Universitat Autònoma de Barcelona

The Role of Pharmacovigilance and Drug Utilisation studies in the Track of Antimicrobial Resistance

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DOCTORAL THESIS

The Role of Pharmacovigilance and Drug Utilisation studies in the Track of Antimicrobial Resistance

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Albert Figueras i Suñé, Doctor en Medicina i antic Professor del Departament de Farmacologia, Terapèutica i Toxicologia, de la Universitat Autònoma de Barcelona (2010-2020),

F A C O N S T A R:

Que la Tesi Doctoral ***The Role of Pharmacovigilance and Drug Utilisation studies in the Track of Antimicrobial Resistance***, elaborada per **Jean Marie Vianney Habarugira**, ha estat realitzada sota la meva direcció per tal d'optar al títol de Doctor en Farmacologia per la Universitat Autònoma de Barcelona, i considero que reuneix les condicions necessàries per a ser presentada i defensada al davant del tribunal corresponent.

Per a què consti als efectes oportuns, signo aquest document a Barcelona, el sis de setembre dos mil vint-i-u.

Albert Figueras i Suñé

Table of Contents

SUMMARY

Antimicrobial resistance (AMR) has become a real public health concern, challenging all existing prevention and treatment options, and requiring multidisciplinary innovative solutions. Health systems in developed countries can rely on the well-established laboratory services that can carry out microbial cultures and drug-susceptibility tests. However, for many low- and middle-income countries (LMICs) with limited laboratory resources, it still requires long-term investments into health have systems that provide laboratory-based AMR monitoring activities. Exploring the potential use of other indirect measures that can provide estimates of the growing AMR burden in settings with weak laboratory capacity, this thesis aims at describing the potential contribution of the global network of Pharmacovigilance centers and databases in the process of mapping and estimating the AMR burden in settings with less laboratory coverage and capacity, within the framework of AMS. In a large study based on safety data retrieved from the global pharmacovigilance database (VigiBase), from a long list of more than 23,000 MedDRA codes for Preferred Terms, we have isolated a short list of 17 codes that are relevant to antimicrobial stewardship. The 17 codes should be the basis of a further discussion on how to integrate MedDRA-based data collection into antimicrobial resistance surveillance strategies. In a pilot study carried out in a country with a mature pharmacovigilance system, we analysed adverse drug reaction (ADR) reports from The Netherlands Pharmacovigilance database. Results confirming use of the AMR-relevant MedDRA codes in a national database are presented in this thesis.

Antimicrobial stewardship is complex program which includes a heterogenous set of measures and activities aiming to reduce inappropriate use of antimicrobials. In this thesis, we propose a new antimicrobial stewardship tool which as the same time gives another dimension to existing functions of Pharmacovigilance. Specifically, we describe a set of MedDRA codes relevant to AMR surveillance as they carry a message of suspected resistance, suspected ineffectiveness, off label use and medication error. The 17 codes are messengers with safety information, and we propose to read their message through an antimicrobial stewardship lens. The global Pharmacovigilance network covers more than 170 countries using unique codes from the MedDRA dictionary to collect and collate ADR reports. Data mining technologies can be used to pull out important information on

suspicion of antimicrobial resistance and suspected cases of inappropriate use of antimicrobials.

This could also lead to potentially symbiotic approach which contributes to the strengthening of PV systems while addressing the issue of AMR data scarcity, especially in resource-limited settings.

Acknowledgement

It is a life we live with the help and support from others. And without naming all, I would like to thank those who may be saying "it's OK, don't thank me".

The trio which fills me with love, joy, and inspiration every morning before I see the outside world. The wonderful trio making my home, my little tribe, Annemiek, Kenza and Olivia. They only, can tell how many nights and how many weekends have seen me socked deep into this research. They only, can tell how normal it is to see me with a laptop on holiday trip. And I do appreciate all that loving support, that fuel which keeps me aspiring for greater. To my three best friends, my home tribe, thanks for climbing the hill with me. I do not take any of that for granted.

In our quest for knowledge, we all have met teachers, educators, mentors, and coaches. But, as I embarked on this PhD project, I have had a one in a lifetime opportunity of working with a gifted teacher, a dedicated educator, a coach with a vision, Albert Figueras. As my Thesis Director, he guided me into the right direction, and when time to almost give up came, he reminded me of the value of the puzzle we were trying to solve. A patient mentor, a respected expert who agreed to guide me with a firm belief in the mission we came to share.

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"*Education is the exit card out of the kingdom of the underman*", a father once told his little boy, me.

List of Abbreviations

- ADE – Adverse drug event
- ADR – Adverse drug reaction
- AE – Adverse Event
- AM- Antimicrobial
- AMR – Antimicrobial resistance
- AMS – Antimicrobial Stewardship
- ATC – anatomical and chemical classification
- AWaRe – Access, Watch, Reserve
- CBG/MEB - College ter Beoordeling van Geneesmidellen/Dutch Medicines Evaluation Board
- DUR – Drug Utilisation Research
- DUS – Drug Utilisation studies
- EDCTP – European and Developing Countries Clinical Trials Partnership
- ICSR – individual case safety report
- Lareb – Landelijke registratie en evaluatie van bijwerkingen (National registration and evaluation of adverse reactions)
- LMIC- low- and middle-income countries
- MedDRA – Medical dictionary for drug regulatory affairs
- NDA – National Drug Authority
- PASS – Post-Authorisation safety studies
- PIDM – Programme for International Drug Monitoring
- PT – preferred term
- PV – Pharmacovigilance
- SAE – Serious adverse event
- SOC – system organ class
- UAB – Universitat Autonoma de Barcelona

- UMC – Uppsala Monitoring Centre
- WHO – World Health Organisation

Glossary (key concepts)

- **Adverse drug reaction –** an adverse drug reaction is referred to when causality analysis has taken place and the link between the medicine and a suspected adverse effect is beyond uncertainty [1]

- **Adverse event** – any undesirable experience associated with the use of a medical product in a patient [2]

- **Antibiotic** – a medicinal product that kills or inhibits the growth of bacteria

- **Antimicrobial** - a medicinal product that kills of inhibits the growth of microbes, incl. bacteria, viruses and fungi

- **Antimicrobial resistance** [3] – the ability of a microbe (bacteria, virus, fungi to resist the effects of medicinal products used to kill it or inhibit its growth

- **Antimicrobial stewardship** – a coordinated program that promotes the appropriate use of antimicrobials, improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms [4].

- **Lareb – La**ndelijke **R**egistratie en **E**valuatie van **B**ijwerkingen (in Dutch) or National registration and evaluation of adverse reactions (in English) is the National Pharmacovigilance Center for The Netherlands.

- **MedDRA –** or the Medical Dictionary for Regulatory Activities is standardised terminology published by the International Council for Harmonisation (ICH) for coding cases of adverse effects in clinical study reports and Pharmacovigilance databases [5].

- **Pharmacovigilance** – the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems [6,7]

- **Serious adverse event** – an adverse event resulting in any of the following: death, live-threating experience, hospitalisation (or prolongation of initial hospitalisation), disability or permanent damage, congenital anomaly or birth defect

- **VigiBase** – the WHO Global database of individual case safety reports [8]

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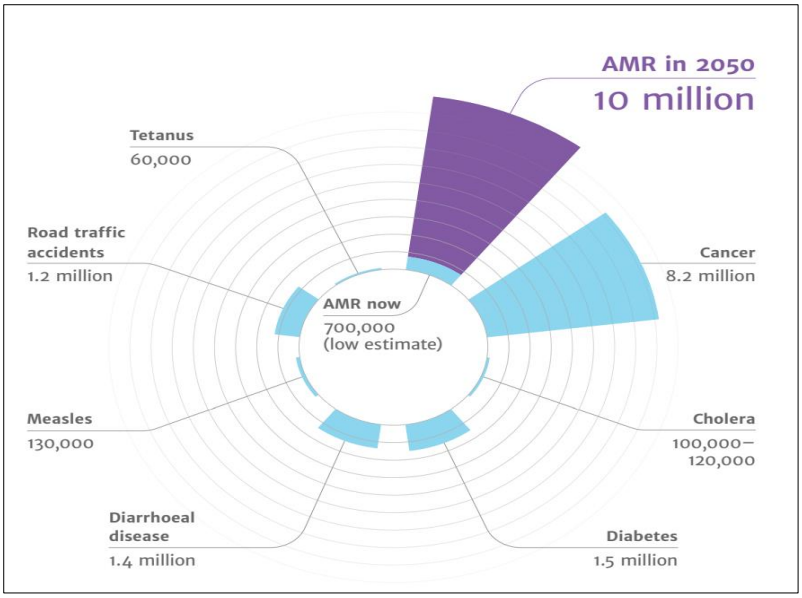
CHAPTER 1 - GENERAL INTRODUCTION

1.1. Antimicrobial Resistance – the growing global crisis

Antimicrobial resistance (AMR) poses a dangerous threat to modern medicine, and this is observed in daily practice where infections are becoming more and more untreatable. There are multiple factors contributing to this rapidly growing global crisis. In low- and middle-income countries, there is a high level of antibiotic consumption caused by multiple factors, including the high burden of infectious diseases, lack of regulations or weak regulatory enforcement to prevent over-the-counter sale of antibiotics, inadequate training of healthcare professionals, and the limited availability of diagnostics leads to empirical use of antibiotics [1]. The review by Jim O'Neill and colleagues recommends 10 fronts on which AMR must be tackled, listing *public awareness, antibiotics in agriculture, surveillance, human capital, global innovation fund, sanitation and hygiene, vaccines and alternatives, rapid diagnostics, drugs, and international coalition for action*. This thesis is addressing themes that are directly related to surveillance, but also in the context of raising public awareness, to ensure increased attention to this silent global crisis. The alarming figures provided by the review are an estimate of what we should expect to see by 2050 based on scenarios of rising resistance for six pathogens: as illustrated in **Figure 1**, we can expect a yearly death toll of 10 million by 2050 which would mean one human life lost every three seconds.

The ramifications of antimicrobial resistance can be felt and see in all important areas of modern medicine, causing a whole range of other public health problems including increases in hospital admissions, longer hospitalisations, burden on intensive care units. One major consequence of the rising AMR burden is its effect on cancer care outcome. Cancer patients are more susceptible to infections as they have a very low immunity. About 20% of hospitalized cancer patients are admitted due to an infection, and they rely on antibiotics to avoid death or health worsening caused by other diseases. Pneumonia and sepsis are among the leading cause of further admission intensive care, and when the antibiotic options are limited due to resistance, these patients face bad treatment outcomes, including death [2,3].

Figure 1 Deaths attributable to AMR every year



Source: TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATION. THE REVIEW ON ANTIMICROBIAL RESISTANCE CHAIRED BY JIM O'NEILL. MAY 2016

The causes of AMR can be explained through various steps of the process in which a drug gets to the patient and the actual use by the patient. The process starts with production, distribution, prescription, dispensing, and ends with the use in a patient or in animal production [4]. In this thesis we look at the steps of prescription and use, in the context of appropriate use of antibiotics.

Inappropriate use of antibiotics

The most important driver behind the AMR wheel is the inappropriate use of antimicrobials. Several studies have confirmed concerning evidence of antimicrobial prescription practices that do not meet criteria for appropriateness based on the choice of drug, dose, and treatment duration [5]. It is not just an issue of inappropriate prescribing, as it carries on the level of dispensing where antibiotics are sold without prescription, with or without involvement of specialized health care professionals in the dispensing chain [6].

Laboratory capacity gap

Laboratories to test antibiotic susceptibility are not available or well-equipped in many parts of the developing world. If not aware of the microbial resistance, it becomes impossible to make a proper prescription, and as a result, prescribers rely on broad-spectrum antibiotics (e.g. macrolides). To keep resistance under control, a proper use of the existing antibiotics is very

crucial. In the case of countries with strong laboratory capacity, it is common or at least feasible to carry out antimicrobial susceptibility tests, to inform prescribing decisions on health care facility level or serve as evidence for national guidelines on antimicrobial prescribing. In many resource-limited countries, there are certainly laboratory professional with the required knowledge, but these may be limited in numbers and can serve only a few hospitals. At the same time, developing countries are confronted with problems of resources and cannot guarantee such services as routine practice in patient care in most of their healthcare delivery centers. A recent study carried out in the United States shows that susceptibility testing is important not only at pathogen species level but also at the level of subspecies [7], confirming again the importance of highly skilled professionals and appropriate equipment for laboratories involved in AMS.

1.2. Antimicrobial stewardship – a growing arsenal of strategies

The term "antimicrobial stewardship" has been used over the last years to refer to the complex and heterogenous as the set of strategies used at different levels of healthcare delivery, all with the aim of improving and promoting a better use of antimicrobials. Patient safety is not just about a concept of safety of a product in a patient, it goes beyond just one patient, and certainly involves much more than one product. Patient safety is the whole set of activities [8] which include processes and procedures, technologies and healthcare settings that are put on place to lower the risk of avoidable harm, to reduce chances of making errors, and to minimise further impact of already occurred harm. In the context of this thesis, antimicrobial resistance is considered as an avoidable harm, not just in one patient but for every future patient looking for an antimicrobial to prevent or cure an infectious disease, anywhere in the world, rich or poor, young, or old.

AWaRE Classification – an antimicrobial stewardship equipment

The WHO has designed an important tool for the antimicrobial stewardship programs. Since 2017, as part of the update of the Model List of Essential Medicines, the WHO introduced a new classification of antimicrobials into three categories known as "Access", "Watch" and "Reserve" (AWaRe), based on the indication, availability, and awareness to guide prescriptions and treatment while monitoring consumption. In 2019, the WHO launched a campaign urging

governments to implement to implement the AWaRe tool through national guidelines to reduce antimicrobial resistance and ensure access [9,10].

1.3. Pharmacovigilance

An adverse effect of a medicinal product is a negative or harmful patient outcome that seems to be associated with the treatment, including there being no effect at all, and adverse drug reaction is used in late-stage analysis when the association between a medicine and an adverse effect has moved beyond 'unmeasurable' or 'uncertain' [11]. In medicinal safety research, Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems [12]. In this thesis, ADR reports submitted to PV centers are discussed, in the context of antimicrobial use, where at least one antibiotic is the suspected drug associated with the reported ADR. In its January 2017 report, the WHO Collaborating Centre for International Drug Monitoring, or the Uppsala Monitoring Centre (UMC) published a report [13] with a special feature on the role of Pharmacovigilance in tackling AMR. PV experts made a point that AMR is an overlooked adverse event which should be included wider patient safety programs.

The WHO Programme for International Drug Monitoring

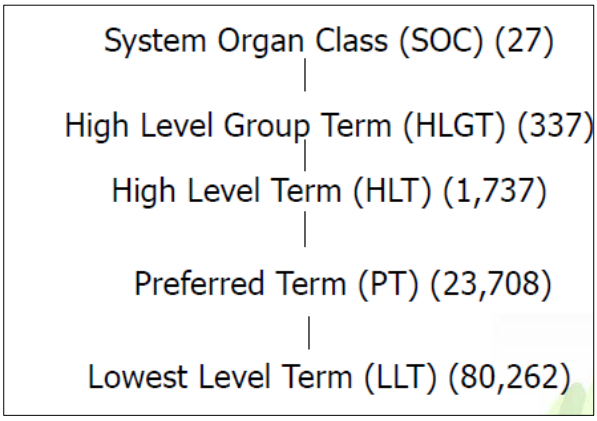
To safeguard patient safety and generate safety signals on new medicinal products, the World Health Organisation (WHO) created in 1968 the Programme for International Drug Monitoring (PIDM), currently coordinated by the Uppsala Monitoring Center (UMC) which collects ADR reports on medicinal products worldwide. As of July 2021, 148 countries are full members, and 23 countries are associate members of the PIDM [14]. As the scope of Pharmacovigilance has been widening over the years, databases of ADRs have become an important resource for evidence-based decision making in public health, and in this thesis, we have looked at how the growing crisis of antimicrobial resistance can be addressed using available pharmacovigilance data. PIDM collects safety data on medicinal products, and the network uses standardised keywords or codes, with a set of keywords that can be used to detect inappropriate use of antimicrobials and potential resistance to antimicrobials. In settings with limited laboratory capacities, data-driven knowledge on these two aspects (inappropriate use of antimicrobials and potential resistance to antimicrobials) can contribute to AMS programs

that can be adapted to national and local context. Countries, including those with limited laboratory capacity, have functioning pharmacovigilance centers which carry out systematic collection of such data inappropriate use of antimicrobials and potential resistance to antimicrobials.

MedDRA – the Medical Dictionary for Regulatory Activities

MedDRA is an international medical terminology used by regulatory authorities and the biopharmaceutical industry, through the whole regulatory process, from pre-marketing to post marketing stages of a product's lifecycle. It its structure [15], the MedDRA dictionary has 6 levels of terms used to code reported events, starting from the System Organ Class (SOC) to the Lowest Level Term (LLT). To identify AMR-relevant MedDRA terms, in this project we focussed on the 4th level or Preferred Term (PT) as it is the label used to classify publicly available safety ADR data from the VigiBase, the largest drug safety database with open access for the public and research community. In its latest version (version 22.0), MedDRA has a pool of 23,708 PTs which are used by ADR reporters to classify each event with codes that are understood across the globe.

Figure 2 MedDRA structure



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CHAPTER 2 - HYPOTHESIS, OBJECTIVES AND METHODOLOGY

2.1. Hypothesis

Antimicrobial resistance is an overlooked adverse event that should be reported as part of events around drug ineffectiveness. Among the millions of ADR reports in global and national database, there must be reported events that can serve a signal of suspected resistance to antimicrobials and/or events of inappropriate use relevant to stewardship programs.

2.2. Objectives

The primary objective is to investigate the potential role of the worldwide network of pharmacovigilance (PV) databases and drug utilisation studies (DUS) in the track of antimicrobial resistance and antimicrobial misuse.

Specific objectives:

1) To explore availability of ADRs reports on suspected resistance to antimicrobials and cases of inappropriate use, both in national and international pharmacovigilance databases
2) To identify strengths and limitations of the pharmacovigilance systems as a tool to generate signals on suspected resistance to antimicrobials and cases of inappropriate use.

Chapter 1 is an **introduction** to this research and Chapter 2 outlines the **hypothesis and objectives** of this thesis which cuts across the science of pharmacovigilance (PV) and the growing public health threat posed by antimicrobial resistance (AMR) globally. As we, the research community seek and proposes multidisciplinary solutions to address AMR, in this thesis, we specifically look at what PV can and should offer. Chapter 2 also summarises the **methodology** used to address the main and specific study objectives.

Chapter 3 presents the 2 **published articles** (included in this compendium) in sub-chapters **3.1** and **3.2**.

Sub-chapter 3.1. is an article published in *Pharmacoepidemiology and Drug Safety*, describing a study which dived into the largest global pharmacovigilance database and describes a list of

seventeen MedDRA Preferred Terms used to report adverse drug reactions, with relevance to the monitoring of AMR.

Sub-chapter 3.2. is an article published in the *European Journal of Clinical Pharmacology*, describing in detail what PV can offer to solve the issue of AMR data scarcity especially in resource-limited settings. The global PV network is described and key instruments, including the medical dictionary (MedDRA) and the international drug safety database (VigiBase) are discussed.

Chapter 4 is a **general discussion**, where an emphasis on the symbiotic relation between PV and AMS programs is made. In the same chapter, **limitations** of the results and ideas presented in this thesis are discussed, and a few remarks are made based on preliminary results from other ongoing studies.

Chapter 5 provides key **conclusions** from this Thesis.

Appendix 1 includes a manuscript on country-level study carried out in The Netherlands to confirm the use of AMR-relevant MedDRA Preferred Terms in a well-established and experienced national PV centre. The sub-chapter provides a description on how these PTs have been used by reporters over a period of 20 years.

2.3. Methodology

In the following paragraphs, a brief description of data source is provided and in addition, a general introduction to the tools used for data analysis is outlined. Further in chapter 3 and in Appendix 1, a detailed description of the methodology per study is provided.

Data sources and search strategy

Global database

Based on the AWaRe (Access, Watch and Reserve) list and the WHO Priority Pathogens List, we established a list of antimicrobials and carried out a VigiBase search via VigiAccess, looking for ADR reports with Preferred Terms (PTs) that contained AMR-relevant information.

For each selected antimicrobial, a VigiAccess search was performed to identify reporting terms which suggest existing or potential resistance, lack antimicrobial response or events of off label use and medication errors that could indirectly lead resistance. The search in VigiBase was conducted between June and December 2018. Identified Terms were matched with codes from the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1).

Country level database

To test the hypothesis further in a country level data, we retrieved and analysed AMR-relevant ADR reports from The Netherlands Pharmacovigilance Centre (Lareb) database and the Ugandan National Drug Authority (NDA) Pharmacovigilance database. In both databases, we searched for ADR reports on antibiotics, coded with at least one of AMR-relevant MedDRA Preferred Terms (based on the list established after analysis of data from the global database).

Description and analysis

Matching with codes

MedDRA is the dictionary currently used globally for the reporting of ADRs to Pharmacovigilance Centers, MedDRA (version 21.1) terminology was used in our search strategy, both in global and national databases. In all the studies we focussed on the Preferred Term (PT), which is the MedDRA level used in the VigiBase publicly accessible information via VigiAccess. The same PT level is used by national pharmacovigilance centers during collection and sharing of safety data.

The AWaRe Tool

The WHO AWaRe classification is increasingly becoming a reference tool for many antimicrobial stewardship programs. In this thesis, we have analysed and described findings using the three AWaRe classes, emphasizing on the need to preserve the Watch and Reserve or last resort antibiotics.

CHAPTER 3 – PUBLICATIONS IN THIS COMPENDIUM

3.1. Article 1 – "Pharmacovigilance network as an additional tool for the surveillance of antimicrobial resistance"

Pharmacoepidemiol Drug Saf. 2021 Aug;30(8):1123-1131. Doi: 10.1002/pds.5249. Epub 2021 Apr 27. PMID: 33864401. https://onlinelibrary.wiley.com/doi/10.1002/pds.5249

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ORIGINAL ARTICLE

WILEY

Pharmacovigilance network as an additional tool for the surveillance of antimicrobial resistance

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Funding information
European and Developing Countries Clinical Trials Partnership

Abstract

Background: The WHO Programme for International Drug Monitoring (PIDM) is a large Pharmacovigilance network of countries sharing Adverse Drug Reaction (ADR) reports. Pharmacovigilance Experts have suggested that antimicrobial resistance (AMR) is an overlooked adverse event. We undertook this study to investigate the potential role of Pharmacovigilance databases in the surveillance of AMR.

Methods: Using the AWaRe (Access, Watch and Reserve) list and the WHO Priority Pathogens List, we established a list of antimicrobials and carried out a VigiBase search via VigiAccess, looking for ADR reports with Preferred Terms (PTs) that contained AMR-relevant information. Identified Terms were matched with codes from the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1).

Results: Records on 86 drugs were retrieved with a total of 1 170 751 ADR reports submitted between 1968 and 2018. Seventeen PTs suggesting suspected resistance, ineffectiveness, inappropriate use, or medication error were used to code 15 250 reports. The most frequently used PTs were "Drug Ineffective" (45.6%), "Off label use" (9.5%) and "Pathogen Resistance" (8.9%). A group of six agents (Amoxicillin, Cefalotin, Ciprofloxacin, Clarithromycin, Levofloxacin and Daptomycin) accounted for 38% ($n = 5806$) of all 15 250 AMR-relevant ADR reports. The PTs most frequently used in 5806 reports were grouped in 4 categories: drug ineffectiveness (62.5%), resistance (19.2%), off-label use (12.1%) and prescription errors (6.2%).

Conclusion: Our findings suggest that Pharmacovigilance databases could serve as a tool in tracking antimicrobial use and resistance especially in settings where laboratory capacity is still in its development stages. National Pharmacovigilance centers could play a proactive role in stimulating the reporting of AMR-relevant ADRs which can serve as a basis for resistance suspicion alerts. Further studies focusing on the narrative and other clinical pharmacology details in ADR reports are required.

KEYWORDS
adverse drug reaction, antimicrobial resistance, antimicrobial use, AWaRe, MedDRA, Pharmacovigilance, VigiAccess, VigiBase

1. INTRODUCTION

Antimicrobial resistance (AMR) has become one of the most pressing global health concerns. In May 2015, the 68th World Health Assembly endorsed a global action plan to tackle antimicrobial resistance, including antibiotic resistance, the most urgent drug resistance trend [1]. In 2016, at the United Nations annual General Assembly, AMR was among the topics discussed in a High-Level Meeting of Heads of States [2]. The Assembly recognised the menace that the AMR poses to the successful fulfilment of the Sustainable Development Goals (SDGs). In September 2016, the World Bank published a report titled "Drug Infections: a threat to our Economic Future", providing a detailed understanding of the economic consequences of antimicrobial resistance [3]. It is in this context that several initiatives and policies are being put in place with the aim of reducing inappropriate antimicrobial consumption at all levels, under the One Health Initiative perspective.

Many strategies engaged in the fight against AMR shared the key objectives of tracking resistant microorganisms to reduce treatment failures and to ensure appropriate prescription of existing antimicrobials. However, this is a difficult task in resource-limited settings with low laboratory capacity, both in terms of infrastructure and skilled professionals.

Key Points

- Reports on suspected Resistance or Inappropriate use of antimicrobials have been submitted as adverse drug reactions to the WHO Programme for International Drug Monitoring. The reports have been identified using the public available access tool – VigiAccess
- 17 Preferred Terms have been used to code more than 15,000 adverse drug reactions or events suggesting resistance, ineffectiveness, or off-label use of antimicrobials.
- The most frequently AMR-relevant PTs used are 'Drug Ineffective', 'Off Label Use' and 'Pathogen Resistance'
- Daptomycin, a "Reserve" agent on the market since 2004 is a subject of reports on resistance and off-label use. Further research is required to safeguard last resort antimicrobials such as Daptomycin.

In an analysis published in 2017, Wernli et al. [4] shortlisted five policy frames that should guide AMR initiatives: AMR as a healthcare problem, a development issue, an innovation challenge, a security issue and as a One Health challenge. For resource-limited settings all these frames apply, but most importantly for developing countries AMR is a development and security issue.

1.1. Pharmacovigilance as a toolkit

An adverse effect of a medicinal product is a negative or harmful patient outcome that seems to be associated with the treatment, including there being no effect at all. An adverse drug reaction (ADR) is referred to when causality analysis has taken place and the link between the medicine and a suspected adverse effect is beyond uncertainty [5]. The largest database of ADR reports is hosted by the Uppsala Monitoring Centre (UMC) on behalf of the WHO Programme for International Drug Monitoring (PIDM), bringing together safety data from across all corners of the globe. In the interest the researchers referring to the UMC ADRs database, it is important to clarify the tentative and variable nature of retrievable data [6]. The reports submitted to UMC are based on suspicion; in some cases, there may be enough information for a proper causality assessment to confirm the link between the product and the event, but in many other cases that is possible. There are also differences based on the source where some countries may collect and share reports from medical professionals while other countries are likely to include reports obtained directly from users or patients. Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems [7]. If the drug suspected of leading to an ADR report is an antimicrobial, then Pharmacovigilance becomes the tool that could allow the detection, understanding, and prevention antimicrobial-related problems. In a recent editorial, a case was made on this potential role of pharmacovigilance networks in addressing antimicrobial stewardship questions [8]. In the same area of studies cutting across pharmacovigilance and antimicrobial resistance, researchers have been looking at what can be pulled out of existing databases, such as national healthcare records. A good example is the study by Brauer R et al. [9] which looked at healthcare databases of seven European countries to assess the prevalence of antibiotic use. The same databases could be used in tracking adverse events associated with the reported antimicrobials.

1.2. VigiAccess – the window into VigiBase

Since 1968, a group of countries which were later to form the PIDM started a systematic collection of ADRs worldwide, under the coordination of the Uppsala Monitoring Centre (UMC). As of end of 2018, the UMC had received and stored in VigiBase over 20 million ADRs reports from more than 170 countries [10]. Since 2015, data stored in *VigiBase* can be freely accessed by the public via *VigiAccess*™.

1.3. MedDRA – the medical dictionary

To code suspected ADRs, two medical dictionaries have been developed and widely adopted by reporters, and both contain terms which suggest lack of, or poor effect of medicines in general [11]. The first is the WHO Adverse Reaction Terminology (WHO-ART) which was developed and maintained by UMC [12]. It was developed in 1968 to serve as a terminology for coding ADR terms, covering most medical terms needed in adverse reactions reporting. The second is the Medical Dictionary for Regulatory Activities, known as MedDRA [13]. Up until 2008, WHO-ART was the only available terminology for coding adverse drug reactions in VigiBase, and then MedDRA was introduced. Therefore, in this study we have used MedDRA as it is the dictionary currently used by Pharmacovigilance centres.

As there are ADR reporting terms which describe or refer to lack of effectiveness and suspicion of resistance to the administered drugs, we designed the present study with the main objective of investigating the potential role of pharmacovigilance databases in the track of AMR. Specifically, the study aimed: (1) to analyse ADR reporting terms suggesting suspicion of resistance to antimicrobials or referring to cases of inappropriate use of antimicrobials, and (2) to describe the extent to which these terms have been used to code antimicrobial ADR reports to the PIDM database.

2. METHODS

To address the two specific objectives, the study was carried out in the following consecutive steps: 1) identifying products of interest, 2) search for ADRs reports with terms suggesting suspected ineffectiveness, resistance, or inappropriate use antimicrobials, and 3) linkage of these terms with codes from existing dictionaries used in pharmacovigilance databases.

2.1. Identification of the antimicrobials to include in the study

To focus on antimicrobials, there was no better reference than the WHO AWaRe classification. The AWaRE categorisation puts antimicrobials in three groups, 'Access', 'Watch' and 'Reserve' [14, 15], according to their indication, availability and degree of awareness. The categorisation was proposed by the WHO in 2017 and updated in 2019 with additional details per group [16] and launched with a WHO Global campaign urging governments to implement the AWaRe tool to reduce the spread of antimicrobial resistance. Further reference was made to the Priority Pathogen list [17] established by the WHO to inform the discovery and development of new antimicrobials. We established a list of antimicrobials ensuring representation of all AWaRe categories, and including several other antimicrobials that are not on the AWaRe (which focusses on the Essential Medicines List)

2.2. Data source, collection and analysis

2.3. Search for reports of ADRs with suspicion of AMR-relevant event

For each selected antimicrobial, a *VigiAccess* search was performed to identify reporting terms which suggest suspicion of resistance, lack of antimicrobial response or events of inappropriate prescription that that could lead to resistance. The search was conducted between June and December 2018.

VigiAccess is a free access portal to the PIDM [18] database allowing retrieval of medicinal products safety reports received by the UMC. Thus, records on each antimicrobial were retrieved and a set of AMR-relevant preferred terms used to report ADRs was established.

2.3.1. Linkage of Preferred Terms to existing drug safety Codes used in medical dictionary

Considering the preferred terms included in the retrieved reports, a review of codes in the ADRs medical dictionary (MedDRA) was conducted to make a link between a Term and a Code and to ensure that the identified terms can be part of a reporting and signal detection strategy.

MedDRA is a hierarchical terminology with five levels of terms which provide specificity for data entry and flexibility for data retrieval. Reporting Terms used in MedDRA were derived from several dictionaries [19] including the WHO's adverse reaction terminology (WHO-ART), among others. The five MedDRA levels are: System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT) and Lowest Level Term (LLT) [20]. In the present study we focussed on the PTs, which is the level used in the VigiBase publicly accessible information via *VigiAccess*.

3. RESULTS

Based on the list from the *AWaRe* classification and including antimicrobials used to treat pathogens on the priority list, a list of 86 different antimicrobials were identified and used to run the *VigiAccess* search. There AwaRE were more 'Access' and 'Watch' drugs than 'Reserve': beta lactamic penicillins (mostly 'Access'), cephalosporins (1st generation, 'Access'; 2 and 3rd generation, 'Watch'; 4th generation, 'Reserve'), carbapenems, vancomycin, macrolides, and fluoroquinolones ('Watch'), and daptomycin ('Reserve). As shown in **Table 1,** out of the 86 products, the most represented chemical subgroups (ATC 4th level) were Third generation cephalosporins (16 of 86), followed by Second-generation cephalosporins (13), First-generation cephalosporins (12) and Fluoroquinolones (10).

Table 1 Chemical subgroup (ATC 4th level) of drugs included in the search

Chemical subgroup	Nr of products included
Third-generation cephalosporins	16
Second-generation cephalosporins	13
First-generation cephalosporins	12
Fluoroquinolones	10
Penicillins with extended spectrum	8
Beta-lactamase resistant penicillins	6
Beta-lactamase sensitive penicillins	5
Carbapenems	5
Fourth-generation cephalosporins	3
Glycopeptide antibacterials	2
Macrolides	2
Combinations of sulfonamides and trimethoprim, incl. Derivatives	1
Other antibacterials	1
Other antibiotics for topical use	1
Other cephalosporins and penems	1
Total	**86**

Table 2 The 17 PTs on six selected antimicrobials

ANTIBIOTICS AWaRe classification Year of 1st report to UMC Number of ADR reports with AMR-relevant PT, *n* (%)		AMOX. Access 1972	CEFAL. Access 1968	CIPROFLO. Watch 1985	CLARITHRO. Watch 1991	LEVOFLO. Watch 1996	DAPTO. Reserve 2004	TOTAL Total	AMR RELEVANCE CATEGORY
17AMR-relevant PT	Drug ineffective	588 (67.4)	2 (1.3)	791 (45.2)	538 (54.2)	621 (46.3)	167(23.8)	*2707*	*I*
	Pathogen resistance	153 (17.5)	143 (94.7)	140 (8.1)	115 (11.6)	116 (8.6)	82 (11.7)	*749*	*R*
	Off label use	52 (6.0)		204 (11.7)	49 (4.9)	126 (9.4)	102 (14.6)	*533*	*OL*
	Treatment failure	25 (2.9)		49 (2.8)	26 (2.6)	39 (2.9)	99 (14.1)	*238*	*I*
	Product use in unapproved indication	16 (1.8)		44 (2.5)	11(1.1)	35 (2.6)	43 (6.1)	*149*	*OL*
	Drug resistance	12 (1.4)	1 (0.7)	112 (6.4)	41(4.1)	89 (6.6)	95 (13.6)	*350*	*R*
	Drug effect decreased	10 (1.1)		32 (1.8)	10 (1.0)	33 (2.5)	3 (0.4)	*88*	*I*
	Drug effect incomplete	9 (1.0)		12 (0.9)	6 (0.6)	10 (0.7)	3 (0.4)	*40*	*I*
	Decreased activity	4 (0.4)		40 (2.3)		57 (4.2)		*101*	*I*
	Drug ineffective for unapproved indication	3 (0.3)		29 (1.7)	4 (0.5)		61 (8.7)	*97*	*I*
	Therapeutic product ineffective	1 (0.1)		3 (0.2)	1 (0.1)	3 (0.2)		*8*	*I*
	Therapeutic response decreased		2 (1.3)	63 (3.6)	53 (5.3)	46 (3.4)	5 (0.7)	*169*	*I*
	Medication error			119 (6.8)	94 (9.5)		20 (2.9)	*233*	*E*
	Drug prescribing error		3 (2.0)	40 (2.3)	33 (3.3)	49 (3.6)		*125*	*E*
	Multiple-drug resistance			17 (1.0)				*17*	*R*
	Therapy non-responder			53 (3.0)	10 (1.0)	96 (7.1)	21 (2.9)	*180*	*I*
	Contraindicated product administered					22 (1.6)		*22*	*OL*
Total		**873 (0.9)**	**151 (5.9)**	**1748 (2.0)**	**991 (2.5)**	**1342 (1.7)**	**701 (12.3)**	**5806 (1.8)**	
Number of ADR reports (all types), *n* (%)									
Total		**102 794 (100)**	**2550 (100)**	**88 748 (100)**	**40 246 (100)**	**77 330 (100)**	**5706 (100)**	**317 374 (100)**	

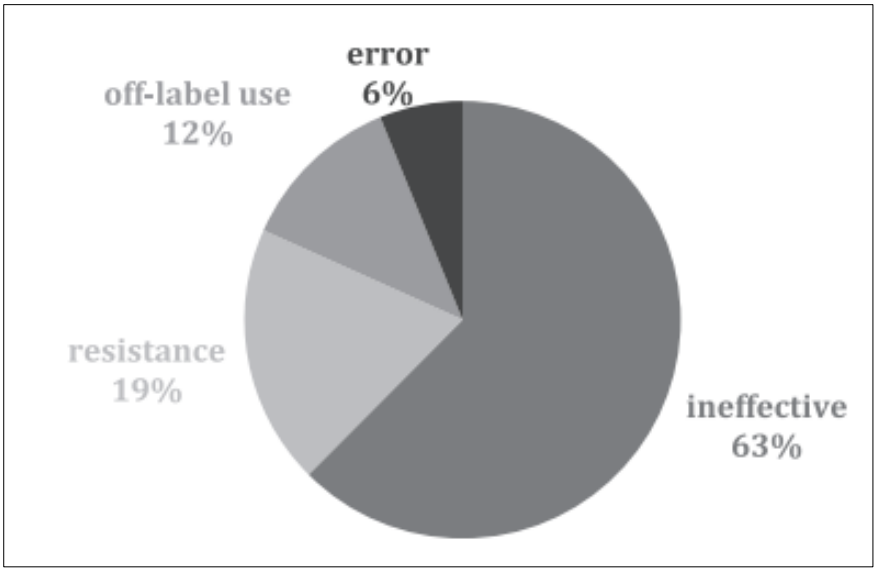
Table 3 Preferred Terms (PT) found in the VigiAccess reports involving antimicrobials and suggesting antimicrobial resistance (AMR) or poor effect, linked with corresponding MedDRA codes

System organ class (SOC)	Preferred term (PT)	MedDRA code	Nr reported for the 86 studied AM (%)	Nr reported for the six selected AM[a] (%)	Grouped terms
Infections and infestations	Pathogen resistance	10034133	1327 (8.97)	749 (12.9)	R
General disorders and administration site conditions	Drug Resistance	10059866	6659 (45.63)	350 (6.0)	R
	Multiple drug resistance	10048723	762 (5.00)	17 (0.3)	R
	Drug Ineffective	10013709	778 (5.10)	2707 (46.6)	I
	Treatment Failure	10066901	196 (1.29)	238 (4.1)	I
	Therapy non-responder	10051082	148 (0.97)	180 (3.1)	I
	Therapeutic response decreased	10043414	19 (0.12)	169 (2.9)	I
	Decreased activity	10011953	380 (2.49)	101 (1.7)	I
	Drug ineffective for unapproved indication	10051118	148 (0.97)	97 (1.7)	I
	Drug Effect decreased	10013678	202 (1.32)	88 (1.5)	I
	Drug effect incomplete	10013682	1293 (8.48)	40 (0.7)	I
	Therapeutic product ineffective	10060769	84 (0.55)	8 (0.1)	I
Injury, poisoning, and procedure complications	Off label use	10053762	1455 (9.54)	533 (9.1)	OL
	Product use in unapproved indication	10076476	1026 (6.73)	149 (2.6)	OL
	Contraindicated product administered	10078504	250 (1.64)	22 (0.4)	OL
	Medication error	10027091	27 (0.18)	233 (4.0)	E
	Drug prescribing error	10064296	196 (1.29)	125 (2.2)	E
TOTAL	-	-	15 250 (100)	5806 (100)	

Abbreviations: AM, antimicrobial; E, "error of use"; I, "ineffectiveness"; OL, "off-label use"; R, "resistance".

[a] Amoxicillin, cefalexin, ciprofloxacin, levofloxacin, clarithromycin and daptomycin.

FIGURE 1 Distribution of the 5806 adverse drug reactions (ADRs) suggesting resistance to antimicrobials coded in 17 different preferred terms (PTs) for the six selected antimicrobials in the study (amoxicillin, cefalotin, ciprofloxacin, clarithromycin, levofloxacin and daptomycin). These PTs have been grouped by categories with the following topics: PTs suggesting "ineffectiveness", "resistance", "off-label use" and possible medication "error"

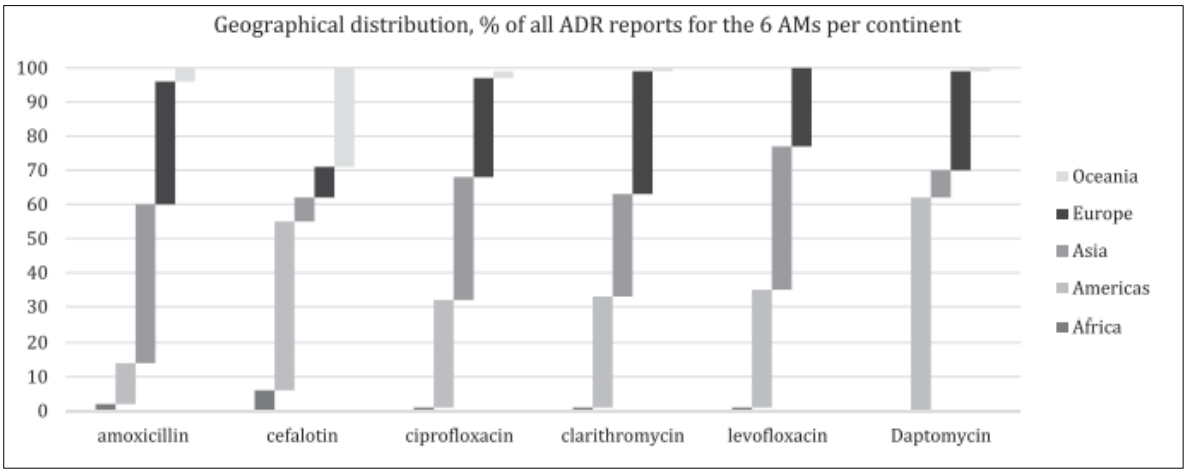


For the selected 86 antimicrobials, 1.170.751 ADR reports submitted to the UMC and were available for the analysis. 15.250 (1.3%) of the 1.170.751 ADR reports were recorded with AMR-relevant terms that suggested suspicion of resistance, ineffectiveness, or inappropriate use. The AMR-relevant reports were classified under three System Organ Classes (SOCs): '*infections and infestations*', '*general disorders and administration site conditions*', and '*injury, poisons and procedure complications*. A list of 17 Preferred Terms (PTs) with MedDRA codes (version 21.1) used to code all 15.250 ADRs was established. The following PTs were the most frequently used in these 15.520 reports: '*Drug Ineffective*' (n=6959, 45.6%); '*Off Label Use*' (n=1455, 9.5%), and '*Pathogen Resistance*' (n=1327, 9.0%).

Out of the 86 antimicrobials for which ADR reports were retrieved from *VigiAccess*, 6 agents (amoxicillin, cefalotin, ciprofloxacin, levofloxacin, clarithromycin and daptomycin) were with highest numbers of reports using three most frequent PTs (see Table 2). The 6 agents alone – 2 Access (amoxicillin, cefalotin), 3 Watch (ciprofloxacin, levofloxacin, clarithromycin) and 1 Reserve (daptomycin) were featured in 5,806 (38%) of 15,250 AMR-relevant ADRs.

For these specific 6 agents, the proportion of reports with AMR-relevant PTs compared to the total number of all reported ADRs per drug was as follows: amoxicillin (873/102,794 ADR reports; 0.9%) and cefalotin (151/2,550; 5.9%); ciprofloxacin (1,748/88,748; 2.0%), levofloxacin (1,342/77,330; 1.7%) and clarithromycin (991/40,246; 2.5%), and daptomycin (701/5,706; 12.3%).

FIGURE 2 Geographical distribution (in %) of all 315 774 ADRs for each of the six selected antimicrobials (amoxicillin, cefalotin, ciprofloxacin, clarithromycin, levofloxacin and daptomycin) according to the continent where the reports were originated.



* ADR, Adverse Drug Reaction; AM, antimicrobial

Table 3 shows the 17 PTs suggesting suspected resistance or inappropriate use, as well as the three SOCs where they were classified and 17 MedDRA codes they are linked to.

For the six selected AM, 5.806 ADRs were reported using these PTs. Almost half of reports were coded with the term 'drug ineffective' (2,707 cases; 46.6%), followed by 'pathogen resistance' (749; 12.9%) and 'off-label use' (533; 9.1%). By grouping these 17 PTs based on their meaning in the AMR context, we noted that almost two thirds (9 of 17) were terms suggesting treatment failure or drug ineffectiveness (3.628; 62.5%), followed by three PTs suggesting resistance (1,116; 19.2%), three PTs suggesting off-label use (704; 12.1%) and two PTs suggesting errors in prescription (358 reports; 6.2%) (see Figure 1).

Figure 2 shows the distribution of the reports received involving the six studied AM according to the Region in which the report was originated. It should be highlighted that these numbers include all types ADRs for the 6 Ams, not just the 17 PTs. This study did not look at the number of reports with just the 17 PTs, but the low number of reports (all types) from the African region is worth highlighting and should be further investigated.

4. DISCUSSION

The present study showed that different events suggesting suspicion of resistance to a given antimicrobial have been reported as adverse drug reactions through PIDM, using specific codes already included in medical dictionaries.

A sample of 6 agents (2 Access, 3 Watch and 1 Reserve) with a total number of 315,774 of ADR reports had almost 2% of the reports recorded with a PT describing either 'ineffectiveness' of the drug, 'resistance', 'off-label use' or forms of 'error' with the medication use. The same 6 (of 86) agents accounted for 38% (n= 5,806) of all 15,250 reports with AMR-relevant ADRs in a pool of 86 drugs. With these findings in hand, it is possible to suggest the use of the pharmacovigilance network across the 140 PIDM member states (plus 30 associate members), as a useful complementary way to alert on suspected resistance to antimicrobials or their inappropriate use, especially in settings where microbiology laboratories are scarce or inexistent. It is in the same kind of settings where establishing additional surveillance systems could be expensive and difficult and, sometimes, qualified microbiologists for laboratory research are lacking. Both sides could benefit from sharing the pharmacovigilance intelligence and tools. On the one hand, synergies could contribute to pharmacovigilance strengthening and raising awareness among health professionals on unwanted effects of medicines in general. On the other hand, such network, already active even in remote places of LMICs, could be used as a basis for generation of geotagged alerts to the WHO Global Antimicrobial Resistance Surveillance System (GLASS) [21]. Reports spontaneously sent to the PIDM for the six selected antimicrobials since the origin of the pharmacovigilance program to December 2018 showed that 17 different terms have been used by reporters, specifying 'pathogen resistance' or 'drug ineffective' in almost two-thirds of the 5,806 cases, or other terms suggesting situations in which the effect of the antimicrobial was not in line with the prescriber's expectation.

4.1. Resistance, ineffectiveness, off label use and error

If already existing pharmacovigilance programmes are to be promoted as tools to collect information on AMR, the grouping of relevant PTs in these 4 subcategories – Resistance, Ineffectiveness, Off Label use and Error of Use (or RIOLE) can be suggested and a systematic use can generate important information on suspicion or resistance and/or inappropriate use. Beyond counting "Resistance" € reports, the information filled in the reporting formulary could be analysed with other linked details such as the *AWaRe* classification of the suspected drug, co-administered medicines, or indication of use (diagnosed infection). If available, this information adds a more in-depth perspective to the report, from the public health level and the design of stewardship strategies adapted to the findings in a country or region.

On individual patient level, "Resistance" € and "ineffectiveness" (I), whether suspected or confirmed, should trigger a decision to consider another treatment option. "Off Label use" (OL) should be carefully monitored and must be in line with the user guidance as issued by the prescriber or as indicated in the Summary of Product Characteristics. "Error in use" € reports could be a reason to investigate and address potential diagnostic problems or misuse of antimicrobials, and in the interest of the patient, action must be taken to avoid serious ADRs because of the error.

On a country level, these PTs can provide rich national information regarding the characteristics of use of antimicrobials in real world conditions. A rise in numbers of reports on "Resistance" € and "ineffectiveness" (I) of antimicrobials must be a considered as a warning of potential AMR rise. Stewardship programs could use such information as part of their surveillance plans. ADR reports with PT coded as "Off Label use" (OL) should be carefully analysed, especially when the involved antimicrobials belong to the "Reserve" group. Such data on off label use must be considered when designing tailored interventions to ensure rational use of antimicrobials. "Error in use" € reports could be used to address specific issues at the health care workers level, including lack of appropriate training, incomplete or non-clear user guidance, and this is an area where Marketing Authorisation Holders (MAHs) can be involved to ensure completeness and clarity in the promotional information on prescribing and administering any specific antimicrobials.

If the use of the PIDM network is to be promoted as an efficient way to identify potential cases of AMR, it will be necessary to highlight the existence of these PTs and promote their usefulness among potential reporters. Teams working on the AMR surveillance programs will have to include specific guidelines on the pharmacovigilance network sites and how it works in each country, to ensure appropriate on-time reporting. Of course, in countries where reporting by smart phone applications is already in place, specific geographical identification of the reporting place would be an asset.

4.2. Preserving the "Reserve" list – The daptomycin case

From this initial study based on data from *VigiAccess*, other aspects related AMR should be highlighted, and perhaps one of the most worrying issues is the inappropriate use of 'Reserve' antimicrobials, as illustrated by one of the six medicinal products included in our detailed analysis. Daptomycin was marketed in 2004 and by December 2018 a total of 5,706 reports had been included in the PIDM database. What should be underscored is that 12% (701) of these reports were coded with PTs suggesting suspicion of resistance or inappropriate use. Among the 701 ADR reports, 143 (20,4%) described events of "off-label use" or "product use in unapproved indication". The existence of these reports suggests that in some PIDM member countries this last resort antimicrobial has been used inappropriately, a signal which should be carefully analysed to design specific intervention

campaigns or stewardship programmes to timely prevent a potential resistance to this "Reserve" antibiotic. Additionally, this is another example showing that pharmacovigilance databases could also be useful in alerting on problems of inappropriate use of medicines in general and serving as evidence generator for policy makers and drug authorities involved in resistance prevention campaigns.

4.3. Limitations

Our study has some limitations. Pharmacovigilance systems based on spontaneous reporting of suspected adverse drug reactions have well known problems of underreporting and incomplete filling of the reporting forms. The same limitations would apply for reports specifically describing any of these 17 PTs.

Another limitation in the differentiation between the suspected drug and the true drug causing an AMR-relevant event. We know that each ADR report has a tag of the main suspected drug, but at the same time VigiAccess does not give access to some crucial details such as, concomitant medication and suspected interacting drugs, seriousness of the event, action taken following suspicion of an ADR. VigiAccess is just a window into VigiBase, providing the number of reports on the suspected event, the involved drug(s), the year of report, the origin (continent) of the report, the year of first and the year of last report. Only the detailed report can give a conclusive assessment on the AMR suspicion of a specific drug, and such details can be obtained via a direct request to a country pharmacovigilance centre. This study focused on the global picture and therefore, was limited to qualitative (which Preferred Terms, which antimicrobials) and quantitative (how many reports, in which period) analysis of high-level data accessible via VigiAccess. As we noted the need to carry out a more in-depth analysis on reports content or narrative, we requested access to country safety reports and were informed that "due to the new General Data Protection Regulations (GDPR) rules [22], the WHO-UMC was no longer providing country level information on reports" and were advised to directly contact the national pharmacovigilance centres. Other limited sets of VigiBase data (e.g., continent level) for specific studies can be provided against an established fee. We have initiated another set of studies focusing on selected countries where access to a more detailed dataset has been given, and the findings will be published as follow up to this work.

4. CONCLUSION

As an additional tool to track AMR, the pharmacovigilance systems [23] already existing in many countries could play a crucial role in settings where laboratory capacity for causality confirmation is still in its development stages. By using existing PV systems to generate real-time and possibly geo-tagged data on suspected or potential resistance to antimicrobials, PV systems will have an added function on top of their safety signals detection role. By promoting the use of the Pharmacovigilance systems and tools as part of the AMR surveys, could also raise awareness among reporters aware of the adverse drug reactions caused by other medicines, for example those listed as concomitant while they may be the primary cause of the suspected ADR. Promoting the well-established Pharmacovigilance network will strengthen the capacity of PIDM members with a less active collection and sharing of ADR reports. However, to confirm or solidify our hypothesis, further studies are necessary to look at what is in the report, to ensure there is possibility to conclude whether the primary suspected ADR is attributable to the antimicrobial or not, because an ADR report contains information of different medicinal products and comorbities. The list of 17 PTs has been proposed based on the sample of 86 drugs for which reports were searched, but further studies to extend or shorten the list are still required. In addition, further research focusing on the narrative and other clinical details in the ADR reports is required. Currently, we are carrying out a more in-depth analysis using country-specific data from national pharmacovigilance centers of two different countries, one in Africa and another in Europe. Through this in-depth analysis, we are pulling out key details that may be relevant to antimicrobial stewardship discussion, including demographics of patients, concomitant medication, suspected interacting drug, reported comorbities, seriousness of the reported events and types of reporters bringing the information from the antimicrobial user to the databases. We encourage the AMR research community to explore data collected by the Pharmacovigilance community, through the 17 MedDRA codes or Preferred Terms, but also welcome suggestions on any other code or PT that may be relevant to AMR.

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3.2. Article 2 – "Antimicrobial stewardship: can we add pharmacovigilance networks to the toolbox?"

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POINT OF VIEW

Antimicrobial stewardship: can we add pharmacovigilance networks to the toolbox?

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Abstract

Background Antimicrobial resistance (AMR) is no longer an expected upcoming threat; it has become a real public health concern, challenging all existing control tools, requiring multidisciplinary innovative solutions. Antimicrobial stewardship (AMS) programs require a set of tools and skills which can be put to service by health systems. However, there is an immense capacity gap between health systems in developed countries compared to developing ones. Systems in developed countries can rely on well-established laboratory services that can carry out microbial cultures and drug susceptibility tests. For many low- and middle-income countries (LMICs) with limited laboratory resources, it will take time and long-term investments to have systems that can timely and reliably perform laboratory-based AMR monitoring. In the meantime, we must explore the possibility of using other indirect measures that can provide estimates of the growing burden of AMR in settings with weak laboratory capacity.

Objectives In this point of view, we describe the potential contribution of the global pharmacovigilance (PV) networkers in the process of mapping and estimating the AMR burden in settings with less laboratory coverage and capacity, within the framework of AMS.

Conclusion The heavy toll caused by AMR will not be brought down by a singular interventional approach, it will require a multidisciplinary and multifaceted set of strategies. Closing the laboratory capacity gap will require tremendous long-term investments, but the AMR data scarcity is a question that cannot wait any longer. The global pharmacovigilance network is a robust scientific community with experience in tracking suspected adverse events caused by new and old medicinal products. As AMR becomes a global health issue, AMS programs need all available tools to address resistance data scarcity and inform appropriate of antimicrobials. The solid global pharmacovigilance infrastructure could play an important role in countries with limited laboratory coverage and capacity.

Keywords Antimicrobial resistance · Pharmacovigilance · Antimicrobial stewardship · Antimicrobial surveillance · spontaneous reporting

INTRODUCTION

Antimicrobial resistance (AMR) is no longer an expected upcoming threat, it has become a real public health concern, challenging all existing control tools, requiring multidisciplinary innovative solutions. Today, AMR is a reality in every corner of the globe, both in developed and developing regions. Antimicrobial stewardship (AMS), the process of planning and managing of the use of antimicrobials, requires a lot of tools and skills that are offered by science. These tools and skills can be made available and put to service by health systems. The problem lies in the immense capacity gap between health systems in different countries and regions. Systems in developed countries can rely on the well-established laboratory services that can carry out microbial cultures and drug-susceptibility tests. But, for many low- and middle-income countries (LMICs) with limited laboratory resources, it will take time and long-term investments to have systems that can timely and reliably perform laboratory-based AMR monitoring activities, which play a crucial role in AMS programmes. In the meantime, we must explore the possibility of using other indirect measures that can provide estimates of the growing burden of AMR in settings where laboratory capacity is weak or absent. The heavy toll caused by AMR will not be brought down by a singular interventional approach, it will require a multidisciplinary and multifaceted set of strategies.

This paper aims at describing the potential contribution of global network of Pharmacovigilance centers and databases in the process of mapping and estimating the AMR burden in settings with less laboratory coverage and capacity, within the framework of AMS.

HOW BIG IS THE AMR DATA SCARCITY PROBLEM?

Antimicrobial Resistance: a crisis we saw coming

The global health research community was warned on AMR for the first time by the very person who discovered penicillin. In his 1945 Nobel Lecture [1], Fleming warned that there may be a danger in underdosage as it was then clear that microbes became resistant to penicillin when exposed to concentrations that were not high enough to kill them. After penicillin, many more antibiotics of different spectra were developed and commercialised. Exposed to various natural conditions and medicinal products in varying doses, pathogens have progressively become resistant to our best remedies against deadly infections. It is generally acknowledged that one

of the most important causes of mutations and acquisition of resistance is the inaccurate prescription and use of antibiotics.

AMR data scarcity - a capacity gap issue

Many years after Fleming's 1945 Lecture, further in the 21st century, we have problems with understanding how big the problem is. We all know it is here with us, but we lack reliable data from many parts of the world. In the Review [2] on AMR, chaired by Jim O'Neil and published in 2014, there is a troubling statement about scarcity of reliable estimates of the true burden of the damaging effects of AMR. The authors gave estimates of at least 50,000 lives claimed each year across Europe and US alone, and many hundreds of thousands more dying "in other areas of the world". The unavailability of burden estimates for what is called "other areas of the world" is troubling. The authors say that many hundreds of thousands were dying; such estimates seem to be within very large intervals due to unavailability of reliable data, one must think. In an ideal world, resistance to an antimicrobial should be confirmed by laboratory susceptibility tests conducted in accordance with clear international standards [3,4].

In practice, we know that the capacity and skills to carry out susceptibility test differ from country to country and can even vary within one country. The required capacity and skills for such tests are limited in LMIC [5]. In many resource-limited settings, there are regional pockets of remote places where access to healthcare is much more limited. These remote places are less covered by Nationally implemented programs such vaccination campaigns, or mass drug administration campaigns. Resource-limited settings have limited access to laboratory diagnosis services, limited access to quality-assured medicinal products and consequently very limited coverage by both passive and active health data collection programs.

In their presentation of a project that aimed at measuring and mapping the global burden of AMR, Hay et al. [6] touch upon the issue of scarcity of data from LMICs. The authors have stated that major gaps in data on prevalence and incidence as well as on types of resistance, treatment failures and studies on the attributable mortality and morbidity of AMR, particularly in LMICs, have made it nearly impossible to reliably estimate the global impact of AMR.

Prescribing antimicrobials: evidence-based or empiric trial-and-error?

Beyond the enormous use of antimicrobials in livestock, which is another urgent global health challenge, the review by Jim O'Neill puts an accent on the role of (inappropriate) prescribing practices and over the counter (OTC) medication in facilitating the misuse of antimicrobials, contributing to the development of resistance over time. In a paper on the Pivotal role of Pharmacovigilance Programme of India in containment of AMR, Agrawal V et al. [7] reported on ADRs caused by over-the-counter medical products. Their findings confirmed that more than 40% of ADRs were associated with antibiotics sold to patients without any prescription.

WHAT CAN PHARMACOVIGILANCE OFFER?

The first question to answer is what AMR and AMS have to do with Pharmacovigilance. In 2017, the Uppsala Monitoring Centre published a report [8] in which authors agreed that AMR is an overlooked adverse event. Explaining the role of pharmacovigilance in suspected AMR identification, the report distinguished two major public health issues which can be indicated by a disproportionally greater reporting on antimicrobial treatment failure: *resistance* and/or *poor-quality medicines*. Resistance cases are reported as part of safety data, and in the context of AMR, reporting terms such as "pathogen resistance" or "treatment failure" carry a very important message. It is, therefore, at least worth exploring the terminology used in drug safety reporting and understanding the data relevance to AMS activities. In the absence of laboratory confirmed safety issues or resistance, the strength of Pharmacovigilance lies in its capacity to generate large amounts of data on suspected events, providing a pool for generation of important signals.

The Global Pharmacovigilance Network – a solid infrastructure

Created in 1968, the WHO Programme for International Drug Monitoring (PIDM) has become a network of 170 countries [9] (in 2020: 140 Full and 30 Associate members) that collaborate to monitor and identify the harm caused by medicinal products, to reduce the risks for patients. Through their National Pharmacovigilance Centers, these countries have become a worldwide Pharmacovigilance network of systems that use the same standards, for reporting, analysing, and sharing safety data [10], including safety signals which would be difficult to pick without large and lengthy cohort studies. What makes this network a solid infrastructure is its presence in most countries, (including LMICs) on the one hand and the benefits participant countries

have some benefits [11] for participant countries for the other. Key participants benefits are *1) access to the largest medicine safety database -VigiBase [12]; 2) Early information about potential safety hazards; 3) Access to tools for reporting, storing, structuring, searching, and analysing Individual Case Safety Reports (ICSRs); 4) Getting support, training on pharmacovigilance practice and tools; and 5) Access to the international network with knowledge and expertise from other member countries.*

A skilled global workforce safeguarding drug safety

Pharmacovigilance stakeholders such as clinical pharmacologists and pharmacists are closer to the patient than to the laboratory, they have a close eye towards the patient and see how s/he is responding or not responding to a treatment. In the whole PV process, the most important stakeholder is the patient of course, and next to the patient is a reporter who observes and captures the adverse event information. Only after the reporter has transmitted that safety concern report, the Pharmacologist and/or Pharmacist who carry out the analysis and causality assessment will be able include the information in databases, enabling further inclusion on in risk communications messages fed back to health professionals and authorities. The Global Pharmacovigilance networks provide a platform for a systematic collection of data on drug adverse events and reactions, including those suspected to be related to antimicrobial ineffectiveness. The available resources, human and systems, engaged in the global Pharmacovigilance activities of drug safety monitoring, constitute a skillful workforce that can be tasked to monitor and generate data on suspected antimicrobial resistance.

Individual Case Safety Report (ICSR) – more than just a report

ICSRs are submitted to a Pharmacovigilance center at national level and shared further to the Global pharmacovigilance community (PIDM) through the UMC database. Key features of such report include details that carry vital information on drug(s) and suspected adverse reaction(s). An ICSR also includes information on the indication, the drug suspected to cause an adverse event, the co-administered drugs, the potentially interacting drugs, the affected system organ class (SOC), the preferred Term (PT) which describes the reported ADR using an internationally agreed code. An ICSR carries information on the patient such age, gender, co-morbidities, outcome (e.g. prolonged hospitalisation, deaths) and actions taken (e.g. drug withdrawal, switch). If any antimicrobial is mentioned in an ICSR as a suspected, co-administered or one of

the potentially interacting drugs, that should the start of a tracking process. The strength lies in the aggregated data from millions ICSRs.

A broader use of safety reporting Codes and Terms

The Medical Dictionary for Regulatory Activities (MedDRA) codes have been widely adopted by Pharmacovigilance professionals and can serve the AMS programs if used well in conjunction with other stewardship methods. These codes do not need to be reinvented or changed; the signal detection methods are well polished to capture safety issues on medicinal products, including antimicrobials. Key relevant codes must be carefully selected and used to design systems that can target specific products in specific geographical areas. Codes linked to terms such as "pathogen resistance", "treatment failure" or "off-label use" have the potential to provide valuable data on AMR burden or risks.

Putting Novel communication technologies to work

The use of novel communication tools and technologies can drive faster and better data collection from settings that have traditionally been left out of existing heath data collection programs. Geo-tagging technologies should be explored and used to ensure the real-time localisation component is integrated in the surveillance programs. Of course, careful data protection and privacy concerns should be a priority both at conception, development and use of surveillance tools.

CONCLUSION

Closing the laboratory capacity gap will require tremendous investments, but the AMR data scarcity is a question that cannot wait any longer. Complementarity between disciplines should be explored to make sure we are confident in our mapping of the global AMR burden, including estimates from less medically equipped corners of the globe, which should not be left behind by AMS programmes.

Pharmacovigilance is a worldwide network with well-established tools to collect data on antimicrobial treatment failure in places where laboratory confirmation is impossible. More work should be done to advocate for the usefulness of MedDRA terms suggesting suspected cases of resistance, to make use of the Pharmacovigilance network which could prove to be an outstanding tool for this public health challenge. Thus, Pharmacovigilance could become a

part of the antimicrobial stewardship programs through the collaboration of sensitized reporters (medical and non-medical stakeholders involved in drug safety).

Additionally, databases on drug safety have specific terms and codes for capturing inappropriate prescribing practices or misuse of medicinal products. Such databases constitute a unique resource of information on potential misuse of medicines, which in the case of antimicrobials should be systematically monitored as part of AMS programs. Amounts of antimicrobials taken without prescription are in many places unknown and very difficult to estimate. By collecting data on ADRs caused by antimicrobials taken without prescription, inappropriate use can be timely addressed.

The Pharmacovigilance network has become a robust scientific community with experience in tracking suspected adverse events caused by new and old medicinal products. As AMR becomes a global health issue and AMS needs all the available tools to ensure the best use of antimicrobials, let us add pharmacovigilance networks to the toolbox, especially for communities with limited access to other rather expensive tools such as laboratory coverage and capacity. We must address antimicrobial resistance as a safety issue because it is a safety issue.

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CHAPTER 4 - GENERAL DISCUSSION

The studies presented in this thesis have shown that global and national PV centers have events in their databases, that suggest suspicion of resistance to a given antimicrobial or cases of inappropriate use that could lead to resistance.

These events were coded with messages that carry such information because ADRs reporters were able to find codes and terms which applied to the reported suspicion. The MedDRA dictionary has been in use for many years, and we are not coming up with new codes. But with this thesis, we are shedding light on an existing set of MedDRA codes carrying an additional message if the suspected drug is antimicrobial.

We have shown that a group of at least 17 PTs with an AMR-relevant meaning can serve as a basis for systematic or programmatic collection of reports suggesting suspicion of resistance or inappropriate use.

From a global database, a sample of 6 agents with a total number of 315,774 of ADR reports had almost 2% of the reports recorded with a PT describing either 'ineffectiveness' of the drug, 'resistance', 'off-label use' or forms of 'error' with the medication use. With these findings in hand, it is possible to suggest the use of the pharmacovigilance network as a useful complementary way to alert on suspected resistance to antimicrobials or their inappropriate use, especially in settings where microbiology laboratories are scarce or inexistent. The use of these PTs was confirmed by the study which focused on a country-level database in The Netherlands where 252 ADR reports with AMR-relevance. In the Ugandan study (to be published), none of the 17 PTs was found in ADR reports with antibiotics a suspected drug. This may be explained by the level of skills and experience in the use of MedDRA terms by the those receiving and analysing the ADR reports. But it could also be suggested that resources and experience matter in the world of pharmacovigilance. Resources can allow a pharmacovigilance unit to have appropriate teams with the required expertise to filter and analyse the raw reports receive from various reporters. And centers with a strong and long experience can capitalize on the knowledge acquired over the years. MedDRA has more 23, 000 Preferred Terms, but this thesis has revealed a short list of 17 PTs and corresponding codes which are AMR-relevant. Less experienced PV centers may be less aware of these codes, but it

is also an AMR context which is needed for the assessors reading and classifying ADR reports. This list of 17 PTs and codes is what we are offering to the global antimicrobial stewardship community, across all involved disciplines, including pharmacovigilance, microbiology, clinical pharmacology, informatics, and others.

Systematic collection of data on use-related issues should be used to provide a bigger picture to prescribers who have a choice to make during each consultation. Reports on off-label use or drug use in contraindicated indications should be shared with those in the antimicrobials supply and use chain to timely inform their decision-making process.

Drug utilisation studies are an integral part of Pharmacovigilance, especially in the context of post-authorisation safety studies (PASS). Data on off-label use, drug misuse and medication error are an important element of drug utilisation research and Pharmacovigilance. In the context of this thesis, using standardised MedDRA codes (see shortlisted 17 PTs), Pharmacovigilance allows collection of data on suspected misuse of antimicrobials, antimicrobial off-label use or medication errors involving antimicrobials.

From the Lareb database, we have found that 91 Off label ADR reports included tobramycin (Watch) and colistin (Reserve) as the suspected drug with 53 (58%) and 24 (26%) reports, respectively. Special attention should be given to these groups, and AMS programs can make important steps in the right direction if all involved parties.

By using existing PV systems to generate real-time and possibly geo-tagged data on suspected or potential resistance to antimicrobials, PV systems will have an added function on top of their safety signals detection role. By promoting the use of the Pharmacovigilance systems and tools as part of the AMR surveys, awareness will be raised among reporters who aware of the adverse drug reactions caused by other medicines, for example those listed as concomitant while they may be the primary cause of the suspected ADR. Promoting of the well-established Pharmacovigilance network will strengthen the capacity of PIDM members with a less active collection and sharing of ADR reports.

However, to confirm or solidify our hypothesis, further studies are necessary to look at what is in the report, to ensure there is possibility to conclude whether the primary suspected ADR is attributable to the antimicrobial or not, because an ADR report contains information of different medicinal products and comorbities. The list of 17 PTs has been proposed based on

the sample of 86 drugs for which reports were searched, but further studies to extend or shorten the list are still required. In addition, further research focusing on the narrative and other clinical details in the ADR reports is required.

Future research should consider details such demographics of patients, concomitant medication, suspected interacting drug, reported comorbities, seriousness of the reported events and types of reporters. We encourage the AMR research community to explore data collected by the Pharmacovigilance community, through the 17 MedDRA codes or Preferred Terms, but also welcome suggestions on any other code or PT that may be relevant to AMR.

The search for AMR-relevant PTs has focused on three main terms classified under three System Organ Classes (SOCs): '*infections and infestations'*, '*general disorders and administration site conditions*', and '*injury, poisons and procedure complications*. We cannot exclude the existence of other relevant terms classified under other SOCs and suggest future research to investigate other SOCs for potentially relevant PTs.

Limitations

The hypothesis presented and studied in this thesis has several limitations to be taken when considering or analysing the results and ideas presented here. The main limitations include the following:

The required synergy between two fields

This is a proposal of new approach that requires a synergy between two different fields of pharmacology: on the one had we have pharmacovigilance researchers working on monitoring adverse events associated with medical products including antimicrobials and there are teams gathering laboratory-confirmed data on antimicrobial resistance. Our proposed AMR surveillance strategy involves a collaboration between groups or teams that are usually working from different angles of pharmacology, and the initiation of such a new collaboration could constitute a limitation, especially in early implementation stages.

The suspicion character of reported events

Pharmacovigilance detects suspicion of events, and this remains true to antibiotics. The reported ADRs are not confirmed through microbiological laboratory testing, but collection of data on suspected events could be a step in the right direction for countries with weak or no

laboratory infrastructure that can allow proper microbiological confirmation. In areas with weak infrastructure to timely generate laboratory confirmed data, it is important to note the weight of data on suspected events. In pharmacovigilance, the suspicion character is maintained until one has robust amount of data that support establishment of a causal link. It is therefore very important to see data on suspicion of resistance or inappropriate use as another way of gathering evidence in settings with no other easy to reach data collection infrastructure.

The skills and capacity gap

The differences in pharmacovigilance skills will also lead to different levels of quality of collected data. Understaffed and resource-limited pharmacovigilance units are confronted with the reality of large amounts of data that require advanced expertise and appropriate equipment.

An opportunity to innovate

Large amounts of data may require advanced expertise and specific infrastructure. However the field of pharmacovigilance has on many occasions capitalised on large data to inform decisions and minimise risks. Specifically, pharmacovigilance experts have in the past developed algorithms such as the Naranjo scale used to assess adverse drug reaction probability. In the track of AMR using large amounts of PV data, the suspected events can be used in algorithms that bring suspicion to the lowest possible level. It is up to us the pharmacovigilance and AMR research community to come up with such tools or algorithms. A collaboration with other fields such as informatics and mathematics could enable the development of tools that analyse ADRs data and give reliable evidence on the rising AMR or its contributing factors. Whilst this thesis is a first step towards future implementation of surveillance of AMR using PV capabilities, it provides key elements that can serve as important variables in an AMR causal link assessment algorithm. It may be a challenge for many PV centers to navigate through the large amounts of ADRs data being shared across the globe through the global PV network. But, for the specific aim of using the available data to fill the AMR data scarcity gap, we have shortlisted the relevant codes to be tested and used on various data mining and synthesis techniques, and we call upon interested researchers, including but not limited to clinical pharmacologists, pharmacists, microbiologists, data scientists, to think and innovate.

CHAPTER 5 - CONCLUSIONS

1) Considering the importance of antimicrobial stewardship activities across the globe, and having noted the AMR data scarcity, especially in LMIC, we have studied the possibility of using an existing medicines safety surveillance network to capture data on adverse events related to antimicrobial resistance.

2) From the MedDRA Preferred Terms used to report ADRs to the UMC database, we have identified 17 PTs which indicate suspicion of antimicrobial resistance or inappropriate use of antimicrobials. Pharmacovigilance networks can use these PTs to generate data on suspected antimicrobial resistance and antimicrobial misuse.

3) Testing further our hypothesis, we have looked at the largest global database – VigiBase and found reports describing antimicrobial resistance and inappropriate use of antimicrobials

4) We have tested the hypothesis on a country level database in a high-income country (The Netherlands) and noted that reporters have submitted spontaneous reports which are coded with the AMR-related Preferred Terms.

5) Considering the relative low number of reports coded with the 17 PTs, one way of optimizing the impact of the proposed approach would be the strengthening of Pharmacovigilance systems, through training of reporters, with an emphasis on the PTs related to suspicion of antimicrobial resistance and antimicrobial misuse.

6) We encourage the AMR research community to explore data collected by the pharmacovigilance community, through the 17 MedDRA codes or PTs, but also welcome suggestions on any other code or PT that may be relevant to AMR.

7) The global Pharmacovigilance network is a robust scientific community with experience in tracking suspected adverse events caused by new and old medicinal products. In settings with limited laboratory capacity, this has the potential to fill the AMR data scarcity gap.

Annex 1 - *Manuscript under review* "Adverse Drug Reaction Reports Containing AMR-Relevant MedDRA Terms in the Dutch Pharmacovigilance Database"

Habarugira, J.M.V.; Harmark, L.; Figueras, A. **Adverse Drug Reaction Reports Containing AMR-Relevant MedDRA Terms in the Dutch Pharmacovigilance Database.** *Preprints* **2021**, 2021080031 (doi : 10.20944/preprints202108.0031.v1). https ://www.preprints.org/manuscript/202108.0031/v1

Abstract

Background: Antimicrobial resistance (AMR) requires urgent multidisciplinary solutions, and Pharmacovigilance (PV) has the potential to strengthen current antimicrobial stewardship (AMS) strategies. This study aimed to characterise AMR-relevant adverse drug reaction (ADR) reports submitted to The Netherlands Pharmacovigilance Centre (Lareb)

Methods: We carried out a descriptive analysis of ADR reports submitted to Lareb, coded with AMR-relevant MedDRA Preferred Terms (PTs).

Results: Between 1998 and Jan 2019, 252 AMR-relevant ADR reports were submitted to Lareb. The most frequent antibiotics were tobramycin (n=89; 35%), colistin (n=30; 11,9%), ciprofloxacin (n=16; 6,3%), doxycycline (n=14; 5,5%) and aztreonam (n=12; 4,8%). The PTs used included Off label use (n=91; 36,1%), drug ineffective (n=71; 28,2%), product use in unapproved indication (n=28; 11,1%), pathogen resistance (n=14; 5,6%) and drug resistance (n=13; 5,2%). 54% of the reports were on Watch antibiotics and 19% involved the Reserve group. In the Watch group, "Off label use" and "Product use in unapproved indication" were the most frequent PTs and majority of reports on Reserve antibiotics were coded as "Off label".

Conclusions: Addressing AMR using the PV methods will provide an opportunity for PV expansion, especially in resource-limited settings, encouraging further investments into AMS programs and PV systems.

Keywords: *antibiotics, antimicrobial resistance, antimicrobial stewardship, AWaRe, Pharmacovigilance, Lareb, adverse drug reactions,*

1. Introduction

Antimicrobial resistance (AMR) and antimicrobial stewardship (AMS)

Antimicrobials include a wide category of medicines used to prevent and treat infections in humans, animals, and plants [1]. These medicines are designed to kill or inhibit growth of microorganisms responsible for infections, but with time, antimicrobial resistance (AMR) occurs as the same microorganisms develop the ability to resist to the antimicrobial action of medicines previously effective [2]. Antimicrobial Stewardship (AMS) designates the set of programmes and actions conducted at different levels of the value chain to encourage the responsible use of antimicrobials through the delivery of multiple evidence-based interventions, with the final aim of ensuring an optimal selection of the antibiotic when it is needed, and its prescription at the required dosage and duration of treatment resulting in the best clinical outcome, with minimized toxicity to the patient and minimum impact on subsequent resistance [3,4]. Whilst measures have been put in place to address AMR at hospital or country level, there is still lack of a globally coordinated strategy to curb the increasing resistance [5], especially because less AMS interventions cover primary health care, the dispensing of antimicrobials without prescription in pharmacies, as well as the extended use of antimicrobials in non-human sectors [6]. As a program, AMS is a set of all interventions used to enhance the rational use of antibiotics [7]. Various forms of antimicrobial stewardship programs have been established in different countries [8] at different levels of care delivery with involvement of a wide range of stakeholders including clinicians, pharmacists, nurses, and administrators and healthcare facilities [9,10,11]. As the world puts in place various measures to curb the rising threat caused by the rising resistance to existing antibiotics, Pharmacovigilance methods could constitute an important part of the wider multi-disciplinary approaches used for resistance surveillance and warning.

Pharmacovigilance and Antimicrobial Resistance

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems [12]. Adverse effects and other drug-related problems include a range of effects that follow use of a medicinal product with varying degree of harm and causality certainty. An adverse effect of a medicinal product is a negative or harmful patient outcome that seems to be

associated with the treatment, including there being no effect at all. An adverse drug reaction (ADR) is referred to when causality analysis has taken place and the link between the medicine and a suspected adverse effect is beyond uncertainty [13]. In the context of this study, the terms adverse drug reaction (ADR) reports refer to reports sent by health professionals or patients when an adverse effect has occurred in a patient taking one or more antimicrobial. The scientific community continues to propose innovative approaches, and some have suggested pharmacovigilance databases and methods as a potential tool to consider for the setup of antimicrobial stewardship [14]. Recent studies have underlined the potential role of Pharmacovigilance in containing the rising antimicrobial resistance [15,16] proposing methods and tools that PV can offer to programs that monitor suspected resistance or cases of inappropriate use of antimicrobials. A recent study conducted in Russia concluded that the most frequent types of medication errors associated with the use of beta-lactams were the leading risk factors of growing bacterial resistance [17], and the authors emphasized on the need to have proper code to report medication error events involving antibiotics. Other researchers have looked at therapeutic failure as a reportable event but recognised the need to use the right definition of failure [18] if pharmacovigilance systems are to systematically collect data on failure. Researchers have also emphasized on the importance of PV databases which constitute a unique resource of information on potential misuse of medicines, including antimicrobials, and potentially containing AMR-relevant data [19]. A recent study has identified a set of 17 MedDRA Preferred Terms which suggest suspicion of Resistance, Ineffectiveness, Off-label use, and medication errors [12].

Pharmacovigilance in The Netherlands

Established in 1968, the WHO Programme for International Drug Monitoring (PIDM) had The Netherlands as one its ten founding members. Since then, the program has expanded to include 145 full member countries and 26 associate member countries [21]. The Netherlands Pharmacovigilance Center Lareb manages a spontaneous reporting system, which involves collection and evaluation of suspected adverse drug reactions (ADRs) of medicinal products, aiming to identify new safety signals. Lareb codes the reports using MedDRA, and the reports are assessed by qualified assessors before entry into the database and prior to sharing with the global community via PIDM. To determine if specific reports can be qualified for signal review, a rigorous scientific review must take place, and signals are shared with the Dutch

Medicines Evaluation Board (CBG/MEB) which will decide, often in the European context, if further regulatory action is necessary [22]. As a founding member of the IPDM, The Netherlands has a rich experience in ADR reports collection and sharing with the world through the UMC database. The Netherlands Pharmacovigilance Centre (Lareb) was designated in 2013 as the WHO collaborating centre for patient reporting [23] and the strength of the centre lies among other things, in the collection of reports directly via the patient reporting scheme initiated in 2003 and went on to become a reliable of source of safe data [24,25].

The Access, Watch and Reserve (AWaRe) classification for availability and appropriate use

Antibiotic resistance affects people of all ages in all countries. Yearly, an estimated 5.7 million deaths occur from treatable infectious diseases, mostly in low- and middle-income countries (LMICs), and many of these lives could have been saved if effective antibiotics were available. At the same time, there are about 700,000 annual deaths worldwide due to antibiotic resistance. The development of resistance, while threatening the right to best medical care, has another side of the coin showing us that resource-limited settings are more affected by lack of access to antibiotics than by the resistance. Preserving antibiotic effectiveness while ensuring universal access is at the heart of public health dilemmas, as policies for good access must be accompanied with strong measures to minimise inappropriate use that would lead to further resistance [26]. To address the issue of availability while ensuring appropriate use, since 2017, the Word Heal Organisation (WHO) Essential Medicines List (EML) includes a classification of antimicrobials into three categories known as "Access", "Watch" and "Reserve" (AWaRe), based on the indication, availability, and awareness [28]. A global campaign was launched in 2019 urging governments to implement to implement the AWaRe tool through national guidelines to reduce antimicrobial resistance and ensure access [29]**.**

Study objective

In a previous study [20], a list seventeen of MedDRA Preferred Terms relevant to AMR or inappropriate use of antimicrobials was established based on global data from VigiBase. Focusing on country-specific data, the objective of this research was to characterise ADR reports submitted to The Netherlands Pharmacovigilance Centre (Lareb) following use of

antibiotics and coded with MedDRA Preferred Terms that suggest suspicion of Resistance, Ineffectiveness, Off-label use or medication Errors.

2. Materials and Methods

Data source and Search strategy

We carried out a descriptive analysis of ADR reports submitted to The Netherlands Pharmacovigilance Center (Lareb) database, fulfilling the following criteria:

a) Reports on Antibiotics classified under *ATC J01 or ATC J04*.
b) Reports coded with at least one of the following MedDRA (version 21.1) Preferred Terms and codes: Pathogen resistance (10034133); Drug ineffective (10013709); Treatment failure (10066901); Drug resistance (10059866); Therapeutic product ineffective (10060769); Therapy non-responder (10051082); Decreased activity (10011953); Drug ineffective for unapproved indication (10051118); Therapeutic response decreased (10043414); Multiple drug resistance (10048723); Off label use (10053762); Medication error (10027091); Product use in unapproved indication (10076476); Contraindicated product administered (10078504)

For each report meeting the criteria in a) and b), the following information was collected and included in the dataset for further analysis: Report identifier; Suspected ADR; Year of report; Reporter type; Suspected drug; Indication and Action taken.

3. Results

3.1. ADR reports with AMR-relevant codes

Between 1998 and January 2019, a total of 252 ADR reports (study sample) were submitted to Lareb using a PT or a combination of PTs that suggested suspicion of AMR or use-related issues (inappropriate use or medication errors). The following antibiotics were the most frequently reported as suspected causes of AMR-relevant ADRs: tobramycin (n=89; 35%), colistin (n=30; 11,9%), ciprofloxacin (n=16; 6,3%), doxycycline (n=14; 5,5%) and aztreonam (n=12; 4,8%). The most frequently used PTs were *off label use* (n=91; 36,1%), *drug ineffective* (n=71; 28,2%), *product use in unapproved indication* (n=28; 11,1%), *pathogen resistance* (n=14; 5,6%) and *drug resistance* (n=13; 5,2%)

3.2. Most frequently used PTs in cases of suspected resistance or use-related issues

As shown in **Table 1**, 98 reports (39% of the study sample) suggested suspicion of resistance using PTs such as *drug ineffective*, *pathogen resistance* and *drug resistance*. A larger group of reports (n=119; 47% of the study sample) included PTs suggesting use-related issues such as *off label use* (n=91; 76%) and *product use in unapproved indication* (28; 15%). More than half of the 91 reports coded with PT *off label use* described events in patients on tobramycin as the suspect drug *(n*= 53; 58%); additionally, 24 (26%) were on colistin. The reports coded with the PT *product use in unapproved indication* were predominantly on tobramycin (n= 27; 96% of the cases). Out of the 252 reports of the study sample, 35 (14%) were coded each with more than 1 PT, combining PTs that refer to suspicion of both resistance and use-related issues.

3.3. Applying the AWaRe Classification to the reports

As shown in **Table 2**, the Watch category was involved in 137 (54%) of the 252 ADR reports with a predominance of tobramycin with 89 of the 147 Watch reports (n=89; 78%). The second leading group is Reserve with 45 reports (19%), followed by the Access group with 40 reports (16%), and the remaining 11% include combination of antibiotics from different AWaRe groups or non-AWaRe classified antibiotics. In the Watch group, "Off label use" and "Product use in unapproved indication" were the most frequent PTs, used in 57 (42%) and 27 (20%) reports,

respectively. Majority (25 or 76%) of reports involving Reserve antibiotics were submitted as Off label. In the Access group, "drug ineffective" was the most frequent PT in 25 (63%) out of 40 reports.

3.3. "Off label use" and "product use in an unapproved indication": tobramycin and colistin

In the current study we found that out of the 252 ADR reports, 119 (47%) are suggesting use-related issues. Of these 119 reports, 91(76%) are coded as "off label use" and the remaining 28 (15%) reports are coded "product use in an unapproved indication". The 91 off label ADR reports include predominantly tobramycin (Watch) and colistin (Reserve) as the suspected drug with 53 (58%) and 24 (26%) reports, respectively. A focus on 89 ADR reports with tobramycin as the suspected drug, 30 (33.7%) reports included chronic obstructive pulmonary disease as the primary indication while 25 (28%) reports had bronchiectasis as the indication. 53 of the 89 ADR reports were coded as off label use in treating chronic obstructive pulmonary disease (22 cases) and bronchiectasis (13 cases).

3.4. The 2015 peak in numbers of AMR-relevant ADR reports to Lareb

From the 252 ADR reports submitted over a period of about 20 years, 82 (34%) reports were submitted in 2015 as illustrated by **Figure 1.** A sharp increase in the number of reports was observed in the three consecutive years with 21 in 2013, 54 in 2014 and 83 in 2015. The numbers dropped to 26 reports in 2016, but in just these four years, Lareb received 73% (183 of 252) of AMR-relevant reports received over a period of 20 years. In this short period of sharp increase, there was a clear increase of tobramycin reports passing from 11 in 2013 to 30 in 2014 and reaching 39 in 2015. Colistin shows a visible increase of ADR reports in this period, passing from 0 in 2013 to 10 in 2014 and 14 in 2015. Other drugs with increasing ADR reports numbers in the spike period include aztreonam and doxycycline.

Of the 183 reports submitted in the period 2013-2016, 84 reports were on suspected "off label use" with a predominance of tobramycin that was the suspect drug in 50 (of 84) reports. 39 of the 183 reports were submitted with the PT ``drug ineffective" and diverse antibiotics were reported as suspected drugs. However, with reports coded using the PT ``product use in unapproved indication" indication, a clear predominance of tobramycin was observed.

Table 1 The most frequently used PTs and reported antibiotics per RIOLE group

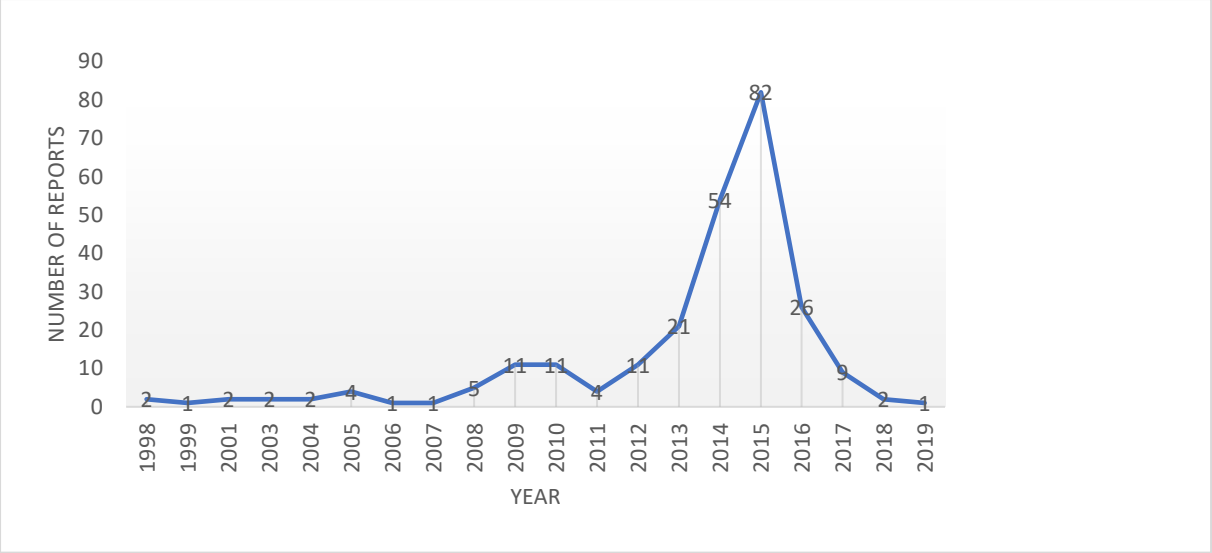
AMR-relevant PT	PT (n; %) in the RIOLE category	Most reported antibiotics (n; %)
Suggesting AMR (98; 39%)	drug ineffective (71; 72%),	aztreonam (9; 13%)
		amoxicillin+Beta-lactamase inhibitor (6; 8%)
		doxycycline (6; 8%)
	pathogen resistance (14; 14%)	ceftazidime (5; 36%)
		ciprofloxacin (2; 14%)
		linezolid (2; 14%)
	drug resistance (13; 13%)	tobramycin (3; 23%)
		ciprofloxacin (2; 15%)
Suggesting use-related issues (119; 47%)	off-label use (91; 76%)	tobramycin (53; 58%)
		colistin (24; 26%)
		doxycycline (6; 7%)
	product use in unapproved indication (28; 15%)	tobramycin (27; 96%)
Suggesting both AMR and use-related issues (35; 14%)	Combinations of PTs Suggesting both AMR and use-related issues (35; 14%)	ciprofloxacin (7; 20%) azithromycin (3; 9%)
TOTAL=252; 100% ADR reports		-

Table 2 The most reported antibiotics and used PTs per AWaRe class

AWaRe categories	Most reported antibiotics (n; %)	Most used PTs per AWaRE category (n; %) *
Access (40;16%)	doxycycline (14;35%)	drug ineffective (25; 63%) off label use (6; 15%)
	amoxicillin+Beta-lactamase inhibitor (7;18%)	
	sulfamethoxazole + trimethoprim (4; 10%)	
Watch (137; 54%)	tobramycin (89; 78%)	Off label use (57; 42%) Product use in unapproved indication (27; 20%) drug ineffective (20; 15%) pathogen resistance (8; 6%)
	ciprofloxacin (16; 33%)	
	azithromycin (8; 17%)	
	moxifloxacin (7; 15%)	
Reserve (45;19%)	colistin (30; 91%)	off label use (25; 76%)
	aztreonam (12; 11%)	
Combination of different classes (17; 6%)	concomitant from different classes	drug ineffective (7; 41%) drug resistance (3; 18%)
Other or not classified (13; 5%)		drug ineffective (8; %)
TOTAL (252;100%)	-	-

*Most frequently used PT per AWaRe class (access, watch, reserve)

FIGURE 1 Yearly reports from 1998 to Jan 2019



3. Discussion and Conclusion

As the world seeks and puts in place strategies to tackle the rising AMR, living reviews of Pharmacovigilance data should be seen as a strong potential source of data on trends in suspected resistance and possible inappropriate use of antimicrobials, especially in countries with less resources and few testing laboratories. This study revealed an increase in AMR-relevant reports with a peak in 2015, and tobramycin appeared to be involved in majority of reports. Such a cluster in time and maybe geographically localisable could be used by AMS programs to trigger a drug-focussed monitoring, e.g. tobramycin in this case. The present analysis of the Lareb database, a consolidated pharmacovigilance program has shown that this use of PV databases to investigate AMR issues is possible. Even more, despite the phenomenon of underreporting (common to most PV programmes based on spontaneous reporting) and the lack of proactive promotion of these preferred terms in the PV dictionaries, 252 reports were identified. Furthermore, 19% of these reports involved a Reserve antibiotic and 54% a Watch antibiotic, both belonging to categories of products of special interest from the AMR perspective.

Systematic collection of data on use-related issues should be used to provide a bigger picture to prescribers who have a choice to make during each consultation. Reports on off label use of drug use in contraindicated indications should be shared with those in the antimicrobials supply and use chain to timely inform their decision-making process.

The 91 Off label ADR reports included tobramycin (Watch) and colistin (Reserve) as the suspected drug with 53 (58%) and 24 (26%) reports, respectively. Special attention should be given to these groups, and AMS programs can make important steps in the right direction if all involved parties

Tobramycin is an aminoglycoside used to treat several conditions, including superficial and deep infections [30]. Depending on the indication and route of administration, various forms of tobramycin are marketed, including inhaled tobramycin used to treat cystic fibrosis [31], ophthalmic solution to treat bacterial conjunctivitis [32], intramuscular injection and intravenous infusion for the treatment of other bacterial infections.

Less used as of the 1980s due to safety issues after more than 30 decades on the market, colistin, a polymyxin antibiotic, became later in the 21st century, a last-resort drug for multi-drug resistant Gram-negative organisms [33,34]. In this study, we found that this Reserve antimicrobial is reported as the suspected drug in 24 reports with ADRs coded as "off label use". The leading indications for which colistin was prescribed are chronic obstructive pulmonary disease and bronchiectasis

The antimicrobials supply and use chain, important stakeholders include marketing authorisation holders (MAH), prescribers, pharmacists, and patients. It should be noted that in many countries, the function of pharmacist is supported by other distribution services such drug stores that provide over the counter (OTC) medicines. MAHs have the obligation to regularly submit safety reports to National competent authorities (NCAs). But, more than just an obligation pharmacists and other products distributors play an important role in collecting safety data and submitting high quality safety reports to competent authorities. In countries where OTC medicines include antibiotics, the supply chain must be considered in all AMS programs using local PV systems to collect AMR-relevant data.

In this study we have noted an increased number of reports in the period 2013-2015 and majority of these reports were collected and submitted by MAHs. Beside regulatory obligation, there should be a collaborative approach between MAHs and PV centers such as Lareb, to facilitate joint assessment of suspected cases if necessary. PV centers are part of a large global network sharing safety data through PIDM, and the AMR PV researchers can benefit from reports that have gone through causality assessment by both MAHs and PV centers.

In many countries, health care professionals play a crucial role in gathering and submitting safety data to competent authorities. MAHs rely on health care professionals working on clinical trials or seeing patients in clinics to provide solicited or unsolicited safety data on products. In their risk management plans (RMPs), MAHs are required to address undesirable clinical outcomes and for which there is sufficient scientific evidence that they are caused by the medicinal product [35]. If the drug safety community agrees that resistance or ineffectiveness are undesirable clinical outcomes caused by the antimicrobial, the MAHs should consider the use of AMR-relevant MedDRA terms in collecting data to inform their RMPs. The Guideline on good pharmacovigilance practices (GVP) Module V (*see V.B.5.9. RMP part II, module SVIII "Summary of the safety concerns"*) also indicates that reports of adverse reactions may be derived from multiple sources including spontaneous data sources and may be linked to situations such as off label use and medication errors. If the concerned medicinal product is antimicrobial, regulatory activities should consider the risk associated with off label use and medication in the antimicrobial stewardship context.

Expanding the role of PV requires both promotion of existing tools and education for the potential reports of observed or suspected effects. In this study, a large portion of analysed reports were collected and submitted by MAHs and there may be other potential similar cases that went unreported by prescribers and patients.

Promoting the existence of AMR-relevant MedDRA terms and explaining their relevance to surveillance of antimicrobial resistance could lead to increased submission of similar reports from prescribers and patients. Public health will gain from different angles if PV is integrated in the AMS programmes package. PV centers at country level should be encouraged to actively promote these AMR relevant PTs and invite reporters to collect and send this information to relevant agencies. By getting actively involved in this process, (1) PV centres will receive more spontaneous reports, the centres work will be more visible and appreciated by other public health stakeholders, (2) suspected AMR could be timely detected, potential clusters could be highlighted and, if necessary, ad-hoc microbiological tests could be conducted. The integration of PV in this process could lead to a win-win situation for different scientific disciplines tackling AMR from traditionally isolated perspectives.

Pharmacovigilance is already a multidimensional science with potential to expand further. Tackling AMR questions using the existing PV methods will also provide an opportunity for PV as a field to evolve further and countries will see more value in investing in their PV systems. As technology drives further the field of Pharmacovigilance, methods traditionally used in post-marketing drug safety monitoring have the potential to serve as surveillance strategies for Antimicrobial Stewardship programs.

Conflicts of Interest: The authors declare no conflict of interest.

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ANNEX 2 – Full Copy published Article 1 "***Pharmacovigilance network as an additional tool for the surveillance of antimicrobial resistance***"

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ORIGINAL ARTICLE

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Pharmacovigilance network as an additional tool for the surveillance of antimicrobial resistance

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Abstract

Background: The WHO Programme for International Drug Monitoring (PIDM) is a large Pharmacovigilance network of countries sharing Adverse Drug Reaction (ADR) reports. Pharmacovigilance Experts have suggested that antimicrobial resistance (AMR) is an overlooked adverse event. We undertook this study to investigate the potential role of Pharmacovigilance databases in the surveillance of AMR.

Methods: Using the AWaRe (Access, Watch and Reserve) list and the WHO Priority Pathogens List, we established a list of antimicrobials and carried out a VigiBase search via VigiAccess, looking for ADR reports with Preferred Terms (PTs) that contained AMR-relevant information. Identified Terms were matched with codes from the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1).

Results: Records on 86 drugs were retrieved with a total of 1 170 751 ADR reports submitted between 1968 and 2018. Seventeen PTs suggesting suspected resistance, ineffectiveness, inappropriate use, or medication error were used to code 15 250 reports. The most frequently used PTs were "Drug Ineffective" (45.6%), "Off label use" (9.5%) and "Pathogen Resistance" (8.9%). A group of six agents (Amoxicillin, Cefalotin, Ciprofloxacin, Clarithromycin, Levofloxacin and Daptomycin) accounted for 38% ($n = 5806$) of all 15 250 AMR-relevant ADR reports. The PTs most frequently used in 5806 reports were grouped in 4 categories: drug ineffectiveness (62.5%), resistance (19.2%), off-label use (12.1%) and prescription errors (6.2%).

Conclusion: Our findings suggest that Pharmacovigilance databases could serve as a tool in tracking antimicrobial use and resistance especially in settings where laboratory capacity is still in its development stages. National Pharmacovigilance centers could play a proactive role in stimulating the reporting of AMR-relevant ADRs which can serve as a basis for resistance suspicion alerts. Further studies focusing on the narrative and other clinical pharmacology details in ADR reports are required.

KEYWORDS
adverse drug reaction, antimicrobial resistance, antimicrobial use, AWaRe, MedDRA, Pharmacovigilance, VigiAccess, VigiBase

1 | INTRODUCTION

Antimicrobial resistance (AMR) has become one of the most pressing global health concerns. In May 2015, the 68th World Health Assembly endorsed a global action plan to tackle AMR, including antibiotic resistance, the most urgent drug resistance trend.[1] In 2016, at the United Nations annual General Assembly, AMR was among the topics discussed in a High-Level Meeting of Heads of States.[2] The Assembly

recognised the menace that the AMR poses to the successful fulfilment of the Sustainable Development Goals (SDGs). In September 2016, the World Bank published a report titled "Drug Infections: a threat to our Economic Future", providing a detailed understanding of the economic consequences of AMR.[3] It is in this context that several initiatives and policies are being put in place with the aim of reducing inappropriate antimicrobial consumption at all levels, under the One Health Initiative perspective.

Many strategies engaged in the fight against AMR shared the key objectives of tracking resistant microorganisms to reduce treatment failures and to ensure appropriate prescription of existing antimicrobials. However, this is a difficult task in resource-limited settings with low laboratory capacity, both in terms of infrastructure and skilled professionals. In an analysis published in 2017, Wernli et al[4] shortlisted five policy frames that should guide AMR initiatives: AMR as a healthcare problem, a development issue, an innovation challenge, a security issue and as a One Health challenge. For resource-limited settings all these frames apply, but most importantly for developing countries AMR is a development and security issue.

Key points

- Reports on suspected Resistance or Inappropriate use of antimicrobials have been submitted as adverse drug reactions to the WHO Programme for International Drug Monitoring. The reports have been identified using the public available access tool – VigiAccess
- Seventeen Preferred Terms have been used to code more than 15 000 adverse drug reactions or events suggesting resistance, ineffectiveness, or off-label use of antimicrobials.
- The most frequently AMR-relevant PTs used are "Drug Ineffective", "Off Label Use" and "Pathogen Resistance"
- Daptomycin, a "Reserve" agent on the market since 2004 is a subject of reports on resistance and off-label use. Further research is required to safeguard last resort antimicrobials such as Daptomycin.

1.1 | Pharmacovigilance as a toolkit

An adverse effect of a medicinal product is a negative or harmful patient outcome that seems to be associated with the treatment, including there being no effect at all. An adverse drug reaction (ADR) is referred to when causality analysis has taken place and the link between the medicine and a suspected adverse effect is beyond uncertainty.[5] The largest database of ADR reports is hosted by the Uppsala Monitoring Centre (UMC) on behalf of the WHO Programme for International Drug Monitoring (PIDM), bringing together safety data from across all corners of the globe. In the interest the researchers referring to the UMC ADRs database, it is important to clarify the tentative and variable nature of retrievable data.[6] The reports submitted to UMC are based on suspicion; in some cases, there may be enough information for a proper causality assessment to confirm the link between the product and the event, but in many other cases that is possible. There are also differences based on the source where some countries may collect and share reports from medical professionals while other countries are likely to include reports obtained directly from users or patients. Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.[7] If the drug suspected of leading to an ADR report is an antimicrobial, then Pharmacovigilance becomes the tool that could allow the detection, understanding, and prevention antimicrobial-related problems. In a recent editorial, a case was made on this potential role of pharmacovigilance networks in addressing antimicrobial stewardship questions.[8] In the same area of studies cutting across pharmacovigilance and AMR, researchers have been looking at what can be pulled out of existing databases, such as national healthcare records. A good example is the study by Brauer et al[9] which looked at healthcare databases of seven European countries to assess the prevalence of antibiotic use. The same databases could be used in tracking adverse events associated with the reported antimicrobials.

1.2 | VigiAccess - The window into VigiBase

Since 1968, a group of countries which were later to form the PIDM started a systematic collection of ADRs worldwide, under the coordination of the Uppsala Monitoring Centre (UMC). As of end of 2018, the UMC had received and stored in VigiBase over 20 million ADRs reports from more than 170 countries.[10] Since 2015, data stored in *VigiBase* can be freely accessed by the public via *VigiAccess*™.

1.3 | MedDRA - The medical dictionary

To code suspected ADRs, two medical dictionaries have been developed and widely adopted by reporters, and both contain terms which suggest lack of, or poor effect of medicines in general.[11] The first is the WHO Adverse Reaction Terminology (WHO-ART) which was developed and maintained by UMC.[12] It was developed in 1968 to serve as a terminology for coding ADR terms, covering most medical terms needed in adverse reactions reporting. The second is the Medical Dictionary for Regulatory Activities, known as MedDRA.[13] Up until 2008, WHO-ART was the only available terminology for coding ADRs in VigiBase, and then MedDRA was introduced. Therefore, in this study we have used MedDRA as it is the dictionary currently used by Pharmacovigilance centres.

As there are ADR reporting terms which describe or refer to lack of effectiveness and suspicion of resistance to the administered drugs,

we designed the present study with the main objective of investigating the potential role of pharmacovigilance databases in the track of AMR. Specifically, the study aimed: (1) to analyse ADR reporting terms suggesting suspicion of resistance to antimicrobials or referring to cases of inappropriate use of antimicrobials, and (2) to describe the extent to which these terms have been used to code antimicrobial ADR reports to the PIDM database.

2 | METHODS

To address the two specific objectives, the study was carried out in the following consecutive steps: (1) identifying products of interest, (2) search for ADRs reports with terms suggesting suspected ineffectiveness, resistance, or inappropriate use antimicrobials, and (3) linkage of these terms with codes from existing dictionaries used in pharmacovigilance databases.

2.1 | Identification of the antimicrobials to include in the study

To focus on antimicrobials, there was no better reference than the WHO AWaRe classification. The AWaRe categorisation puts antimicrobials in three groups, "Access", "Watch" and "Reserve",[14,15] according to their indication, availability and degree of awareness. The categorisation was proposed by the WHO in 2017 and updated in 2019 with additional details per group[16] and launched with a WHO Global campaign urging governments to implement the AWaRe tool to reduce the spread of AMR. Further reference was made to the Priority Pathogen list[17] established by the WHO to inform the discovery and development of new antimicrobials. We established a list of antimicrobials ensuring representation of all AWaRe categories, and including several other antimicrobials that are not on the AWaRe (which focusses on the Essential Medicines List).

2.2 | Data source, collection and analysis

2.2.1 | Search for reports of ADRs with suspicion of AMR-relevant event

For each selected antimicrobial, a *VigiAccess* search was performed to identify reporting terms which suggest suspicion of resistance, lack of antimicrobial response or events of inappropriate prescription that that could lead to resistance. The search was conducted between June and December 2018.

VigiAccess is a free access portal to the PIDM[18] database allowing retrieval of medicinal products safety reports received by the UMC. Thus, records on each antimicrobial were retrieved and a set of AMR-relevant preferred terms (PTs) used to report ADRs was established.

2.2.2 | Linkage of preferred terms to existing drug safety codes used in medical dictionary

Considering the PTs included in the retrieved reports, a review of codes in the ADRs medical dictionary (MedDRA) was conducted to make a link between a Term and a Code and to ensure that the identified terms can be part of a reporting and signal detection strategy.

MedDRA is a hierarchical terminology with five levels of terms which provide specificity for data entry and flexibility for data retrieval. Reporting Terms used in MedDRA were derived from several dictionaries[19] including the WHO's adverse reaction terminology (WHO-ART), among others. The five MedDRA levels are: System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT) and Lowest Level Term (LLT).[20] In the present study we focussed on the PTs, which is the level used in the VigiBase publicly accessible information via *VigiAccess*.

3 | RESULTS

Based on the list from the *AWaRe* classification and including antimicrobials used to treat pathogens on the priority list, a list of 86 different antimicrobials were identified and used to run the *VigiAccess* search. There AWaRE were more "Access" and "Watch" drugs than "Reserve": beta lactamic penicillins (mostly "Access"), cephalosporins (1st generation, "Access"; 2nd and 3rd generation, "Watch"; 4th generation, "Reserve"), carbapenems, vancomycin, macrolides and fluoroquinolones ("Watch"), and daptomycin ("Reserve"). As shown in Table 1, out of the 86 products, the most represented chemical

TABLE 1 Chemical subgroup (ATC 4th level) of drugs included in the search

Chemical subgroup	Nr of products included
Third-generation cephalosporins	16
Second-generation cephalosporins	13
First-generation cephalosporins	12
Fluoroquinolones	10
Penicillins with extended spectrum	8
Beta-lactamase resistant penicillins	6
Beta-lactamase sensitive penicillins	5
Carbapenems	5
Fourth-generation cephalosporins	3
Glycopeptide antibacterials	2
Macrolides	2
Combinations of sulfonamides and trimethoprim, incl. Derivatives	1
Other antibacterials	1
Other antibiotics for topical use	1
Other cephalosporins and penems	1
Total	**86**

TABLE 2 The 17 PTs on six selected antimicrobials

ANTIBIOTICS AWaRe classification Year of 1st report to UMC Number of ADR reports with AMR-relevant PT, *n* (%)		AMOX. Access 1972	CEFAL. Access 1968	CIPROFLO. Watch 1985	CLARITHRO. Watch 1991	LEVOFLO. Watch 1996	DAPTO. Reserve 2004	TOTAL Total	AMR RELEVANCE CATEGORY
17AMR-relevant PT	Drug ineffective	588 (67.4)	2 (1.3)	791 (45.2)	538 (54.2)	621 (46.3)	167(23.8)	***2707***	***I***
	Pathogen resistance	153 (17.5)	143 (94.7)	140 (8.1)	115 (11.6)	116 (8.6)	82 (11.7)	***749***	***R***
	Off label use	52 (6.0)		204 (11.7)	49 (4.9)	126 (9.4)	102 (14.6)	***533***	***OL***
	Treatment failure	25 (2.9)		49 (2.8)	26 (2.6)	39 (2.9)	99 (14.1)	***238***	***I***
	Product use in unapproved indication	16 (1.8)		44 (2.5)	11(1.1)	35 (2.6)	43 (6.1)	***149***	***OL***
	Drug resistance	12 (1.4)	1 (0.7)	112 (6.4)	41(4.1)	89 (6.6)	95 (13.6)	***350***	***R***
	Drug effect decreased	10 (1.1)		32 (1.8)	10 (1.0)	33 (2.5)	3 (0.4)	***88***	***I***
	Drug effect incomplete	9 (1.0)		12 (0.9)	6 (0.6)	10 (0.7)	3 (0.4)	***40***	***I***
	Decreased activity	4 (0.4)		40 (2.3)		57 (4.2)		***101***	***I***
	Drug ineffective for unapproved indication	3 (0.3)		29 (1.7)	4 (0.5)		61 (8.7)	***97***	***I***
	Therapeutic product ineffective	1 (0.1)		3 (0.2)	1 (0.1)	3 (0.2)		***8***	***I***
	Therapeutic response decreased		2 (1.3)	63 (3.6)	53 (5.3)	46 (3.4)	5 (0.7)	***169***	***I***
	Medication error			119 (6.8)	94 (9.5)		20 (2.9)	***233***	***E***
	Drug prescribing error		3 (2.0)	40 (2.3)	33 (3.3)	49 (3.6)		***125***	***E***
	Multiple-drug resistance			17 (1.0)				***17***	***R***
	Therapy non-responder			53 (3.0)	10 (1.0)	96 (7.1)	21 (2.9)	***180***	***I***
	Contraindicated product administered					22 (1.6)		***22***	***OL***
Total		**873 (0.9)**	**151 (5.9)**	**1748 (2.0)**	**991 (2.5)**	**1342 (1.7)**	**701 (12.3)**	5806 (1.8)	
Number of ADR reports (all types), *n* (%)									
Total		**102 794 (100)**	**2550 (100)**	**88 748 (100)**	**40 246 (100)**	**77 330 (100)**	**5706 (100)**	**317 374 (100)**	

TABLE 3 Preferred Terms (PT) found in the VigiAccess reports involving antimicrobials and suggesting antimicrobial resistance (AMR) or poor effect, linked with corresponding MedDRA codes

System organ class (SOC)	Preferred term (PT)	MedDRA code	Nr reported for the 86 studied AM (%)	Nr reported for the six selected AM[a] (%)	Grouped terms
Infections and infestations	Pathogen resistance	10034133	1327 (8.97)	749 (12.9)	**R**
General disorders and administration site conditions	Drug Resistance	10059866	6659 (45.63)	350 (6.0)	**R**
	Multiple drug resistance	10048723	762 (5.00)	17 (0.3)	**R**
	Drug Ineffective	10013709	778 (5.10)	2707 (46.6)	**I**
	Treatment Failure	10066901	196 (1.29)	238 (4.1)	**I**
	Therapy non-responder	10051082	148 (0.97)	180 (3.1)	**I**
	Therapeutic response decreased	10043414	19 (0.12)	169 (2.9)	**I**
	Decreased activity	10011953	380 (2.49)	101 (1.7)	**I**
	Drug ineffective for unapproved indication	10051118	148 (0.97)	97 (1.7)	**I**
	Drug Effect decreased	10013678	202 (1.32)	88 (1.5)	**I**
	Drug effect incomplete	10013682	1293 (8.48)	40 (0.7)	**I**
	Therapeutic product ineffective	10060769	84 (0.55)	8 (0.1)	**I**
Injury, poisoning, and procedure complications	Off label use	10053762	1455 (9.54)	533 (9.1)	**OL**
	Product use in unapproved indication	10076476	1026 (6.73)	149 (2.6)	**OL**
	Contraindicated product administered	10078504	250 (1.64)	22 (0.4)	**OL**
	Medication error	10027091	27 (0.18)	233 (4.0)	**E**
	Drug prescribing error	10064296	196 (1.29)	125 (2.2)	**E**
TOTAL	-	-	15 250 (100)	5806 (100)	

Abbreviations: AM, antimicrobial; E, "error of use"; I, "ineffectiveness"; OL, "off-label use"; R, "resistance".
[a]Amoxicillin, cefalexin, ciprofloxacin, levofloxacin, clarithromycin and daptomycin.

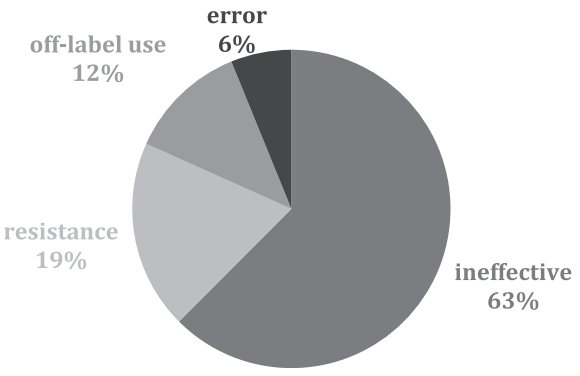

FIGURE 1 Distribution of the 5806 adverse drug reactions (ADRs) suggesting resistance to antimicrobials coded in 17 different preferred terms (PTs) for the six selected antimicrobials in the study (amoxicillin, cefalotin, ciprofloxacin, clarithromycin, levofloxacin and daptomycin). These PTs have been grouped by categories with the following topics: PTs suggesting "ineffectiveness", "resistance", "off-label use" and possible medication "error"

subgroups (ATC 4th level) were Third-generation cephalosporins (16 of 86), followed by Second-generation cephalosporins (13), First-generation cephalosporins (12) and Fluoroquinolones (10).

For the selected 86 antimicrobials, 1.170.751 ADR reports submitted to the UMC and were available for the analysis. 15 250 (1.3%) of the 1.170.751 ADR reports were recorded with AMR-relevant terms that suggested suspicion of resistance, ineffectiveness, or inappropriate use. The AMR-relevant reports were classified under three SOCs: "*infections and infestations*", "*general disorders and administration site conditions*" and "*injury, poisons and procedure complications*". A list of 17 PTs with MedDRA codes (version 21.1) used to code all 15 250 ADRs was established. The following PTs were the most frequently used in these 15 520 reports: "*Drug Ineffective*" ($n = 6959$, 45.6%); "*Off Label Use*" ($n = 1455$, 9.5%), and "*Pathogen Resistance*" ($n = 1327$, 9.0%).

Out of the 86 antimicrobials for which ADR reports were retrieved from *VigiAccess*, 6 agents (amoxicillin, cefalotin, ciprofloxacin, levofloxacin, clarithromycin and daptomycin) were with highest numbers of reports using three most frequent PTs (see Table 2). The 6 agents alone - 2 Access (amoxicillin, cefalotin), 3 Watch (ciprofloxacin, levofloxacin, clarithromycin) and 1 Reserve (daptomycin) were featured in 5806 (38%) of 15 250 AMR-relevant ADRs.

For these specific six agents, the proportion of reports with AMR-relevant PTs compared to the total number of all reported ADRs per drug was as follows: amoxicillin (873/102 794 ADR reports; 0.9%)

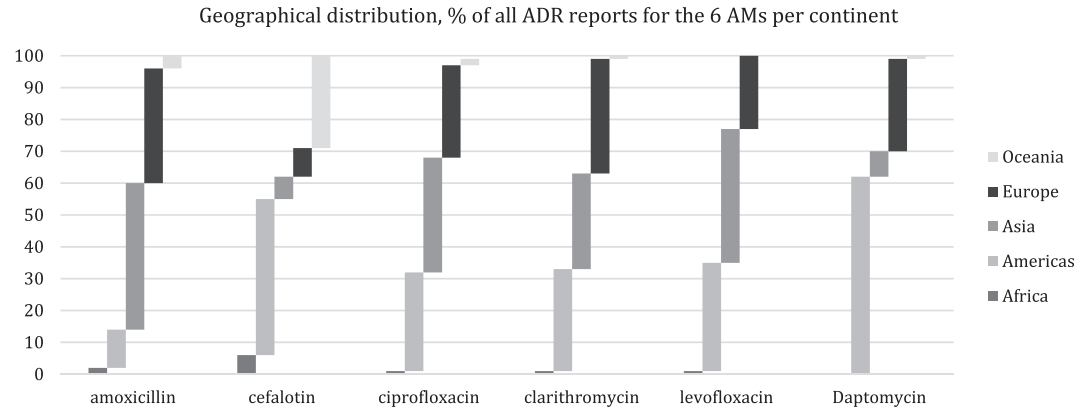

FIGURE 2 Geographical distribution (in %) of all 315 774 ADRs for each of the six selected antimicrobials (amoxicillin, cefalotin, ciprofloxacin, clarithromycin, levofloxacin and daptomycin) according to the continent where the reports were originated. ADR, Adverse Drug Reaction; AM, antimicrobial

and cefalotin (151/2550; 5.9%); ciprofloxacin (1748/88 748; 2.0%), levofloxacin (1342/77 330; 1.7%) and clarithromycin (991/40 246; 2.5%), and daptomycin (701/5706; 12.3%).

Table 3 shows the 17 PTs suggesting suspected resistance or inappropriate use, as well as the three SOCs where they were classified and 17 MedDRA codes they are linked to.

For the six selected AM, 5.806 ADRs were reported using these PTs. Almost half of reports were coded with the term "drug ineffective" (2707 cases; 46.6%), followed by "pathogen resistance" (749; 12.9%) and "off-label use" (533; 9.1%). By grouping these 17 PTs based on their meaning in the AMR context, we noted that almost two thirds (9 of 17) were terms suggesting treatment failure or drug ineffectiveness (3628; 62.5%), followed by three PTs suggesting resistance (1116; 19.2%), three PTs suggesting off-label use (704; 12.1%) and two PTs suggesting errors in prescription (358 reports; 6.2%) (see Figure 1).

Figure 2 shows the distribution of the reports received involving the six studied AM according to the Region in which the report was originated. It should be highlighted that these numbers include all types ADRs for the 6 AMs, not just the 17 PTs. This study did not look at the number of reports with just the 17 PTs, but the low number of reports (all types) from the African region is worth highlighting and should be further investigated.

4 | DISCUSSION

The present study showed that different events suggesting suspicion of resistance to a given antimicrobial have been reported as ADRs through PIDM, using specific codes already included in medical dictionaries.

A sample of 6 agents (2 Access, 3 Watch and 1 Reserve) with a total number of 315 774 of ADR reports had almost 2% of the reports recorded with a PT describing either "ineffectiveness" of the drug, "resistance", "off-label use" or forms of "error" with the medication use. The same 6 (of 86) agents accounted for 38% ($n = 5806$) of all 15 250 reports with AMR-relevant ADRs in a pool of 86 drugs. With these findings in hand, it is possible to suggest the use of the pharmacovigilance network across the 140 PIDM member states (plus 30 associate members), as a useful complementary way to alert on suspected resistance to antimicrobials or their inappropriate use, especially in settings where microbiology laboratories are scarce or inexistent. It is in the same kind of settings where establishing additional surveillance systems could be expensive and difficult and, sometimes, qualified microbiologists for laboratory research are lacking. Both sides could benefit from sharing the pharmacovigilance intelligence and tools. On the one hand, synergies could contribute to pharmacovigilance strengthening and raising awareness among health professionals on unwanted effects of medicines in general. On the other hand, such network, already active even in remote places of LMICs, could be used as a basis for generation of geotagged alerts to the WHO Global Antimicrobial Resistance Surveillance System (GLASS).[21] Reports spontaneously sent to the PIDM for the six selected antimicrobials since the origin of the pharmacovigilance program to December 2018 showed that 17 different terms have been used by reporters, specifying "pathogen resistance" or "drug ineffective" in almost two-thirds of the 5806 cases, or other terms suggesting situations in which the effect of the antimicrobial was not in line with the prescriber's expectation.

4.1 | Resistance, ineffectiveness, off label use and error

If already existing pharmacovigilance programmes are to be promoted as tools to collect information on AMR, the grouping of relevant PTs in these four subcategories - Resistance, Ineffectiveness, Off Label use and Error of Use (or RIOLE) can be suggested and a systematic use can generate important information on suspicion or resistance and/or inappropriate use. Beyond counting "Resistance" (R) reports, the information filled in the reporting formulary could be analysed with other linked details such as the *AWaRe* classification of the suspected drug, co-administered medicines, or indication of use (diagnosed infection). If available, this information adds a more in-depth perspective to the report, from the public health level and the design

of stewardship strategies adapted to the findings in a country or region.

On individual patient level, "Resistance" (R) and "ineffectiveness" (I), whether suspected or confirmed, should trigger a decision to consider another treatment option. "Off Label use" (OL) should be carefully monitored and must be in line with the user guidance as issued by the prescriber or as indicated in the Summary of Product Characteristics. "Error in use" (E) reports could be a reason to investigate and address potential diagnostic problems or misuse of antimicrobials, and in the interest of the patient, action must be taken to avoid serious ADRs because of the error.

On a country level, these PTs can provide rich national information regarding the characteristics of use of antimicrobials in real world conditions. A rise in numbers of reports on "Resistance" (R) and "ineffectiveness" (I) of antimicrobials must be a considered as a warning of potential AMR rise. Stewardship programs could use such information as part of their surveillance plans. ADR reports with PT coded as "Off Label use" (OL) should be carefully analysed, especially when the involved antimicrobials belong to the "Reserve" group. Such data on off label use must be considered when designing tailored interventions to ensure rational use of antimicrobials. "Error in use" (E) reports could be used to address specific issues at the health care workers level, including lack of appropriate training, incomplete or non-clear user guidance, and this is an area where Marketing Authorisation Holders (MAHs) can be involved to ensure completeness and clarity in the promotional information on prescribing and administering any specific antimicrobials.

If the use of the PIDM network is to be promoted as an efficient way to identify potential cases of AMR, it will be necessary to highlight the existence of these PTs and promote their usefulness among potential reporters. Teams working on the AMR surveillance programs will have to include specific guidelines on the pharmacovigilance network sites and how it works in each country, to ensure appropriate on-time reporting. Of course, in countries where reporting by smart phone applications is already in place, specific geographical identification of the reporting place would be an asset.

4.2 | Preserving the "Reserve" list - The daptomycin case

From this initial study based on data from *VigiAccess*, other aspects related AMR should be highlighted, and perhaps one of the most worrying issues is the inappropriate use of "Reserve" antimicrobials, as illustrated by one of the six medicinal products included in our detailed analysis. Daptomycin was marketed in 2004 and by December 2018 a total of 5706 reports had been included in the PIDM database. What should be underscored is that 12% (701) of these reports were coded with PTs suggesting suspicion of resistance or inappropriate use. Among the 701 ADR reports, 143 (20.4%) described events of "off-label use" or "product use in unapproved indication". The existence of these reports suggests that in some PIDM member countries this last resort antimicrobial has been used inappropriately, a signal which should be carefully analysed to design specific intervention campaigns or stewardship programmes to timely prevent a potential resistance to this "Reserve" antibiotic. Additionally, this is another example showing that pharmacovigilance databases could also be useful in alerting on problems of inappropriate use of medicines in general, and serving as evidence generator for policy makers and drug authorities involved in resistance prevention campaigns.

4.3 | Limitations

Our study has some limitations. Pharmacovigilance systems based on spontaneous reporting of suspected ADRs have well known problems of underreporting and incomplete filling of the reporting forms. The same limitations would apply for reports specifically describing any of these 17 PTs.

Another limitation in the differentiation between the suspected drug and the true drug causing an AMR-relevant event. We know that each ADR report has a tag of the main suspected drug, but at the same time VigiAccess does not give access to some crucial details such as, concomitant medication and suspected interacting drugs, seriousness of the event, action taken following suspicion of an ADR. VigiAccess is just a window into VigiBase, providing the number of reports on the suspected event, the involved drug(s), the year of report, the origin (continent) of the report, the year of first and the year of last report. Only the detailed report can give a conclusive assessment on the AMR suspicion of a specific drug, and such details can be obtained via a direct request to a country pharmacovigilance centre. This study focused on the global picture and therefore, was limited to qualitative (which PTs, which antimicrobials) and quantitative (how many reports, in which period) analysis of high-level data accessible via VigiAccess. As we noted the need to carry out a more in-depth analysis on reports content or narrative, we requested access to country safety reports and were informed that "due to the new General Data Protection Regulations (GDPR) rules,[22] the WHO-UMC was no longer providing country level information on reports" and were advised to directly contact the national pharmacovigilance centres. Other limited sets of VigiBase data (e.g., continent level) for specific studies can be provided against an established fee. We have initiated another set of studies focusing on selected countries where access to a more detailed dataset has been given, and the findings will be published as follow up to this work.

5 | CONCLUSION

As an additional tool to track AMR, the pharmacovigilance systems[23] already existing in many countries could play a crucial role in settings where laboratory capacity for causality confirmation is still in its development stages. By using existing PV systems to generate real-time and possibly geo-tagged data on suspected or potential resistance to antimicrobials, PV systems will have an added function on top of their safety signals detection role. By promoting the use of the Pharmacovigilance systems and tools as part of the AMR surveys, could also raise awareness among reporters aware of the ADRs

caused by other medicines, for example those listed as concomitant while they may be the primary cause of the suspected ADR. Promoting of the well-established Pharmacovigilance network will strengthen the capacity of PIDM members with a less active collection and sharing of ADR reports. However, to confirm or solidify our hypothesis, further studies are necessary to look at what is in the report, to ensure there is possibility to conclude whether the primary suspected ADR is attributable to the antimicrobial or not, because an ADR report contains information of different medicinal products and comorbities. The list of 17 PTs has been proposed based on the sample of 86 drugs for which reports were searched, but further studies to extend or shorten the list are still required. In addition, further research focusing on the narrative and other clinical details in the ADR reports is required. Currently, we are carrying out a more in-depth analysis using country-specific data from national pharmacovigilance centers of two different countries, one in Africa and another in Europe. Through this in-depth analysis, we are pulling out key details that may be relevant to antimicrobial stewardship discussion, including demographics of patients, concomitant medication, suspected interacting drug, reported comorbities, seriousness of the reported events and types of reporters bringing the information from the antimicrobial user to the databases. We encourage the AMR research community to explore data collected by the Pharmacovigilance community, through the 17 MedDRA codes or PTs, but also welcome suggestions on any other code or PT that may be relevant to AMR.

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CONFLICTS OF INTEREST

Authors have no conflicts to declare.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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ANNEX 3 – Full Copy published Article 1 "Antimicrobial stewardship: can we add pharmacovigilance networks to the toolbox?"

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POINT OF VIEW

Antimicrobial stewardship: can we add pharmacovigilance networks to the toolbox?

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Abstract

Background Antimicrobial resistance (AMR) is no longer an expected upcoming threat; it has become a real public health concern, challenging all existing control tools, requiring multidisciplinary innovative solutions. Antimicrobial stewardship (AMS) programs require a set of tools and skills which can be put to service by health systems. However, there is an immense capacity gap between health systems in developed countries compared to developing ones. Systems in developed countries can rely on well-established laboratory services that can carry out microbial cultures and drug susceptibility tests. For many low- and middle-income countries (LMICs) with limited laboratory resources, it will take time and long-term investments to have systems that can timely and reliably perform laboratory-based AMR monitoring. In the meantime, we must explore the possibility of using other indirect measures that can provide estimates of the growing burden of AMR in settings with weak laboratory capacity.

Objectives In this point of view, we describe the potential contribution of the global pharmacovigilance (PV) networkers in the process of mapping and estimating the AMR burden in settings with less laboratory coverage and capacity, within the framework of AMS.

Conclusion The heavy toll caused by AMR will not be brought down by a singular interventional approach, it will require a multidisciplinary and multifaceted set of strategies. Closing the laboratory capacity gap will require tremendous long-term investments, but the AMR data scarcity is a question that cannot wait any longer. The global pharmacovigilance network is a robust scientific community with experience in tracking suspected adverse events caused by new and old medicinal products. As AMR becomes a global health issue, AMS programs need all available tools to address resistance data scarcity and inform appropriate of antimicrobials. The solid global pharmacovigilance infrastructure could play an important role in countries with limited laboratory coverage and capacity.

Keywords Antimicrobial resistance · Pharmacovigilance · Antimicrobial stewardship · Antimicrobial surveillance · spontaneous reporting

Introduction

Antimicrobial resistance (AMR) is no longer an expected upcoming threat; it has become a real public health concern, challenging all existing control tools, requiring multidisciplinary innovative solutions. Today, AMR is a reality in every corner of the globe, both in developed and developing regions. Antimicrobial stewardship (AMS), the process of planning and managing the use of antimicrobials, requires a lot of tools and skills that are offered by science. These tools and skills can be made available and put to service by health systems. The problem lies in the immense capacity gap between health systems in different countries and regions. Systems in developed countries can rely on the well-established laboratory services that can carry out microbial cultures and drug susceptibility tests. But, for many low- and middle-income countries (LMICs) with limited laboratory resources, it will take time and long-term investments to have systems that can timely and reliably perform laboratory-based AMR monitoring activities, which play a crucial role in AMS programmes. In the meantime, we must explore the possibility of using other

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indirect measures that can provide estimates of the growing burden of AMR in settings where laboratory capacity is weak or absent. The heavy toll caused by AMR will not be brought down by a singular interventional approach; it will require a multidisciplinary and multifaceted set of strategies.

This paper aims at describing the potential contribution of global network of pharmacovigilance (PV) centres and databases in the process of mapping and estimating the AMR burden in settings with less laboratory coverage and capacity, within the framework of AMS.

How big is the AMR data scarcity problem?

Antimicrobial resistance: a crisis we saw coming

The global health research community was warned on AMR for the first time by the very person who discovered penicillin. In his 1945 Nobel Lecture [1], Fleming warned that there may be a danger in underdosage as it was then clear that microbes became resistant to penicillin when exposed to concentrations that were not high enough to kill them. After penicillin, many more antibiotics of different spectra were developed and commercialised. Exposed to various natural conditions and medicinal products in varying doses, pathogens have progressively become resistant to our best remedies against deadly infections. It is generally acknowledged that one of the most important causes of mutations and acquisition of resistance is the inaccurate prescription and use of antibiotics.

AMR data scarcity—a capacity gap issue

Many years after Fleming's 1945 Lecture, further in the twenty-first century, we have problems with understanding how big the problem is. We all know it is here with us, but we lack reliable data from many parts of the world. In the Review [2] on AMR, chaired by Jim O'Neil and published in 2014, there is a troubling statement about scarcity of reliable estimates of the true burden of the damaging effects of AMR. The authors gave estimates of at least 50,000 lives claimed each year across Europe and the USA alone, and many hundreds of thousands more dying "in other areas of the world". The unavailability of burden estimates for what is called "other areas of the world" is troubling. The authors say that many hundreds of thousands were dying; such estimates seem to be within very large intervals due to unavailability of reliable data, one must think. In an ideal world, resistance to an antimicrobial should be confirmed by laboratory susceptibility tests conducted in accordance with clear international standards [3, 4].

In practice, we know that the capacity and skills to carry out susceptibility test differ from country to country and can even vary within one country. The required capacity and skills for such tests are limited in LMICs [5]. In many resource-limited settings, there are regional pockets of remote places where access to healthcare is much more limited. These remote places are less covered by nationally implemented programmes such vaccination campaigns, or mass drug administration campaigns. Resource-limited settings have limited access to laboratory diagnosis services, limited access to quality-assured medicinal products and consequently very limited coverage by both passive and active health data collection programmes.

In their presentation of a project that aimed at measuring and mapping the global burden of AMR, Hay et al. [6] touch upon the issue of scarcity of data from LMICs. The authors have stated that major gaps in data on prevalence and incidence as well as on types of resistance, treatment failures and studies on the attributable mortality and morbidity of AMR, particularly in LMICs, have made it nearly impossible to reliably estimate the global impact of AMR.

Prescribing antimicrobials: evidence-based or empiric trial-and-error?

Beyond the enormous use of antimicrobials in livestock, which is another urgent global health challenge, the review by Jim O'Neill puts an accent on the role of (inappropriate) prescribing practices and over-the-counter (OTC) medication in facilitating the misuse of antimicrobials, contributing to the development of resistance over time. In a paper on the pivotal role of Pharmacovigilance Programme of India in containment of AMR, Agrawal V et al. [7] reported on ADRs caused by OTC medication. Their findings confirmed that more than 40% of adverse drug reactions (ADRs) were associated with antibiotics sold to patients without any prescription.

What can pharmacovigilance offer?

The first question to answer is what AMR and AMS have to do with pharmacovigilance. In 2017, the Uppsala Monitoring Centre (UMC) published a report [8] in which authors agreed that AMR is an overlooked adverse event. Explaining the role of pharmacovigilance in suspected AMR identification, the report distinguished two major public health issues which can be indicated by a disproportionally greater reporting on antimicrobial treatment failure: *resistance* and/or *poor-quality medicines*. Resistance cases are reported as part of safety data, and in the context of AMR, reporting terms such as "pathogen resistance" or "treatment failure" carry a very important message. Therefore, it is at least worth exploring the terminology used in drug safety reporting and understanding the relevance of PV data to AMS activities. In the absence of laboratory-confirmed safety issues or resistance, the strength of pharmacovigilance lies in its capacity to generate large

amounts of data on suspected events, providing a pool for generation of important signals

The global pharmacovigilance network—a solid infrastructure

Created in 1968, the WHO Programme for International Drug Monitoring (PIDM) has become a network of 170 countries [9] (in 2020: 140 full and 30 associate members) that collaborate to monitor and identify the harm caused by medicinal products, to reduce the risks for patients. Through their national pharmacovigilance centres, these countries form a worldwide network of drug safety surveillance systems that use the same standards, for reporting, analysing and sharing safety data [10]. What makes this network a solid infrastructure is its presence in most countries (including LMICs) and the benefits for participating countries [11]. Key participants benefits include (1) *access to the largest medicine safety database—VigiBase* [12]; (2) *early information about potential safety hazards*; (3) *access to tools for reporting, storing, structuring, searching and analysing Individual Case Safety Reports (ICSRs)*; (4) *getting support, training on pharmacovigilance practice and tools*; *and* (5) *access to the international network with knowledge and expertise from other member countries.*

A skilled global workforce safeguarding drug safety

Pharmacovigilance stakeholders such as clinical pharmacologists and pharmacists are closer to the patient than to the laboratory; they have a close eye towards the patient and see how s/he is responding or not responding to a treatment. In the whole PV process, the most important stakeholder is the patient of course, and next to the patient is a reporter who observes and captures the adverse event information. Only after the reporter has transmitted that safety concern report, the pharmacologist and/or pharmacist who carry out the analysis and causality assessment will be able include the information in databases, enabling further inclusion on in risk communication messages fed back to health professionals and authorities. The global pharmacovigilance networks provide a platform for a systematic collection of data on drug adverse events and reactions, including those suspected to be related to antimicrobial ineffectiveness. The available resources, human and systems, engaged in the global pharmacovigilance activities of drug safety monitoring, constitute a skillful workforce that can be tasked to monitor and generate data on suspected antimicrobial resistance.

Individual case safety report—more than just a report

Individual case safety reports (ICSRs) are submitted to a pharmacovigilance centre at national level and shared further to the global pharmacovigilance community through the UMC database. Key features of such report include details that carry essential information on drug(s) and suspected adverse reaction(s). An ICSR also includes information on the indication, the drug suspected to cause an adverse event, the co-administered drugs, the potentially interacting drugs, the affected System Organ Class (SOC), the Preferred Term (PT) which describes the reported ADR using an internationally agreed code. An ICSR carries information on the patient such as age, gender, comorbidities, outcome (e.g. prolonged hospitalisation, deaths) and actions taken (e.g. drug withdrawal, switch). The strength lies really in the aggregated data from millions of ICSRs.

A broader use of safety reporting codes and terms

The Medical Dictionary for Regulatory Activities (MedDRA) codes have been widely adopted by pharmacovigilance professionals and can serve the AMS programmes if used well in conjunction with other stewardship methods. These codes do not need to be reinvented or changed; the signal detection methods are well polished to capture safety issues on medicinal products, including antimicrobials. Key relevant codes must be carefully selected and used to design systems that can target specific products in specific geographical areas. Codes linked to terms such as "pathogen resistance", "treatment failure" or "off-label use" have the potential to provide valuable data on AMR burden or risks. If an antimicrobial is mentioned in an ICSR as a suspected, co-administered or one of the potentially interacting drugs, the safety reporting code or term should be used to used to send an alert and start of a tracking process.

Putting novel communication technologies to work

The use of novel communication tools and technologies can drive faster and better data collection from settings that have traditionally been left out of existing heath data collection programmes. Geo-tagging technologies should be explored and used to ensure the real-time localisation component is integrated in the surveillance programmes. Of course, careful data protection and privacy concerns should be a priority both at conception, development and use of surveillance tools.

Conclusion

Closing the laboratory capacity gap will require tremendous investments, but the AMR data scarcity is a question that cannot wait any longer. Complementarity between disciplines should be explored to make sure we are confident in our mapping of the global AMR burden, including estimates from less medically equipped corners of the globe, which should not be left behind by AMS programmes.

The Pharmacovigilance worldwide network has well-established tools to collect data on suspected antimicrobial treatment failure in places where laboratory confirmation is impossible. More work should be done to advocate for the usefulness of MedDRA terms suggesting suspected cases of resistance, to make use of the pharmacovigilance network which could prove to be an outstanding tool for this public health challenge. Thus, pharmacovigilance could become a part of the antimicrobial stewardship programmes through the collaboration of sensitized reporters (medical and non-medical stakeholders involved in drug safety).

Additionally, databases on drug safety have specific terms and codes for capturing inappropriate prescribing practices or misuse of medicinal products. Such databases constitute a unique resource of information on potential misuse of medicines, which in the case of antimicrobials should be systematically monitored as part of AMS programmes. Amounts of antimicrobials taken without prescription are in many places unknown and very difficult to estimate. By collecting data on ADRs caused by antimicrobials taken without prescription, inappropriate use can be timely addressed.

The global pharmacovigilance network is a robust scientific community with experience in tracking suspected adverse events caused by new and old medicinal products. As AMR becomes a global health issue and AMS programs need all the available tools to ensure the best use of antimicrobials, let us add pharmacovigilance networks to the toolbox, especially for communities with limited laboratory coverage and capacity. We must address antimicrobial resistance as a safety issue because it is a safety issue.

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