European Journal of Clinical Pharmacology (2021) 77:787–790
https://doi.org/10.1007/s00228-020-03035-3

POINT OF VIEW

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

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Received: 10 September 2020 / Accepted: 30 October 2020 / Published online: 16 November 2020
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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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