.3%** (of which 11.2% were serious).

The most common ADR reported within each SOC caused by the consumption of these antibiotics include rash, urticaria and pruritus for skin and subcutaneous tissue disorders, diarrhea, nausea, vomiting and abdominal pain for gastrointestinal disorder and pyrexia, malaise, fatigue and asthenia for general disorders and administration condition sites.

The use of antibiotics can result in ADR, among which hypersensitivity reactions. One of the safest and more effective antibiotic subgroups is the β-lactam antibacterials. Within this subgroup, penicillin is one of the most prescribed antibiotics worldwide and is frequently associated with reported allergic reactions. Around 10% of the global population report an allergy to β-lactams, leading to an increased use of broad-spectrum antibiotics, promoting the risk for the development of resistant bacteria and adverse effects, together with an increased cost. Most reports of penicillin allergy describe an unknown or a mild cutaneous reaction. The estimated frequency of the more serious anaphylactic reactions to penicillin is roughly 0.02% to 0.04%, being rarer after oral or cutaneous exposure [52].

3.2 Special populations: children, pregnant women and older adults

ADR reporting system databases are of great utility in the early detection of medicine safety issues [8]. Most of the available data regarding ADR prevalence refer to adult populations within a hospital context [53]. Thereby, it is extremely important to increase our knowledge and perception on ADR incidence in special populations, such as the pediatric (0–18 years old), pregnant women and older adults (≥ 65 years old), as they may differ regarding the most frequently involved drugs and ADR manifestations, and may be at an increased risk due to their general exclusion from pre-marketing clinical assays.

3.2.1 Children

Antibiotics are among the most commonly prescribed drugs in children. Reports from a study conducted in the US during 2016 revealed that 47.4% of infants between 0 and 4 years old received at least one antibiotic prescription, when compared to 39.8% of the adult population. Although these drugs are very valuable for the treatment of severe infection diseases, its high and inadequate consumption can frequently lead to an increased bacterial resistance, as well as to the occurrence of adverse effects even if mild and spontaneously resolving [54]. Antibiotics have been repeatedly reported as the leading contributors to ADR in children. Children can be at an increased risk due to their anatomical and physiological characteristics, such

as their immature immune systems, especially in the first years of life. Moreover, there is a frequent abuse and misuse of these drugs in pediatric clinical practice due to lack of pharmacokinetics data or dose-finding studies, and many antibiotics are prescribed on an unlicensed or "off-label" basis as they were only tested and authorized for adults. Although many adverse events are equal in children and adults, with age not contributing to the frequency and severity of the ADR, there are a few number of antibiotic-associated ADR depending on the unique pharmacokinetic and pharmacodynamic features of the antibiotic that can differ significantly with age, particularly when administered to newborns and infants [54].

A systematic review [55] of ADR in pediatric patients reported that the overall rates of hospital admissions caused by ADR ranged from 0.4% to 10.3% of all children, while the ADR incidence rate varied between 0.6% and 16.8% among children exposed to a drug during hospital stay [8, 53]. Furthermore, a study performed between 2011 and 2015 in the US, based on 6542 surveillance cases, estimated that approximately 70 thousand annual emergency department visits were made for antibiotic-associated ADR among children. This review also showed that the antibiotic most commonly associated with ADR was, by far, the oral penicillin (55.7%), and the most typical clinical manifestations attributed to antibiotics were allergic reactions. Within the pediatric population, amoxicillin was found to be the antibiotic most frequently implicated among children under 10 years old [56]. The findings obtained from ADR reports of two studies conducted within the Portuguese pediatric population between 2003 and 2012 (age range 0–17 years old) and 2006 and 2016 (age range 10–18 years old) demonstrated that the most representative ADR identified involved the subsequent top 4 SOC: general disorders and administration site conditions, followed by skin and subcutaneous tissue reactions, nervous system disorders and gastrointestinal disorders. Antibacterials for systemic use were the second most represented group after vaccines [8, 53].

The individual safety reports stored at the VigiBase (for I) [50] and EudraVigilance (for II, III and IV) [51] databases revealed that, among all ADR reported specifically for children, the percentage of antibiotic-associated ADR for the antibiotics mostly prescribed in Portugal between 2018 and 2020 was of **16.6%** for **I** (combination of amoxicillin and clavulanic acid), **17.1%** for **II** (azithromycin), **17.7%** for **III** (amoxicillin) and **4.2%** for **IV** (fosfomycin). Moreover, the most affected SOC were[2]:

II. ICSR total = 2297: Skin and subcutaneous tissue disorders – **35%**, Gastrointestinal disorders – **25%** and General disorders and administration site conditions – **19.5%**;

III. ICSR total = 6105: Skin and subcutaneous tissue disorders – **69.3%**, Gastrointestinal disorders – **16.9%** and General disorders and administration site conditions – **14.1%**;

IV. ICSR total = 107: Gastrointestinal disorders – **27.1%**, Skin and subcutaneous tissue disorders – **25.2%** and General disorders and administration site conditions – **22.4%**.

3.2.2 Pregnant women

People are aware about the existent lack of information concerning drug safety during pregnancy, mainly because pregnant women are often excluded from trials

[2] SOC data for the combination of amoxicillin and clavulanic acid (**I**) were not available at VigiBase.

throughout the clinical development of the drug. Since 1980, estimates indicate that only 10% of the authorized drugs have enough data involving child risk in pregnancy. Thus, there is a high need for epidemiological studies in pregnant women aiming to evaluate the incidence of ADR [57].

Since there are no reports of totally innocuous drugs commercially available, pregnant women must be cautious and try to avoid, as much as possible, the consumption of medicines, particularly during the first trimester, and only use them when the benefits to the mother outweigh the fetus risk [58]. Over the last years, it has been observed a rise in the number of women consuming drugs during pregnancy. Antibiotics are among one of the classes most commonly prescribed to treat infections in pregnant women, constituting nearly 80% of all drugs prescription, of which roughly 1 in every 4 women consume at least one antibiotic throughout their pregnancy course. However, its use must be prudent as the first concern is to protect the fetus from potential ADR resulting from antibiotic use [57, 58]. Urinary tract infections, sexually transmitted infections and upper respiratory tract infections represent 3 of the most typical infectious diseases found during pregnancy. When not treated, urinary tract and sexually transmitted infections represent an important risk to the fetus with consequences such as, as low birth weight, prematurity and spontaneous abortion. Moreover, the risk for short-term (congenital abnormalities) and long-term (changes in the gut microbiome, asthma, atopic disease) effects in the newborn, and physiological changes that usually take place during pregnancy, have also been related to antibiotic therapy [57].

Overall, there are several antibiotics that can be generally used during pregnancy without compromising safety, such as β-lactams (with penicillin and derivatives being the most prescribed drugs to pregnant women), vancomycin, macrolides, clindamycin, and fosfomycin, and others that must be mostly avoided, such as fluoroquinolones and tetracyclines [57]. In fact, penicillins have a long safety track record during pregnancy, but are usually substituted by macrolides as alternative for patients with penicillin allergies. Very recently, a cohort population-based study from UK has shown that the prescription of macrolides instead of penicillin antibiotics led to an enhanced risk of major malformation, primarily those derived from the cardiovascular system, but only over the first pregnancy trimester. This study also reported an enhanced risk of genital malformations linked to macrolides prescription in any trimester, advertising for the careful use of this antibiotic subgroup in pregnant women [59]. Some studies have also indicated an increased asthma risk in early childhood, as well as an increased risk of childhood epilepsy and obesity linked to antibiotic use during pregnancy [58].

The use of 3 of the most prescribed antibiotics in Portugal over the last years, namely amoxicillin clavulanate, amoxicillin and fosfomycin, has been considered safe and well-tolerated during pregnancy, with no adverse effects being shown in the fetus or infant [57].

3.2.3 Older adults

Infectious diseases in the elderly population remains a public health concern because of the high mortality and morbidity outcomes. The geriatric population, regarded as a special population by the International Council for Harmonization (ICH), is more prone to develop ADR because they usually exhibit a combination of increased critical risk factors that can promote these reactions. These risk factors comprise multimorbidity, polypharmacy, changes in medication adherence, pharmacokinetics, greater vulnerability, aging-related physiological changes (changes in the body mass distribution, renal function, metabolic capacity and alteration in blood protein levels), deficit in the immune system, weakening cognition, in

addition to a clear lack on drug use information in the older people [60]. Research studies have estimated an ADR risk in older adults of four times higher than the rest of the population. Old age is also a critical factor for extended hospital stays, enhanced prevalence of complication and falls. The large majority of reported ADR in the older adults belong to type A, possibly avoidable and linked to commonly prescribed drugs. Common geriatric syndromes from older adults include delirium, falls, dizziness, urinary incontinence, which can sometimes be mistaken with typical manifestations from older people. Therefore, given their heterogeneity, to efficiently prevent the high ADR incidence in the older people, it is essential to focus on person-centered care intervention allied to good clinical practice [60].

Between 2007 and 2009, data from an US report on hospitalizations after emergency department visits for adverse events revealed that 3.8% of the total hospitalizations were due to the use of antimicrobial agents. In fact, these agents were the 5th most common treatment class involved in hospitalizations. Data showed that the most frequent clinical adverse event manifestations arisen from antimicrobials use leading to hospitalizations were allergic reactions (36.2%), dyspnea and weakness (22.5%), gastrointestinal effects (20.5%), and neurologic effects (18.3%). Some of these adverse events, such as dyspnea, weakness, neurological adverse events, and effects on blood pressure may potentially promote significant negative implications in older patients, leading to altered mental status, falls, and hypotension [61].

The individual safety reports stored at the VigiBase (for I) [50] and EudraVigilance (for II, III and IV) [51] databases revealed that, among all ADR reported specifically for older adults (≥ 65 years old), the percentage of antibiotic-associated ADR for the antibiotics mostly prescribed in Portugal between 2018 and 2020 was of **22.7%** for **I** (combination of amoxicillin and clavulanic acid), **20.7%** for **II** (azithromycin), **22.7%** for **III** (amoxicillin) and **31.5%** for **IV** (fosfomycin). Moreover, the most affected SOC were[3]:

II. ICSR total = 2767: General disorders and administration site conditions – **26.5%**, Gastrointestinal disorders – **21.5%** and Skin and subcutaneous tissue disorders – **21%**;

III. ICSR total = 7813: Skin and subcutaneous tissue disorders – **47.8%**, Gastrointestinal disorders – **18%** and General disorders and administration site conditions – **16.5%**;

IV. ICSR total = 780: Gastrointestinal disorders – **33.2%**, Skin and subcutaneous tissue disorders – **27.1%** and General disorders and administration site conditions – **21.8%**.

4. Conclusions

Overall, antibiotics are undoubtedly among the most successful drug agents in the world. They are attributed to having improved patient care and revolutionized modern medicine. However, the inappropriate prescribing of these agents has led to the development of one of the biggest public health concern: antimicrobial resistances [4, 5]. Therefore, it is vital to understand and overcome the main barriers and challenges resulting from antibiotics usage, aiming to design and develop educational interventions for increase awareness and knowledge within the society, and hopefully be able to change people's and prescribing physician's behavior.

[3] SOC data for the combination of amoxicillin and clavulanic acid (**I**) were not available at VigiBase.

Pharmacovigilance is a global top priority in healthcare systems. It provides instruments for monitoring the safety of medicines on the market through prevention, detection and assessment of adverse reactions, as well as invaluable information on the benefit/risk ratio of a health product throughout its life cycle [12, 36].

Currently, ADR are still ranked among the leading mortality causes in many countries and are recognize as hazards of drug therapy [42, 43]. Although ADR are prevalent in all ages, it is more difficult to predict the effect of the drugs among the special populations that do not take part in clinical trials. Post-marketing surveillance through pharmacovigilance centers is extremely important and the most efficient way to monitor ADR, especially for those groups [12, 42].

Although antibiotics are considered safe when rationally used for treatment and prophylaxis of several infectious diseases, with its prescription being generally high among all ages, these drugs can also substantially contribute to reported ADR, especially β-lactam antibacterials, and macrolides [10, 11, 45]. The most affected organ systems involved are the gastrointestinal system and the skin.

In sum, a visible reduction in global human mortality and morbidity, as well as in health costs, would certainly be noticed with the implementation of international and national campaigns alerting to both the rational use of antibiotics and the importance of reporting ADR, aiming to minimize patient's harm and significantly improve public health.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

ABR	Antibiotic Resistance
ADR	Adverse Drug Reactions
APAC	Asia Pacific region
ATC	Anatomical Therapeutic Chemical
CDC	Centers for Disease Control and Prevention
DDD	Defined Daily Doses
EARS-Net	European Antimicrobial Resistance Surveillance Network
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
ICH	International Council for Harmonization
ICSR	Individual Case Safety Report
SOC	System Organ Classes
US	United States
WHO	World Health Organization

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References

[1] Hutchings MI, Truman AW, Wilkinson B. Antibiotics: past, present and future. *Curr Opin Microbiol* 2019; 51: 72-80.

[2] World Health Organization. Antibiotic Resistance, https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance (2020, accessed 26 October 2020).

[3] Fernandes P, Martens E. Antibiotics in late clinical development. *Biochem Pharmacol* 2017; 133: 152-163.

[4] Sabtu N, Enoch DA, Brown NM. Antibiotic resistance: what, why, where, when and how? *Br Med Bull* 2015; ldv041.

[5] Machowska A, Stålsby Lundborg C. Drivers of Irrational Use of Antibiotics in Europe. *Int J Environ Res Public Health* 2018; 16: 27.

[6] Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; 19: 56-66.

[7] Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health* 2015; 109: 309-318.

[8] Rebelo Gomes E, Ribeiro-Vaz I, Santos CC, et al. Adverse drug reactions in adolescents: a review of reporting to a national pharmacovigilance system. *Expert Opin Drug Saf* 2020; 19: 915-922.

[9] European Parliament. *DIRECTIVE 2010/84/EU*, https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF (2010, accessed 12 November 2020).

[10] Shamna M, Dilip C, Ajmal M, et al. A prospective study on Adverse Drug Reactions of antibiotics in a tertiary care hospital. *Saudi Pharm J* 2014; 22: 303-308.

[11] Kiguba R, Karamagi C, Bird SM. Antibiotic-associated suspected adverse drug reactions among hospitalized patients in Uganda: a prospective cohort study. *Pharmacol Res Perspect* 2017; 5: e00298.

[12] Pitts PJ, Louet H Le, Moride Y, et al. 21st century pharmacovigilance: efforts, roles, and responsibilities. *Lancet Oncol* 2016; 17: e486–e492.

[13] Centers for Disease Control and Prevention. Antibiotic Use Questions and Answers, https://www.cdc.gov/antibiotic-use/community/about/should-know.html (accessed 27 October 2020).

[14] Nicolaou KC, Chen JS, Edmonds DJ, et al. Recent Advances in the Chemistry and Biology of Naturally Occurring Antibiotics. *Angew Chemie Int Ed* 2009; 48: 660-719.

[15] Aminov RI. A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future. *Front Microbiol*; 1. Epub ahead of print 2010. DOI: 10.3389/fmicb.2010.00134.

[16] Ribeiro da Cunha, Fonseca, Calado. Antibiotic Discovery: Where Have We Come from, Where Do We Go? *Antibiotics* 2019; 8: 45.

[17] Antibacterials for Systemic Use, https://www.whocc.no/atc_ddd_index/?code=J01&showdescription=no (accessed 27 October 2020).

[18] Wald-Dickler N, Holtom P, Spellberg B. Busting the Myth of "Static vs Cidal": A Systemic Literature Review. *Clin Infect Dis* 2018; 66: 1470-1474.

[19] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T* 2015; 40: 277-83.

[20] North J. *Challenges to Tackling Antimicrobial Resistance*. Cambridge University Press. Epub ahead of print 30 April 2020. DOI: 10.1017/9781108864121.

[21] Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. *Microbiol Spectr*; 4. Epub ahead of print 1 April 2016. DOI: 10.1128/microbiolspec.VMBF-0016-2015.

[22] European Centre for Disease Prevention and Control. *Antimicrobial consumption in the EU/EEA, annual epidemiological report for 2019*. Stockholm, https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2019 (2020).

[23] Yam ELY, Hsu LY, Yap EP-H, et al. Antimicrobial Resistance in the Asia Pacific region: a meeting report. *Antimicrob Resist Infect Control* 2019; 8: 202.

[24] WHO. *WHO report on surveillance of antibiotic consumption: 2016-2018 early implementation*. Geneva: World Health Organization, https://www.who.int/medicines/areas/rational_use/oms-amr-amc-report-2016-2018/en/ (2018).

[25] CDC. *Antibiotic resistance threats in the United States, 2019*. Atlanta, GA: U.S. Department of Health and Human Services, CDC. Epub ahead of print November 2019. DOI: 10.15620/cdc:82532.

[26] CDC. *Antibiotic Use in the United States, 2018 Update: Progress and Opportunities*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, https://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report-2018-508.pdf (2019).

[27] Nahrgang, Saskia; Nolte, Ellen; Rechel B. Antimicrobial Resistance. In: *The role of public health organizations in addressing public health problems in Europe*. Copenhagen, Denmark: European Observatory on Health Systems and Policies, https://www.ncbi.nlm.nih.gov/books/NBK536193/ (2018).

[28] World Health Organization. One Health, https://www.who.int/features/qa/one-health/en/ (2017).

[29] World Health Organization. *Global action plan on antimicrobial resistance*, https://www.amcra.be/swfiles/files/WHO actieplan_90.pdf (2015).

[30] Centers for Disease Control and Prevention. One Health, https://www.cdc.gov/onehealth/ (2020).

[31] European Commision. *A European One Health Action Plan against Antimicrobial Resistance*, https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf (2017).

[32] Roque F, Teixeira-Rodrigues A, Breitenfeld L, et al. Decreasing antibiotic use through a joint intervention targeting physicians and pharmacists. *Future Microbiol* 2016; 11: 877-886.

[33] Teixeira Rodrigues A, Roque F, Piñeiro-Lamas M, et al. Effectiveness of an intervention to improve antibiotic-prescribing behaviour in primary care: a controlled, interrupted time-series study. *J Antimicrob Chemother* 2019; 74: 2788-2796.

[34] Teixeira Rodrigues A, Ferreira M, Roque F, et al. Physicians' attitudes and knowledge concerning antibiotic prescription and resistance: questionnaire development and reliability. *BMC Infect Dis* 2015; 16: 7.

[35] Oliveira I, Rego C, Semedo G, et al. Systematic Review on the Impact of

Guidelines Adherence on Antibiotic Prescription in Respiratory Infections. *Antibiotics* 2020; 9: 546.

[36] Beninger P. Pharmacovigilance: An Overview. *Clin Ther* 2018; 40: 1991-2004.

[37] Coleman JJ, Pontefract SK. Adverse drug reactions. *Clin Med (Northfield Il)* 2016; 16: 481-485.

[38] Baldo P, Francescon S, Fornasier G. Pharmacovigilance workflow in Europe and Italy and pharmacovigilance terminology. *Int J Clin Pharm* 2018; 40: 748-753.

[39] European Medicines Agency. *Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products*, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf (2017).

[40] Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; 356: 1255-1259.

[41] Aronson JK. Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* 2003; 327: 1222-1225.

[42] Laporte J-R. Fifty years of pharmacovigilance - Medicines safety and public health. *Pharmacoepidemiol Drug Saf* 2016; 25: 725-732.

[43] Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. *Drug Saf* 2015; 38: 437-453.

[44] Akhideno P, Fasipe O, Isah A, et al. Pattern of medications causing adverse drug reactions and the predisposing risk factors among medical in-patients in clinical practice: A prospective study. *J Med Sci* 2019; 39: 18.

[45] Tamma PD, Avdic E, Li DX, et al. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. *JAMA Intern Med* 2017; 177: 1308.

[46] Aronson JK. *Meyler's Side Effects of Drugs - The International Encyclopedia of Adverse Drug Reactions and Interactions*. 16th ed. Elsevier Science, 2015.

[47] Postigo R, Brosch S, Slattery J, et al. EudraVigilance Medicines Safety Database: Publicly Accessible Data for Research and Public Health Protection. *Drug Saf* 2018; 41: 665-675.

[48] System of Information and Monitoring of the Portuguese National Health System. SIM@SNS, https://bicsp.min-saude.pt/pt/investigacao/Paginas/medicamentoprescritor_publico.aspx?isdlg=1 (accessed 12 November 2020).

[49] Serviços Partilhados do Ministério da Saúde (SPMS). Bilhete de Identidade dos Cuidados de Saúde Primários, https://bicsp.min-saude.pt/pt/investigacao/Paginas/medicamentoprescritor_publico.aspx?isdlg=1 (accessed 11 November 2020).

[50] Center UM. VigiBase, http://www.vigiaccess.org/.

[51] EMA. EudraVigilance, http://www.adrreports.eu/en/index.html (accessed 12 November 2020).

[52] Bhattacharya S. The facts about penicillin allergy: a review. *J Adv Pharm Technol Res* 2010; 1: 11-7.

[53] Nogueira Guerra L, Herdeiro MT, Ribeiro-Vaz I, et al. Adverse drug reactions in children: a ten-year review of reporting to the Portuguese Pharmacovigilance System. *Expert Opin Drug Saf* 2015; 14: 1805-1813.

[54] Principi N, Esposito S. Antibiotic-related adverse events in paediatrics: unique characteristics. *Expert Opin Drug Saf* 2019; 18: 795-802.

[55] Smyth RMD, Gargon E, Kirkham J, et al. Adverse Drug Reactions in Children—A Systematic Review. *PLoS One* 2012; 7: e24061.

[56] Lovegrove MC, Geller AI, Fleming-Dutra KE, et al. US Emergency Department Visits for Adverse Drug Events From Antibiotics in Children, 2011-2015. *J Pediatric Infect Dis Soc* 2019; 8: 384-391.

[57] Bookstaver PB, Bland CM, Griffin B, et al. A Review of Antibiotic Use in Pregnancy. *Pharmacother J Hum Pharmacol Drug Ther* 2015; 35: 1052-1062.

[58] Kuperman AA, Koren O. Antibiotic use during pregnancy: how bad is it? *BMC Med* 2016; 14: 91.

[59] Fan H, Gilbert R, O'Callaghan F, et al. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. *BMJ* 2020; m331.

[60] Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. *Br J Clin Pharmacol* 2015; 80: 796-807.

[61] Giarratano A, Green S EL, Nicolau DP. Review of antimicrobial use and considerations in the elderly population. *Clin Interv Aging* 2018; Volume 13: 657-667.