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Maribel Salas, Maribel Salas, Luciane Cruz Lopes, Brian Godman ...+25 more authors

Institutions: University of Pennsylvania, Daiichi Sankyo, Strathclyde Institute of Pharmacy and Biomedical Sciences, Sefako Makgatho Health Sciences University ...+16 more institutions

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Challenges Facing Drug Utilization Research in the Latin American region

Maribel Sales, Daiichi Sankyo Inc, USA, and University of Pennsylvania USA; Luciane Lopes, University of Sorocaba, Brazil; Brian Godman, Karolinska Institute, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK; Ilse Truter, Nelson Mandela University, Port Elizabeth, South Africa; Abraham Hartzema, University of Florida, Florida, USA; Bjorn Wettermark, Karolinska Institute, Stockholm, Sweden; Joseph Fadare, Ekiti State University, Nigeria; Johanita Burger, North West University, South Africa; Kwame Appenteng, Astellas Pharmaceuticals US Inc, USA; Macarius Donneyong, Ohio State University, USA; Ariel Arias, Health Canada, Canada; Daniel Ankrah, Korle Bu Teaching Hospital, Accra, Ghana; Olayinka Ogunleye, Lagos State University College of Medicine, Lagos, Nigeria; Martha Lubbe, North West University, South Africa; Laura Horne, Daiichi Sankyo Inc, USA; Jorgelina Bernet, National University of Colorado, USA; Diana Gomez-Galicia, Autonomous National University of Mexico, Mexico; Miriam Estrada Garcia, University of San Carlos of Guatemala, Guatemala; Margaret Oluka, University of Nairobi, Nairobi, Kenya; Amos Massele, University of Botswana, Botswana; Luis Alesso, University of Cordoba, Cordoba, Spain; Raquel Herrera Comoglio, University of Cordoba, Cordoba, Spain; Elisangela da Cost Lima, Federal University of Rio de Janeiro, Brazil; Carmen Vilaseca, College of Biochemistry and Pharmacy; Ulf Bergman, Karolinska Institute, Sweden

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Key Messages

1. Drug utilization research (DUR) has advanced considerably in developed countries. However, the advance in the Latin America has been slow, which might be associated with fewer resources dedicated to DUR, fragmented or not fully integrated healthcare systems with limited access to electronic health records, registries and computerized decision-support systems.
2. The availability of national data on DU in most countries of the Latin American region is scarce and fragmented and as consequence, decision-makers often have limited qualitative or quantitative information on drug consumption and use to make informed decisions, develop drug policies, establish educational programs or evaluate interventions.
3. In some Latin America countries, decision-makers may be unaware of the importance of DU data in the decision-making process, which has a negative impact not only on the distribution of resources but also on the development of DUR.
4. The limited information of DUR from the Latin America region indicates an increased in the use of medicines overall as well as inappropriate prescribing, dispensing and misuse of medicines leading to medication errors and antimicrobial resistance, polypharmacy, self-medication among others, which is attributed to multiple factors including increased

life expectancy with the consequence of aging of the population, epidemiologic transition from infectious diseases to chronic diseases and increased medicalization of society.

5. The available information for DUR also pointed out some issues particularly those related to validity of information and data collection instruments, insufficient data on medication consumption from the public healthcare sector, fewer quantitative DU studies, lack of studies of some population such as pregnant women, pediatric population or other, or to consumers of a particular healthcare service, and limited focus for future DU interventions to patients with no involvement of health care provider.

Abstract

This document represents an initiative of the International Society of Pharmacoepidemiology (ISPE) in collaboration with the Latin American Drug Utilization Research Group (LatAm-DURG), the Medicines Utilization Research in Africa (MURIA) group, and the Uppsala Monitoring Center, to identify the main challenges associated with drug utilization research (DUR) in the LatAm and African regions. Furthermore, some solutions to overcome those challenges are proposed to accelerate the development of DUR in these regions. As result of this initiative, four separate manuscripts will present the results focused on: 1) challenges facing DUR in the LatAm region; 2) challenges facing DUR in Africa; 3) potential solutions to overcome these challenges, and 4) guidance for researchers interested in carrying out DUR in these regions. This is the first manuscript, and it is related to the challenges identified in the drug utilization research area in the LatAm region. DU researchers in LatAm voluntarily participated in multiple discussions, contributed with local data and reviewed successive drafts and the final document.

Introduction

Drug Utilization Research: Definitions, Value and Regional Challenges

The World Health Organization (WHO) (1977) defined drug utilization (DU) as the “marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social, and economic consequences” [1, 2]. This definition has evolved to emphasize the importance of qualitative studies, analytical observational research and interventions to improve the process of using medicines in society [1], and according to the European Drug Utilization Group (EuroDURG), DU is an “eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes” [3, 4].

Drug utilization research (DUR) provides valuable information about the use of medicines among populations [5], which can offer insights into the effectiveness, efficiency and safety of medicines use [6, 7, 8, 9, 10, 11], help to set priorities for the rational allocation of healthcare budgets [12],

and examine the impact of pharmaceutical policies, including policies to reduce self-purchasing of medicines (the purchase of medications outside the legal distribution channels) where pertinent [13, 14, 15]. Further, DUR forms the cornerstone of pharmaceutical policies promoting equitable access to, and the rational use¹ of medicines across populations [3, 16]. DUR is an essential part of pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure [1], which can be associated with outcomes. For instance, results of a recent database study in the Brazilian general population described the use of cyclosporine or tacrolimus among patients who underwent kidney transplantation between January 1, 2000, and December 31, 2009, suggesting greater effectiveness for cyclosporin versus tacrolimus for continued survival of kidney grafts [17]. DUR may also provide a proxy of denominators in pharmacovigilance [3], as in the Gattas' study where the Instituto Butantan in Brazil used doses of triple influenza vaccine as denominator to estimate the incidence rates of adverse events following immunization [18].

Despite many advances in DUR methodologies, moving from merely descriptive studies to analytic studies with the inclusion of quality indicators, and lately drug use as indicators of the quality of the healthcare system, in some regions, such as Latin America (LatAm), these advances have been slow [19, 20, 21]. This region faces particular challenges because of fewer resources, and/or fragmented or not fully integrated healthcare systems with limited access to electronic health records, registries and computerized decision-support systems.

Consequently, national data on DU are scarce and fragmented in the LatAm region. Decision-makers often have limited qualitative or quantitative information on drug consumption and use to make informed decisions, develop drug policies, establish educational programs or evaluate interventions [22, 23, 24, 25]. Probably more critical is the fact that in some LatAm countries decision-makers may be unaware of the importance of DU data in the decision-making process [26, 27]. Multiple groups have been formed to improve DUR around the world including the Latin American Drug Utilization Research Group (LatAm-DURG) [28], the Medicines Utilisation Research in Africa (MURIA) group [29], The Uppsala Monitoring Center [30], and the WHO through different WHO Collaborative Centers such as the WHO Collaborating Centre of Pharmacovigilance, the WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, and the Pan American Health Organization (PAHO) [31].

This document represents an initiative of the International Society of Pharmacoepidemiology (ISPE) in collaboration with the LatAm-DURG, the MURIA group from Africa, and the Uppsala Monitoring Center, to address current concerns; and it reflects the efforts to accelerate the

¹ According to the WHO "Medicine use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community. Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions is not met." [16].

development of DUR in the LatAm region. Contributors to this project, some of whom are DU researchers in LatAm, voluntarily participated in multiple discussions, contributed with local data and reviewed successive drafts and the final document.

Findings from this project will be presented in four separate manuscripts, focusing on: 1) challenges facing DUR in the LatAm region; 2) challenges facing DUR in Africa; 3) potential solutions to overcome these challenges, and 4) guidance for researchers interested in carrying out DUR in these regions.

The Latin American Region

Population

The LatAm region is a diverse and densely populated region with nearly 646 million people, representing 9% of the global population in 2017 [32, 33]. Approximately a quarter of the population are children under 15 years of age, and 17% are young people aged between 15-29 years [1]. The overall life expectancy is approximately 75 years, and the proportion of the population aged 60 years and above is expected to double in the next three decades (from 12% in 2017 to 25% in 2050) [32, 34].

The LatAm region comprises 41 countries varying in size from <100,000 inhabitants to >190 million inhabitants. It is worth noting that Brazil and Mexico are among the ten largest countries in the world [32, 34]. In the LatAm region, there are high levels of socioeconomic inequality, hosting 10 of the world's 15 countries with the largest gap between low- and high-income citizens [35, 36, 37]. The LatAm region is considered a net² sender of international migrants to developed countries particularly the United States [34], and migration from country to country within the region [31], which might impact DU studies in places with high migration rates.

In the LatAm region, there are more than 800 different indigenous groups primarily concentrated in Bolivia, Guatemala, Peru, Ecuador and Mexico. Compared to the non-indigenous populations, these indigenous populations generally have a low literacy level, low socioeconomic status with high overall morbidity and mortality, particularly infant mortality and maternal mortality, and a higher incidence of infectious diseases. This has resulted in high health-care needs, particularly access to medications [38].

Access to education also remains a challenge in the LatAm region with important regional differences, and in some countries only 35% of young men and women are attending school [39]. In 2017, approximately 184 million people (30.2% of the population) in the LatAm and Caribbean

² Difference between the number of immigrants and the number of emigrants for a given country or group of countries [32].

regions lived below the poverty line, almost 62 million of whom lived in extreme poverty [32, 40]. The main spoken language in the LatAm region is Spanish followed by Portuguese, French and multiple native languages, factors that are important to consider in DUR, particularly in the design of surveys, educational programs or patient-focused interventions.

Socioeconomic Situation

The economic instability produced by financial crises and natural disasters in the LatAm region have hindered the progress of the region [41]. In some countries in the region, social and political instability affects both access to medical care and medicines as well as the use of medicines. Crime, violence, human and drug trafficking, possession of illegal drugs, substandard and counterfeit medicines might influence how people are using their medicines [42]. It is estimated that one quarter of the 600,000 global homicides occur in LatAm [43] with wide variation among countries [44]. Homicides in Central and South America are frequently linked to violence and organized criminal groups, which depends on the availability of weapons, use of psychoactive substances and/or alcohol consumption, factors that will also impact the use of medicines including drug-drug interactions [45]. Furthermore, there are high rates of injuries in the young population, being the leading cause of death among young and middle-aged men (15-59 years of age) [46]. Social inequality, unemployment, urban segregation, illicit drugs and alcohol use are factors associated with high violence in the region [47].

Health and Healthcare

In the LatAm region, there is also an epidemiological transition from communicable diseases to non-communicable diseases with wide variation among countries. Some LatAm countries have a high predominance of non-communicable diseases while others have a predominance of communicable diseases [48, 49]. This explains the heterogeneous mortality trends in the region, where the double burden of communicable and non-communicable diseases is common with significant impact on the healthcare system [50, 51]. Among communicable diseases, the most frequent diseases include cholera, vector-borne diseases (malaria, dengue, Zika, and chikungunya), neglected infectious diseases, vaccine-preventable diseases, communicable chronic diseases such as tuberculosis and leprosy, sexually transmitted diseases, and zoonoses such as rabies and leptospirosis [49]. In terms of chronic diseases, the most frequent diseases include cardiovascular diseases, diabetes, malignant neoplasms, and respiratory diseases, which cause four out of five deaths in the region [50, 52]. Those chronic diseases are increasing because of the aging of the population, health behaviours influenced by globalization, with a subsequent increase in obesity and physical inactivity [53].

In terms of healthcare, most healthcare systems in the LatAm region are fragmented in their provision of services, an important factor in the estimation of national coverage. This also limits

the collection of accurate information on the distribution and access to medicines [54]. Furthermore, not all populations have medical coverage especially the poorest people, those with geographical isolation, unemployed or with low education (social exclusion) [55]. To reduce inequalities in access to health services and outcomes, some LatAm countries have begun social sector reforms of their health systems focusing on expansion of universal health coverage [56]. For example, in Brazil [57], Costa Rica, and Mexico, the expansion of universal financial coverage of healthcare services, including medications, reduced catastrophic health expenditures among the poor [58, 59, 60]. It is estimated that the average expenditures for medicines represent approximately 35% of total health costs [54, 55], which can be increased up to 60% [3], and might be even higher among the non-insured population. This percentage of total health expenditure is almost two-fold higher than for instance in Canada (16%) [61] and in high-income countries (19.7%) [62].

Most countries from the LatAm region have two formal sectors, private and public [63], and an informal sector for the distribution of pharmaceuticals. The informal sector is an unregulated establishment with vendors operating without a license to sell medicines and, in rural areas the informal sector might be the prominent sector for the distribution of medicines. The private sector is licensed to dispense and/or commercialize medicines independent of government programs. The private sector usually has available consumption data collected by private market research organizations, such as IQVIA™ (previously known as QuintilesIMS). The public sector includes institutions under the direct control of the national health agencies (e.g. Ministry of Health), other governmental institutions, or faith-based organizations. The public sector has limited available data for DUR, and usually restricts the use of such data. In some countries like Mexico, the social security system collects data for internal purposes, with no access granted to researchers outside the institution. In Brazil, there is access to research institutions for drug utilisation data to help with DU research including burden of illness studies as well as effectiveness studies [6, 64, 65, 66, 67]. In addition, drug-related policies within a country often change from one government to the next one, and among agencies within the same country. Patients may procure medicines from one, two, all three or none of the sectors depending on the agency policies, their employment status or socioeconomic status, the availability of medicines in public pharmacies, distance to the healthcare facility and agreements between a public institution and private pharmacies [55, 68]. This situation represents a challenge when a researcher is interested in evaluating the use of medicines particularly for DU studies over time and among institutions even within the same country. This means that DU data on a single patient may not always be complete.

Counterfeit and substandard medicines

One important issue in the LatAm region is the trade of substandard and counterfeit medicines, which are medicines deliberately and fraudulently mislabelled with respect to their identity and/or source and might include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients [69]. Counterfeiting of medicines has increased substantially in developing countries where the primary targets are

antimicrobials commonly used in the treatment of life-threatening conditions such as malaria, tuberculosis (TB) and HIV/AIDS [70]. According to the Center for Medicine of the Public Interest in the United States of America, the worldwide sales of counterfeit medicines was around US\$ 75 billion in 2010 [71]. The counterfeit drugs market is a well-organized market that according to the WHO represents approximately 25% of the medicines consumed in developing countries [72, 73], probably because of the costs of legitimate medicines, the existence of high patient co-payments and weak legal controls [71]. Improved access programmes are starting in some countries to make quality medicines affordable to improve care especially in patients with chronic diseases, and this practice may grow.

Counterfeit medicine use is identified as one of the major causes of treatment failures and may lead to serious adverse events resulting in excessive mortality and morbidity; and it is a contributor in the development of drug resistant organisms [68]. Various factors have been associated with the increase of counterfeited medicines in developing countries include poverty, high cost of quality medicines, lack of an official supply chain, legislative lacunae, easy accessibility to computerised printing technology, ineffective law enforcement, and light penalties [74]. As response measures to the issue of counterfeiting, some Latin American governments have implemented new laws and regulatory systems aiming at data collection, raising awareness controlling medicines importation and exportation as well as regulating the circulation of ingredients and goods for making drugs [71]. In addition, the new regulations include the coordination of special programs among various stakeholders to monitor the quality of regulated products and services. Additional measures include stricter control of movement of goods at ports, airports and borders, to ensure the sanitary control of facilities, services and means of transportation, products' import and the protection of travelers' health. In the case of Brazil, products regulated by ANVISA (regulatory authority of Brazil) are subjected to authorizations at borders when entering Brazil and might be subjected to physical inspection. Some classes of medicines may require authorizations prior to their embarkation in the exporting country [75]. A recent study in Brazil found that most counterfeiting products were medicines for erectile dysfunction, and authors recommended that ANVISA train health professionals to identify fake medications, to include methods of traceability of medicines from the manufacturer to distribution and sale points. Further, if smuggled and unregistered medicines are sold at free fairs and clandestine drugstores, health authorities should have the infrastructure to identify them and release alerts quickly [76].

The lack of or insufficient number of quality control centers is a contributing problem in the LatAm region. Various studies have identified substandard local manufacturing quality or inadequate transportation and storage conditions in the supply chain, or both [77, 78]. However, there are now some initiatives trying to quantify drug quality problems in the LatAm region such as the South American Infectious Disease Initiative (“Iniciativa de Enfermedades Infecciosas en América del Sur”) in Peru [79] or to improve the quality of medicines such as the Amazon Malaria Initiative. The South American Infectious Disease Initiative reported that 25% of 62 analyzed medicines did

not reach the approved specifications and 3% of medicines had critical failures. As a consequence, a collaborative effort between some LatAm countries and the USP “Promoting the Quality of Medicine’s (PQM)”, resulted in the creation of the database “Medicines Quality Database (MQDB)” which houses data related to substandard and counterfeit medicines circulating in the LatAm and Caribbean region [80, 81]. Hopefully, this will help to reduce the problem in the future.

Drug Utilization in LatAm

Despite limited DUR in the LatAm region, available studies suggest an increased use of medicines overall as well as inappropriate use of medicines leading to medication errors and antimicrobial resistance. However, study design limitations with the existing DUR limit the possibility of generalization and brings to question the validity of the DU data [3, 82, 83, 84]. The overall use of medicines in the LatAm region accounts for up to 60% of total healthcare spending in some LatAm countries [3]. In May 2012, there was an estimated market size of approximately \$66 billion dollars and rising in the LatAm region [80]. The increase in the use of medicines is attributed to various factors including increased life expectancy with the consequence of aging of the population, epidemiologic transition from infectious diseases to chronic diseases and increased medicalization of society.

Despite this increase in the use of medicines, available DU data remain scarce and fragmented across the region [3], and data quality varies among studies. This result in limited monitoring of medication use and comparison across countries and ultimately hamper the rational use of medications [3, 26]. Drug utilization researchers should identify and acknowledge the strengths and weaknesses of the sources of information. For example, if the Intercontinental Marketing Services (IMS) Health data are used, the investigator should clearly convey in the presentation of study results that the analyzed data covered only the private sector. Since IMS Health collects data mainly from wholesalers, it means that the information is related to medicines sold in the medicine supply system but not necessarily to the medicines used by patients. Interestingly, studies using IMS data in some countries are often not conducted by local researchers [85, 86]. Other sources of data may include community and hospital pharmacies, prescribers and electronic medical records and do also require critical analysis to determine the representativeness of the population covered and the characteristics of the target population.

The lack of local data has forced decision-makers to extrapolate information from studies conducted in other countries and different cultural contexts, which represents a challenge in the interpretation of results for policy interventions in LatAm countries [87, 88, 89]. Although, there are some tools for drug policy-making and drug education programs, such as the information on DU standards that has pointed out gaps between research, therapeutic practice and population health needs, its use by decision-makers remains limited [90]. However, this is likely to change as the number of DU studies in LatAm countries grow.

Although there are limited studies of DUR available in LatAm, those available studies have identified issues in relation to inappropriate prescribing, inappropriate dispensing and misuse of medicines, polypharmacy, self-medication [91], quality of medicine use [3, 92, 93, 94, 95, 96, 97, 98, 99, 100], antimicrobial resistance [101, 102, 103, 104, 105] and poor patient adherence [106]. For example, a population-based cross-sectional study in 1,254 individuals aged 60 years or older from Brazil found 28% of medicines potentially inappropriately used [107]. In Colombia, a study of medication errors using outpatient pharmacy services and national medication dispensing from Jan 2005 to Sep 2013 found a total of 14,873 medication errors where ~16% reached the patient and 0.7% caused harm. Those errors occurred mainly in the administration, dispensing, transcription and interpretation of prescriptions [108]. In Mexico, a study determining the frequency of potential drug-drug and drug-disease interactions among 624 ambulatory patients over 50 years of age with non-malignant pain syndrome, showed that patients received was an average of 5.9 +/- 2.5 prescribed medicines. About 80% of the patients had prescriptions implying one or more potential drug-drug interactions [109]. As mentioned, drug utilization studies in Brazil have questioned the continued preference of tacrolimus over cyclosporin to prevent rejections in kidney transplant patients as well as endorsed the limited use of less effective beta-interferon preparations for the treatment of multiple sclerosis [17, 110].

A literature review to identify methodological issues with DUR in LatAm found that only two systematic reviews of DU studies have been performed in these areas. The most frequent issues identified included: i) scarce number of DUR studies comparing cross-nationally data; ii) validity issues, particularly extrapolation bias, iii) insufficient availability of data on drug consumption from the public healthcare sector [92], iv) limited information on qualitative studies, v) lack of validation of data and/or data collection instruments, vi) studies of specific target population such as pregnant women, pediatric population or other, or to consumers of a particular healthcare service, and vii) limited focus for future DU interventions to patients with no involvement of health care providers [111]. These issues need to be addressed to enhance the use of DU studies especially policy and other studies to enhance the rational use of medicines in LatAm countries.

Specific challenges facing DUR in LatAm

The socioeconomic inequality throughout LatAm is one of the main challenges potentially impacting on DU studies in the region, as it impacts access to care in the region. As mentioned, there is a large income gap between the rich and poor, disparities of social determinants of health, and differences in the quality of public and private health sectors. Access to medical care is also an issue even in those countries with one payer system. As consequence, some patient groups are using litigation as a way to get access to healthcare services and medicines in the LatAm region [112]. Universal healthcare systems cannot guarantee that patients will receive all needed services, and in most cases, the right to healthcare is restricted to the provision of medical and hospital services [113]. Furthermore, the complexity in the provision of services has obligated some citizens to use judicial processes [114], to demand the “right of health” [113, 115, 116, 117, 118,

119, 120, 121], which has been reflected in the creation of training programs targeting judges and courts in Brazil, Argentina and Costa Rica [122].

Although some governments from the LatAm region have created programs to improve access to health services and to narrow the gap between the rich and the poor, inequalities still exist [21], particularly inequitable financing in the region [58]. Some countries such as Colombia and Mexico have used interventions to control the regulation of the healthcare market, the costs of provision, and the standardization and updating of health services plans, which includes updated interventions [122, 123,124,125]. These are important factors to consider when planning a DUR in LatAm countries.

Another important challenge for this region is the organisation of healthcare systems and the extent of healthcare data available to help governments in the identification of emerging health needs coming from social and demographic transitions, or from outbreaks of emerging pathogens. This challenge has been recognized by international organizations such as the WHO particularly with the increase of antimicrobial resistance [126, 127], and some programs to increase microbial surveillance and antimicrobial resistance have been initiated in the LatAm region [126, 128].

Although 26 Latin American countries have adopted the essential drug list (a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions published by the WHO [129, 130], which is frequently used by countries to help develop their own local lists of essential medicines, only a few countries update their essential drug list every two years [131]. In Brazil, the list of essential drugs has been reported to include discrepancies between the WHO recommendations and the drugs included in the Brazilian National Relation of Essential Medicines [132, 133, 134, 135, 136, 137], as well as, that there is low availability of essential medicines in public health units [138]. Because the list is not even in use in most LatAm countries, investigators are encouraged to verify if the essential drug list is up to date and to validate the list prior to implementing any DUR studies.

In relation to scientific information from DUR, the LatAm region faces particular challenges because of the low investment in research and development compared to developed countries [139], limited institutional/organizational resources, language barriers, health education and illiteracy, and sparse and incomplete data sources. There has also been limited training to perform critical appraisals of the literature, to adapt the results to local settings, and to provide continuing education programs for the application of results derived from DUR in policy and clinical decision-making. Despite a relative increase in the number of DUR studies conducted, there is clearly a need for additional support to publish study results, and for a multidisciplinary approach when developing interventions or educational programs in the region. Hopefully this will change as governments in the region recognize the need for DU studies to enhance their understanding of

current drug utilization especially with the growing burden of NCDs and the implications on future medicine use.

Future Direction

In summary, the LatAm region faces particular challenges that might impact DUR. The challenges include high levels of socioeconomic inequality and high migration rates in some countries; high rates of violence, crime, trafficking and/or possession of drugs, existence of indigenous populations that have not reached overall living standards with low education, poor socioeconomic status, high medical needs with limited access to medicines; existence of multiple languages and native languages within the region that limits communication with high rates of unemployment, urban segregation, and low level of literacy mainly in rural and remote areas. In terms of DU studies, there are a number of issues and challenges that have been identified; however, their extent remains unknown at the country and regional level. These include: fragmentation of most healthcare systems; limited medical coverage in some areas and access to medicines; as well as sub-standard and counterfeit medicines and insufficient number of quality control centers for medicines. In addition, there are issues with appropriate use of medicines resulting in increased antimicrobial resistance, over-prescription of antimicrobials, use of inappropriate medicines among the elderly, polypharmacy, self-medication, and poor medication adherence in practice.

In terms of DUR per se, there is a low number of publications generated by local investigators, and some of those available have methodological issues such as lack of representativeness of the population, limited validation of DU data reported, and small sample size [140]. These issues might significantly impact clinical, regulatory and public health decision-making [141]. Longitudinal drug utilization studies to examine time trends in the utilization of drugs in the region are difficult to conduct because of frequently undocumented changes over time in legislation, reimbursement systems and market conditions. Because of the fragmented nature of the health care delivery system, and the problems with data keeping records and access to the data, it is often very difficult to respond to basic questions like the exposed population, i.e., who is getting what drug? at what time? All of those are core questions in drug utilization studies, and researchers in the field trying to find reliable and valid answers, are having difficulties to assess these in the current political and economic climate in Latin America.

In conclusion, DUR is an important discipline and the improvement of tools and resources in the LatAm region could help and facilitate a better understanding of the current state of DU and the health system in the region. Despite the identified challenges of DUR in the LatAm region, important measures could be put in place to strengthen regional DUR capabilities. The follow up publication in this series will outline potential solutions to overcome these challenges and provide some guidance for researchers interested in carrying out DUR in the region. Ultimately, improved DUR should inform effective policies which will promote the rational and efficient use of

medication across LatAm, hopefully resulting in improved health outcomes for all patients in the region within available resources.

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