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Safeguarding human rights to health: a systematic review of supply chain impediments to safe medicines in developing nations

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Safeguarding Human Rights to Health: A Systematic Review of Supply Chain Impediments to Safe Medicines in Developing Nations

Abstract

Purpose

A key feature of human rights in health is access to safe, effective, and affordable medicines. Pharmacovigilance is advocated for monitoring intended/unintended effects of medicines to assure their safety. The purpose of this paper is to synthesize knowledge about supply chain impediments to safe medicines in developing nations and contribute to future development of research in this field.

Design/methodology/approach

This paper conducts a structured literature review based on PRISMA guidelines. It aims at profiling supply chain impediments to safe medicines in developing nations by reviewing 46 recent pharmacovigilance-specific papers published between 2005 and 2020.

Findings

Analysis of reviewed articles identified criticality of supply chain impediments that affect constituents across pharmaceutical in developing nations, which still struggle to maintain robust national pharmacovigilance systems due to lack of awareness, policy, and practices.

Research limitations/implications

Research results can be applied by pharmaceutical industry decision-makers and drug safety professionals in developing nations. Since the review is qualitative in nature, its implication ought to be tested after actual implementation.

Practical implications

This review can help identify under-investigated impediments and methods to aid in developing new pharmacovigilance knowledge areas in developing nation context.

Social implications

The review uncovers gaps in global health equity dialogue in developing nations. It also recognizes that macro-level supply chain impediments exist due to unfair disease burden and health inequities in developing nations.

Originality/Value

The paper examines supply chain impediments to safe medicines in developing nations with insights for future pharmacovigilance research. Identifying and classifying supply chain impediments through this review is the first step towards creating effective interventions for these impediments to safe medicines.

Keywords

Drug safety; Pharmacovigilance; Pharmaceutical supply chains; Impediments; Developing countries; developing nations; LMIC.

Paper type

Review paper.

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Introduction

Health is universally recognized as a fundamental human right. About three-quarters of a century ago, the United Nations adopted the Universal Declaration of Human Rights or UDHR, and its article 25.1 specifically incorporated health as part of human rights to adequate standard of living (UN General Assembly, 1948). A key feature of this human right to health is identified as access to safe, effective, and affordable medicines (Perehudoff, 2020). According to Office of the United Nations High Commissioner for Human Rights or OHCHR, universal access to safe medicines, particularly in developing nations, is impacted by issues related to "…sustainable financing, availability and affordability of essential medicines; price and quality control; dosage and efficacy of medicines; procurement practices and procedures, supply chains, etc." (OHCHR, 2009).

Medicines [1], including prescription drugs, over-the counter medications, complementary treatments, and other ancillary therapeutic interventions, play an essential role in offering effective healthcare treatment and/or prevention of disease. As medicines become more potent over the years, their risks—as witnessed by a dramatic rise in the incidents of adverse drug reactions/events (ADRs/ADEs)—are becoming a cause for grave concern (Giezen, Mantel-Teeuwisse and Leufkens, 2009;Dal Pan, 2014). To ensure access to safe medicines, the World Health Organization advocates pharmacovigilance [2], or PV, for monitoring of intended and unintended effects of medicines to assess risk versus benefit (WHO, 2006). PV consists of a broad range of tasks, including the collection, exchange, aggregation, analysis, interpretation, and communication of data related to

patient experiences and medicine use. It contributes to the protection of patients' and public health by promoting safe and effective use of medicines, through providing timely information about the safety of medicines to patients, healthcare professionals, and the public. It also aims to reduce patient suffering and plays a critical part in assuring that patients receive safe medications. It also promotes safe and rational use of medicines by capturing/reporting on issues of medicine risks before the risk spreads too broadly (WHO, 2006).

PV-related activities have been receiving the limelight with growing scrutiny and regulation of the pharmaceutical industry (Harmark and van Grootheest, 2008). And, the topic of drug safety is attracting considerable media coverage lately, plus attention from professionals from industry, scientific, government, and medical consumer communities (Kolodny, 2020). Past literature has focused on the importance of curbing ADRs in context of healthcare delivery. ADRs or ADEs are undesirable effects associated with the use of medicines that may occur as part of pharmacological drug action, or due to unpredictability of their occurrences (Edwards and Aronson, 2000), and are among the leading causes of mortality and morbidity in health care. Past studies have focused on design, organization, and operations of the healthcare system, instead of medical practitioners or the medicines itself, as enablers of ADRs (Berwick and Leape, 1999;Adenuga *et al.*, 2020). Other studies have focused on patients' personal and social traits, besides pharmacological attributes of medicines, as likely factors for ADRs that need to be monitored as part of an effective PV system (Alomar, 2014).

The rise in political, regulatory, and scientific pressures to attain safe medicines is spurring adoption of national PV systems across the globe (Greener, 2008). And, while instituting and maintaining an effective and robust national PV system is economically viable in the developed

world, such systems are often wishful thinking in developing nations, also known as low- and middle-income countries, or LMICs (Olsson, Pal and Dodoo, 2015;Moscou, Kohler and MaGahan, 2016;Shin *et al.*, 2019). Efforts for viable national PV systems in LMICs are further hampered due to unfair burden of disease and health inequities, suboptimal national health policies, antiquated infrastructure, and bare-bone resources, among other factors (Pirmohamed *et al.*, 2007;Olsson *et al.*, 2010;Isah *et al.*, 2012;Maigetter *et al.*, 2015;Ampadu *et al.*, 2018).

Incidents of ADRs in the developing world, especially in LMICs, are escalating at a much faster pace than their counterparts in the developed world (Mehta, Allen and Barnes, 2010). This issue is further exacerbated by the rampant access to counterfeit, falsified, and/or substandard medicines, insufficient medication efficacy, medication errors, frequent stockouts, abuse and misuse of medicines including for non-approved indications, its side effects leading to acute/chronic/fatal poisoning, and harmful interactions with foods/drinks, chemicals, and other medications (Isah *et al.*, 2012;Alshammari *et al.*, 2019). Another challenging problem in PV is that of the assessment of causality, linking a given ADR to a specific medicine, which is further complicated due to complex interaction dynamics of its supply chain stakeholders in LMICs. Furthermore, impediments to PV in LMICs, as compared to developed countries, are inherently different, and need to be examined in their specific medicine supply chain context (Pirmohamed *et al.*, 2007;Isah *et al.*, 2012). Given the significance of resource-limitations in LMICs, it is imperative to examine the PV across the entire medicine supply chain in such environments.

Medicine supply chains in LMICs can be characterized by very low degree of automation and use of technology, limited ability to enforce national policies and regulations, primarily driven by national essential medicine list for its public sector, a lower performance in terms of availability, low

turnover inventory levels with stock levels measured in months, limited degree of stock level visibility, low levels of efficiency, infrequent (monthly and even quarterly) deliveries, limited capacity, poor storage conditions, etc. (Dowling, 2011). Consecutively, it is imperative for medicine industry professionals, government regulators, and other stakeholders, to fully comprehend supply chain impediments that prohibit realization of successful PV systems.

Past studies have focused on ways to curb ADRs in a broad context of general healthcare delivery but not across the entire medicine supply chain (Bates, Leape and Petrycki, 1993;Cohen, 1999;Rommers, Teepe-Twiss and Guchelaar, 2007;Ferner and Aronson, 2010;Coleman and Pontefract, 2016). In addition, review articles have discussed the importance of effective PV systems but do not substantiate how supply chain-related impediments thwart PV success, specifically in resource-constrained environments of LMICs. This leads to our research question: *What supply chain impediments thwart PV success, and foil realization of safe medicines for all, in developing nations*?

To answer this question, we conducted a systematic literature review in areas of medicines, drug safety, business/supply chain operations, LMICs, etc. It would aid in identifying interventions needed to counter supply chain impediments to PV success and reveal gaps in current PV research. Based on the review, we observed that supply chains impediments to PV success can be categorized into five interrelated categories: LMIC-related impediments, pharmaceutical industry impediments, supply chain network impediments, supply chain stakeholder impediments, and drug safety outcome impediments, as depicted in Figure 1.

Insert Figure 1 about here.

The next section presents the methodology that we employed for the literature review. It is followed by the analysis of our review findings. We conclude our paper with a discussion of our findings and implications.

Methodology

This research presents a systematic review approach to reviewing the literature on drug safety in LMICs. A systematic review of the literature minimizes bias throughout the entire process, pinpoints gaps in theories and research knowledge base, to avoid incorrect/misleading inference due to biases in the review itself or from selection of studies included in the review (Tranfield, Denyer and Smart, 2003;Harden and Thomas, 2005). This systematic literature review is conducted based on the procedure adopted by Tranfield et al. (Tranfield, Denyer and Smart, 2003) , which strives to ensure a transparent and less subjective process of article selection, stating clearly and chronologically all research decisions made.

This systematic review was carried out as per the updated Preferred Reporting Items for the Systematic Reviews and Meta-Analyses (PRISMA) guidelines-2020 statement (Page *et al.*, 2021). As part of carrying out the systematic literature review, the research scope was defined at the start. The first step was to search for specific keywords that were identified for our research. We used both controlled and free text language search strategies. Specifically, medical subject heading (MeSH) terms including “pharmacovigilance,” “drug safety,” “adverse drug reaction,” and “adverse drug event.” were used for controlled searches. The exclusion criteria were applied to PV-related articles that did not address (i) LMICs, emerging economies, or developing countries, (ii) medicine or pharmaceutical supply chains, and (iii) PV-related impediments. Furthermore, meaningful advances

can be documented in the PV discipline in the decade and a half duration (Talbot and Nilsson, 1998), which serves as a meaningful timespan for analysis. The limitation criteria, therefore, consisted of peer-reviewed articles written in English language and published specifically between 2005 and 2020. The search was limited to the following ten medically relevant research databases: CINAHL, EBSCOhost, Emerald Insight, Gale Academic OneFile, ProQuest, PubMed, ScienceDirect, SpringerLink, Taylor & Francis Online, Web of Science, and Wiley Online Library. Figure 2 summarizes the review protocol that was applied to identify, assess, and select existing studies, stating clearly and chronologically all research decisions made while seeking a transparent and less subjective process.

Insert Figure 2 about here.

In the identification phase of the literature selection process, 1,744 documents were identified in the initial literature search of PV-related keywords when limited to LMICs. Out of these, 573 were identified as duplicates, and therefore removed from further consideration, leaving behind 1,171 articles for further consideration. Then, in the screening phase, exclusion criteria were applied. Out of 1,171 articles, 567 did not address medicine or pharmaceutical supply chains and the other 229 did not address PV-related impediments, leaving behind 375 articles remaining that were moved to the next phase. Next, titles and abstracts of these 375 articles were reviewed in the eligibility phase. Out of these, 156 articles were found to be case studies and the other 114 turned out to be editorials and correspondence, and were, therefore, removed from further consideration. After the eligibility phase screen, 105 articles were left remaining and underwent full-text analysis. Out of these, 59 were excluded due to unclear definition of PV and/or for having inadequate scope of analysis. This final screening left behind 46 scholarly articles, which underwent detailed analysis as part of the systematic literature review (Waring, 2005;Eliasson, 2006;Shani and Yahalom,

2008;Mehta, Allen and Barnes, 2010;Olsson *et al.*, 2010;Desai *et al.*, 2011;Isah *et al.*, 2012;Khalili *et al.*, 2012;Khan, 2013;Dal Pan, 2014;Glass, 2014;Jha *et al.*, 2014;Margraff and Bertram, 2014;Zhang *et al.*, 2014;Gibson *et al.*, 2015;Hacker *et al.*, 2015;Maigetter *et al.*, 2015;Olsson, Pal and Dodoo, 2015;Yadav, 2015;Ahmadiani and Nikfar, 2016;Hamilton *et al.*, 2016;Joubert and Naidoo, 2016;Moscou, Kohler and MaGahan, 2016;Suwankesawong *et al.*, 2016;Alsaleh *et al.*, 2017;Agoro *et al.*, 2018;AlHusaini and Al Mubarak, 2018;Ampadu *et al.*, 2018;Elshafie, Zaghloul and Roberti, 2018;Inácio, Cavaco and Airaksinen, 2018;Moscou and Kohler, 2018;Nguyen *et al.*, 2018;Roth *et al.*, 2018;Saleh, Fourrier-Réglat and Diogène, 2018;Zhao *et al.*, 2018;Adisa and Omitogun, 2019;Alshammari *et al.*, 2019;Evans *et al.*, 2019;Guignard *et al.*, 2019;Güner and Ekmekci, 2019;Shin *et al.*, 2019;Tauqeer, Myhr and Gopinathan, 2019;Zawiah *et al.*, 2019;Kohler and Dimancesco, 2020;Barry *et al.*, 2021) .

Analysis of Review Findings

As we identified individual impediments to PV success, we found that these impediments can be broadly placed in five distinctive over-arching categories: LMIC-related impediments, pharmaceutical industry impediments, supply chain network impediments, supply chain stakeholder impediments, and drug safety outcome impediments, as depicted earlier in Figure 1.

LMIC-related Impediments

Literature identifies several LMIC-related impediments that can limit PV effectiveness in those countries. Many LMICs are plagued with limited availability of financial and non-financial resources, making it difficult to establish and maintain effective PV systems (Shani and Yahalom,

2008;Isah *et al.*, 2012;Dal Pan, 2014;Maigetter *et al.*, 2015;Elshafie, Zaghloul and Roberti, 2018;Tauqeer, Myhr and Gopinathan, 2019). LMICs also are marred with inadequate PV infrastructure, including limited access to electricity and communication, which would confound collecting and transmitting data on ADRs in a timely manner (Guignard *et al.*, 2019). Barebone healthcare facilities and outdated equipment in these LMICs could render them ineffective or unsuitable to gather, analyze, and accurately report data on ADRs (Olsson *et al.*, 2010;Zhang *et al.*, 2014;Maigetter *et al.*, 2015;Elshafie, Zaghloul and Roberti, 2018;Tauqeer, Myhr and Gopinathan, 2019).

LMICs are also characterized by weak regulatory systems for medications, which can make it difficult to identify and address safety concerns (Olsson *et al.*, 2010;Glass, 2014;Agoro *et al.*, 2018;Alshammari *et al.*, 2019). A lack of political will to prioritize PV in LMICs due to competing priorities, such as alternate economic development agenda, conflicting public health campaigns, etc. can lead to a climate that is non-conducive to collection/dissemination of ADR data (Mehta, Allen and Barnes, 2010;Olsson *et al.*, 2010). This can also be attributed to perceived negative impact on the reputation of LMIC's pharmaceutical industry or other political considerations. LMICs can also become hampered by a lack of clarity of roles about who is responsible for different PV aspects, which can lead to delays and inefficiencies (Olsson *et al.*, 2010). Furthermore, ineffective monitoring of ADRs may also be attributed to a lack of cooperation among multiple supply chain stakeholders, including drug industry, regulatory agencies, and healthcare professionals in some LMICs (Maigetter *et al.*, 2015;Zhao *et al.*, 2018).

Compared to high-income nations, LMICs are saddled with a larger burden of disease (Elshafie, Zaghloul and Roberti, 2018;Moscou and Kohler, 2018), which raises the drug demand and

makes it harder to identify and resolve PV issues. Additionally, it may be challenging to ensure that the drug safety is appropriately monitored in LMICs as the disease burden may be excessively carried by marginalized populations, including women and children (Gibson *et al.*, 2015). It may also be spurred by unequal healthcare access, patients' lifestyle, diet, and genetic make-up in LMICs (Gibson *et al.*, 2015;Evans *et al.*, 2019). Lack of patients' health history, particularly for the undocumented/migrant population (Hacker *et al.*, 2015), and confounding illnesses/indications (Mehta, Allen and Barnes, 2010;Gibson *et al.*, 2015) may also contribute to impeding PV success.

LMICs may also have limited access to scientific literature, research databases, drug reference materials, and assistance from international NGOs and regulatory agencies, and other specialists, it is difficult for healthcare practitioners to remain up to date on the most recent drug research, ADR data, and the best PV practices (Olsson *et al.*, 2010;Alshammari *et al.*, 2019). Another contributing impediment may be the difficulty in monitoring and compiling sufficient PV data on usage, safety, and efficacy of medicines that are not widely available in LMICs (Elshafie, Zaghloul and Roberti, 2018;Moscou and Kohler, 2018).

Another impediment to PV success in LMICs may be the lack of regulatory competence and PV expertise. LMICs are usually plagued with inadequate PV reporting/monitoring systems and lack of qualified regulatory staff that can handle PV data (Shani and Yahalom, 2008;Khalili *et al.*, 2012;Suwankesawong *et al.*, 2016;Agoro *et al.*, 2018;Ampadu *et al.*, 2018;Elshafie, Zaghloul and Roberti, 2018;Roth *et al.*, 2018;Tauqeer, Myhr and Gopinathan, 2019). LMICs may also suffer from a dearth of trained experts that can deliver PV training to supply chain stakeholders (Olsson *et al.*, 2010;Maigetter *et al.*, 2015;Roth *et al.*, 2018).

LMICs usually are also marred with a shortage of qualified regulatory staff (Olsson, Pal and Dodoo, 2015;Elshafie, Zaghloul and Roberti, 2018;Zhao *et al.*, 2018), which are required to ensure compliance of supply chain stakeholders with PV regulations (Zhao *et al.*, 2018). Other PV-related impediments include gaps in pharmacist regulation and enforcement (Ampadu *et al.*, 2018;Elshafie, Zaghloul and Roberti, 2018;Moscou and Kohler, 2018) and poor tracking of exposures to new marketed potent drugs (Ampadu *et al.*, 2018;Elshafie, Zaghloul and Roberti, 2018). Figure 3 summarizes the key themes of LMIC-related impediments to PV success.

Insert Figure 3 about here.

Pharmaceutical Industry Impediments

Many pharmaceutical industry-related factors impede the PV effectiveness in LMIC context. Among them are clinical trials-associated gaps and limitations (Zhang *et al.*, 2014;Ahmadiani and Nikfar, 2016;Elshafie, Zaghloul and Roberti, 2018). Clinical trials are necessary to evaluate the safety and effectiveness of drugs before they are approved for use. However, these trials are often conducted in high-income countries and may not adequately represent the populations of LMICs. This can lead to a lack of data on the safety and effectiveness of drugs in these populations, making it difficult to accurately assess the potential risks and benefits of these drugs in these populations (Ahmadiani and Nikfar, 2016).

Lack of ethnic diversity in drug clinical trials can be an impediment to PV effectiveness in LMICs. It can lead to a failure to grasp cultural and social understanding, thus undermining the drug safety and effectiveness in different populations. Furthermore, underrepresentation of some populations in drug trials and research in the pharmaceutical industry can results in ADR profiles that

are not generalizable (Eliasson, 2006;Mehta, Allen and Barnes, 2010;Elshafie, Zaghloul and Roberti, 2018), thereby distorting potential risks and benefits of medications in different ethnic groups and contributing to health disparities (Alemayehu, Mitchell and Nikles, 2018).

Another impediment in LMICs is the lack of drug efficacy (Olsson *et al.*, 2010;Agoro *et al.*, 2018;Elshafie, Zaghloul and Roberti, 2018), which may be caused by the pharmaceutical industry in LMICs opting for lower quality standards, or not following Good Manufacturing Practices (Dal Pan, 2014;Agoro *et al.*, 2018;Elshafie, Zaghloul and Roberti, 2018;Evans *et al.*, 2019). These LMICs also lack the capacity to fully assure the quality of medicines circulating in their territory, and the most vulnerable populations are exposed to the risk of receiving poor-quality medicines (Mehta, Allen and Barnes, 2010;Ravinetto *et al.*, 2012;Yadav, 2015). This can lead to negative outcomes for patients, including worsening of their condition or even death (Olsson *et al.*, 2010;Isah *et al.*, 2012). To address this issue, it is important to increase diversity in the pharmaceutical industry and to prioritize research and clinical trials that include diverse populations.

Aggressive marketing and promotion of new drugs can also pose as a challenge in LMICs, leading to overuse or inappropriate use of the medications (Isah *et al.*, 2012;Ahmadiani and Nikfar, 2016;Elshafie, Zaghloul and Roberti, 2018). It can result in ADRs that may not be adequately reported or monitored, leading to a lack of comprehensive data on the safety and effectiveness of these medications. In addition, many people in LMICs cannot afford the high prices of new drugs, which can limit the market for these products (Ahmadiani and Nikfar, 2016). Figure 4 summarizes the key themes of pharmaceutical industry impediments to PV success in LMICs.

Insert Figure 4 about here.

Supply Chain Network Impediments

LMICs are also marred with supply chain network impediments to PV success as these networks are relatively ill-managed, often leading to fragmented distribution of drugs with multiple intermediaries involved in the process (Yadav, 2015). This can make it difficult to trace the origin of a drug and identify any potential issues with quality or safety and makes the network prone to distribution of counterfeit or substandard drugs, thereby posing serious risks to patient safety (Olsson *et al.*, 2010;Glass, 2014;Elshafie, Zaghloul and Roberti, 2018). Drug supply chain networks in LMICs are also plagued with corruption, making it difficult to accurately track and monitor ADRs (Ahmadiani and Nikfar, 2016;Ampadu *et al.*, 2018;Moscou and Kohler, 2018;Kohler and Dimancesco, 2020). This can make it tough to ensure the safety of drugs, as it may be unclear what medications are being distributed and used in a particular area (Ahmadiani and Nikfar, 2016;Kohler and Dimancesco, 2020). Access to healthcare is also limited in LMICs, particularly in underserved districts and remote rural areas, which can often be plagued with limited infrastructure, including limited access to electricity, communication networks, and logistics support thereby making it difficult to store and transport medications (Guignard *et al.*, 2019). It also obstructs communication with PV authorities, making it harder to report ADRs, or to seek treatment for them, thereby rendering supply chain networks ineffective in rural and/or remote areas in LMICs (Yadav, 2015).

Lack of transparency of medicine distribution in LMICs can impede PV efforts as it makes it harder to track medicine usage throughout supply chain and hinder ADR detection (Kohler and Dimancesco, 2020). Tracking the flow of medicines from manufacturers to patients in LMICs can be challenging, specifically when its supply chain is potentially governed by a single supplier or distributor. The inability to determine what medication a patient was taking, or where it was

acquired, can also make it more challenging to identify and report ADRs in LMICs (Kohler and Dimancesco, 2020).

LMICs are also usually plagued with overall shortages of medicine, including hurdles in manufacturer/products licensing, shortage of raw material for a local manufacturer, drug smuggling, and lodging tax government policies (Kohler and Dimancesco, 2020). In addition, frequent shortages of certain medications can make it difficult to monitor the safety of these medicines in LMICs. Patients impacted by drug shortage issues would face increased monitoring, receive suboptimal treatment through alternative medicine, delayed care, being transferred to other institutions, increased length of hospitalization, readmission due to adverse events/treatment failure/relapse, associated care cancellations, or even death, all escalating the ADR rates (Moscou and Kohler, 2018;Phuong *et al.*, 2019). Additionally, the rise of drug sales over the internet has offered abundant access to medications without the oversight of a healthcare professional for people to access, thereby increasing the risk of ADRs. It can be particularly problematic in LMICs with limited capacity of healthcare professionals (Hamilton *et al.*, 2016). This can lead to gaps in data and make it harder to identify potential safety issues. LMICs also get saddled with an escalating risk of shrinkage (theft, pilferage, etc.) of medicine supply making it problematic to accurately track the distribution/use of medications (Kohler and Dimancesco, 2020). It can lead to discrepancies in PV data, thereby obfuscating potential drug safety concerns. Medicines can also be exposed to environmental contamination in some LMICs, such as through exposure to heat, moisture, or other contaminants, which can lead to the distribution of unsafe medications that have decreased effectiveness or even put patients in harm's way (Mehta, Allen and Barnes, 2010). Figure 5 summarizes the key themes of supply chain network impediments to PV success.

Insert Figure 5 about here.

Supply Chain Stakeholder Impediments

Supply chain stakeholder impediments also hinder PV success in LMICs. These impediments are further categorized by the knowledge, attitude, and practice of supply chain stakeholders, including healthcare providers, pharmacists, and patients.

Healthcare Provider (Physicians) Impediments

Several healthcare provider impediments are identified in the literature. Medications may be wrongly prescribed or over-prescribed by the healthcare professionals in LMICs, thereby escalating the risk of ADRs. This can be due to a lack of training or experience among healthcare providers, an unsustainable doctor-patient ratio, or a lack of access to appropriate prescribing guidelines (Elshafie, Zaghloul and Roberti, 2018). Moreover, overworked healthcare professionals may not have the time or resources to report ADRs, resulting in underreporting ADEs in LMICs (Waring, 2005;Jha *et al.*, 2014;Alsaleh *et al.*, 2017;Nguyen *et al.*, 2018). A dearth of continuing education options for health professionals, and lack of financial resources or infrastructure to participate, can lead to prescribing of inappropriate or unsafe medications in LMICs, failure to recognize or report adverse drug reactions, and lack of follow-up care for patients experiencing ADEs (Olsson *et al.*, 2010;Jha *et al.*, 2014). Inadequate PV coverage during medical training of healthcare providers can lead to a lack of understanding and awareness among healthcare professionals in many LMICs (Olsson *et al.*, 2010;Khalili *et al.*, 2012;Jha *et al.*, 2014;Maigetter *et al.*, 2015;Nguyen *et al.*, 2018;Adisa and Omitogun, 2019;Shin *et al.*, 2019). Some healthcare providers also seemed hesitant about reporting

ADRs as there is a potential stigma associated with it in LMICs, due to the worry about being perceived as "complaining" or "difficult". These providers may also be reluctant to report ADEs due to liability concerns associated with it, due to the fear of retribution or legal consequences (Desai *et al.*, 2011;Barry *et al.*, 2021), particularly if the ADR results in harm to a patient. Yet other providers perceived ADR reporting as extra work or effort, without any recognition or incentives (Waring, 2005;Nguyen *et al.*, 2018;Güner and Ekmekci, 2019;Barry *et al.*, 2021).

Pharmacists Impediments

Pharmacist impediments to PV success are also listed in prior research. In LMICs, pharmacists may also lack adequate PV training, which can pose a significant risk to patient safety (Hamilton *et al.*, 2016;Elshafie, Zaghloul and Roberti, 2018). It may be attributed to inadequate emphasis on PV in pharmacy education, lack of standardized training programs, or inadequate resources for continuing education (Khalili *et al.*, 2012;Khan, 2013;Zawiah *et al.*, 2019). In some cases, a robust demand for certain medications may cause pharmacists in LMICs to opportunistically dispense them without proper prescription (Olsson, Pal and Dodoo, 2015;Alsaleh *et al.*, 2017), thereby contributing to ADRs.

Akin to healthcare providers in LMICs, pharmacists also demonstrate reluctance to engage in PV reporting to avert any undesirable consequences, both financial (Joubert and Naidoo, 2016) and cultural (Waring, 2005) in nature. Further, due to limited resources in LMICs, pharmacists may also lack access to adequate supply of assorted medications, so patients may be dispensed medication that may not best fit for their condition (Yadav, 2015). Pharmacists may also perceive PV as leading to reduced sales, as reporting ADRs could result in the withdrawal of a drug from the market or a decrease in its use (Olsson, Pal and Dodoo, 2015;Joubert and Naidoo, 2016;Elshafie, Zaghloul and

Roberti, 2018). And, as reporting ADRs and implementing other PV activities can take time and effort, pharmacists in LMICs may also harbor perception that PV activities are draining on their limited resources (Khan, 2013;Joubert and Naidoo, 2016;Zawiah *et al.*, 2019).

Patient/Caregiver Impediments

Researchers also cite patient impediments to PV success in past literature. Among these impediments is poor health literacy, which can pose a major risk to effective PV efforts in LMICs (Adisa and Omitogun, 2019;Alshammari *et al.*, 2019;Guignard *et al.*, 2019). Health literacy includes knowing patients' rights related to medication therapy, including their right to refuse medication, their right to know about potential side effects and risks associated with their medication, and their right to participate in decisions about their medication therapy. Patients with limited health literacy may have difficulty understanding medication labels, instructions, and other important information related to their medication therapy, increase the risk of medication errors and ADEs (Hacker *et al.*, 2015;AlHusaini and Al Mubarak, 2018;Alshammari *et al.*, 2019;Guignard *et al.*, 2019). Even if patients, who experienced ADEs related to their medication therapy, may submit reports to healthcare providers, pharmacists, or regulators in LMICs, they may not receive feedback on outcome of their report, causing frustration or cynicism (Olsson, Pal and Dodoo, 2015), and leading to marginalized PV reporting (Alsaleh *et al.*, 2017;Elshafie, Zaghloul and Roberti, 2018) and reduced future engagement in PV efforts (Olsson, Pal and Dodoo, 2015;Inácio, Cavaco and Airaksinen, 2018).

Another impediment to PV success in LMICs is patients' reliance on informal sources of information, such as family and friends, social network, or other informal sources (Olsson, Pal and Dodoo, 2015;Elshafie, Zaghloul and Roberti, 2018). Patients who rely on informal information

sources may not receive accurate information about their medication therapy, potential side effects, or about how to report ADRs, thereby further stalling PV success in LMICs.

Patients in LMICs, specifically those who have a low income, are homeless, are from marginalized populations, or are from minority groups, may face barriers to accessing healthcare services. The ones who cannot afford their medication are often forced to make difficult decisions about prioritizing food over medication expenses. They are saddled with a sense of hopelessness, which arguably can be attributed to a drug cost-benefit tradeoff forced upon them due to impoverished conditions (Olsson, Pal and Dodoo, 2015). They may also attribute ADRs to God's-will, fate, or karma due to their socio-/cultural-/religious-beliefs and customs (Waring, 2005;Eliasson, 2006). This can lead to underreporting of ADRs or reluctance to seek appropriate care.

Some of the patients in LMICs also exhibit bias towards medicine overuse (Olsson *et al.*, 2010;Olsson, Pal and Dodoo, 2015;Elshafie, Zaghloul and Roberti, 2018;Saleh, Fourrier-Réglat and Diogène, 2018) as well as misuse/abuse (Alsaleh *et al.*, 2017;Elshafie, Zaghloul and Roberti, 2018). These behaviors can lead to ADRs and other negative health outcomes. In LMICs, patients can also perceive over the counter or generic drugs as adequate and/or cure all for their health conditions (AlHusaini and Al Mubarak, 2018) and may not recognize the need for ongoing monitoring of their health status, thereby further confounding PV efforts. Patient self-medication is yet another impediment to PV success in LMICs (Olsson, Pal and Dodoo, 2015;Alsaleh *et al.*, 2017;Elshafie, Zaghloul and Roberti, 2018), as is the unregulated and/or simultaneous use of drugs along with traditional remedies (Olsson, Pal and Dodoo, 2015). Figure 6 summarizes the key themes of supply chain stakeholder impediments to PV success.

Insert Figure 6 about here.

Drug Safety Outcome Impediments

Past literature lists several drug safety outcome impediments to PV success in LMICs. Foremost among them are the poor management of PV data and the lack of standardization of PV reporting process. PV requires timely and accurate data collection, analysis, and reporting, and poor data management can lead to delays, posting errors, and missed opportunities for identifying and addressing safety issues (Gibson *et al.*, 2015;Adisa and Omitogun, 2019;Tauqeer, Myhr and Gopinathan, 2019). Impediments associated with PV data management in LMICs include: (i) *How and Where to Report*, as PV reporting forms become inaccessible, possibly due to unreliable/expensive Internet access, challenges associated with a hybrid system of paper and electronic reporting; and PV system usability issues (Desai *et al.*, 2011;Khan, 2013;Maigetter *et al.*, 2015;Joubert and Naidoo, 2016;Elshafie, Zaghloul and Roberti, 2018;Saleh, Fourrier-Réglat and Diogène, 2018;Güner and Ekmekci, 2019;Zawiah *et al.*, 2019;Adenuga *et al.*, 2020), (ii) *What to Report*, as the PV reporting forms are perceived as complex, asking for too much information, particularly information that is difficult to find and record (Khan, 2013;Margraff and Bertram, 2014;Joubert and Naidoo, 2016;Elshafie, Zaghloul and Roberti, 2018), and (iii) *What Happens to Report*, with an out of sight, out of mind attitude given the remote handling of PV forms, often with inconsistent, or even no, follow up on serious ADEs (Olsson *et al.*, 2010;Zhang *et al.*, 2014;Joubert and Naidoo, 2016;Inácio, Cavaco and Airaksinen, 2018;Saleh, Fourrier-Réglat and Diogène, 2018;Shin *et al.*, 2019).

PV also requires consistent and standardized reporting across different stakeholders in the healthcare system, including healthcare providers, patients, regulatory agencies, and pharmaceutical companies. Without this standardization, it can be difficult to compare data across different sources,

identify safety issues, and take appropriate action to address them (Khalili *et al.*, 2012;Margraff and Bertram, 2014;Nguyen *et al.*, 2018;Zhao *et al.*, 2018;Shin *et al.*, 2019). Impediments associated with lack of standardization of PV data reporting in LMICs include: (i) *Why to Report*, attributed to low awareness of ADR reporting need and its necessity, the mindset that ADR reporting brings in no practical outcomes, or the cynical attitude towards the inherent value of spontaneous ADR reporting (Shani and Yahalom, 2008;Joubert and Naidoo, 2016;Ampadu *et al.*, 2018;Inácio, Cavaco and Airaksinen, 2018;Zhao *et al.*, 2018;Adenuga *et al.*, 2020), (ii) *Who to Report*, probably due to lack of knowledge about the PV reporting process in remote areas, for marginalized communities or those in vulnerable situations, and lack of awareness about the importance of timely reporting an ADE (Joubert and Naidoo, 2016;Alsaleh *et al.*, 2017;Inácio, Cavaco and Airaksinen, 2018;Shin *et al.*, 2019;Adenuga *et al.*, 2020), and (iii) *When to Report*, attributed to a lack of PV reporting training, or that ADR is deemed not serious enough to report, or with unclear causality (Olsson *et al.*, 2010;Maigetter *et al.*, 2015;Suwankesawong *et al.*, 2016;Elshafie, Zaghloul and Roberti, 2018;Saleh, Fourrier-Réglat and Diogène, 2018). Figure 7 summarizes the key themes of drug safety outcome impediments to PV success.

Insert Figure 7 about here.

Conclusions

To safeguard human rights in healthcare and safe medicines, the trade-off between benefits of medicines and their potential for harm must be carefully evaluated, specifically in developing nations or LMICs. This study contributes to our understanding of the multifaceted nature of supply chain impediments to safe medicines in LMICs. Our preliminary review of disciplines of PV/drug

safety, medicine supply chains, and LMICs show a gap in literature where research and ideas on drug safety impediments are fragmented across these disciplines. We were unable to find a study that comprehensively examines all these disciplines to understand key impediments to drug safety across medicine supply chains in LMICs.

Our systematic literature review indicates that LMIC-related impediments would require national-/global-level interventions, including initiatives such as increasing health access; awareness, and literacy; investing in PV funding, infrastructure, and capacity; implementing population health measures; fostering collaboration/partnerships with global health agencies, etc. Pharmaceutical industry and supply chain network impediments would require initiatives such as simplifying drug supply chains; abating black/grey markets for medicines; improving drug distribution transparency; strengthening regulatory frameworks, etc. And, supply chain stakeholder and drug safety outcome impediments would require initiatives such as investing in electronic health records; incorporating PV training for physicians/pharmacists; initiating PV/drug literacy initiatives for patients; targeted PV educational programs, awareness campaigns, and capacity building activities; prompt and accurate PV/ADR reporting; developing/implementing clear and easy-to-follow protocols for PV data reporting; standardized PV data collection; regular audits and quality checks of PV data management systems, etc. Addressing these PV-related impediments across medicine supply chains in the developing nations landscape will go a long way to safeguard human rights in healthcare by providing a large boost in healthcare quality, effectively ensuring patient care/safety, and enhancing patient quality of life and public health nationally and beyond.

The goal of safe medicine is identified by United Nations' article 25.1 of UDHR. Realizing this ambitious goal is a formidable challenge in developing nations due to a wide range of supply chain

impediments as identified in this research study. It calls for relevant stakeholders across medicine supply chain, regulatory agencies, governments of developing nations, and international NGOs, to collaboratively explore strategies to ensure that medicine supply chains (i) operate in an ever-improving regulatory and PV capacity building framework, (ii) deliver medicines that meet the necessary safety and quality standards, and (iii) offer improved affordability, access, traceability, and accountability of medicines as required by international health guidelines and global conventions on human rights.

Implications

Policy makers in developing nations still need to be mindful of several potential challenging issues that may arise in this journey to achieving universal access to safe medicine in their regions.

1. Developing nations may face inherent key infrastructural challenges, such as inadequate transportation networks and limited access to technology that need to be addressed at the macro (national) level and may call for innovative solutions.
2. Modernizing the medicine supply chain may require substantial investment of capital in the case of developing nations, which are often plagued with limited financial resources. Exploring international partnerships and aid can go a long way to address this issue.
3. As with the realities of any supply chain, any changes made to the medicine supply chain may unleash temporary disruptions, which might threaten the availability of certain medicines. Painstaking efforts and proactive collaboration among supply chain stakeholders is essential to mitigate the risk of any potential disruptions.

4. Digitization of the health data may lead to data privacy and security risk. Protecting sensitive data about patients, care providers, and drug producers is critical for adhering to principles of medical ethics and safeguarding human rights to health.
5. Any modifications in medicine supply chains, either their structure or their operational dynamics, is likely to face opposition from existing stakeholders, especially if their interests or established practices are challenged. Overcoming this opposition and promoting stakeholder collaboration is likely a way forward towards achieving the goal of safe medicines.

As we are ushered into the era of *Industry 5.0* and *Society 5.0*, digital technologies are making strides in offering artificial intelligence (or AI)-based solutions with a focus on human-machine collaboration (Rosak-Szyrocka, Żywiołek and Shahbaz, 2023). It is conceivable that *Pharma 4.0* (Saha *et al.*, 2022), the pharmaceutical supply chain version of *Industry 4.0*, will transform to *Pharma 5.0* to refocus human expertise on higher value tasks in the medicine product cycle. It holds promise for safe medicines to safeguard human rights to health, especially in developing nations, through development of innovative ways of mobilizing collaborative medical supply chain ecosystem, AI and blockchain solutions for digital health records and telemedicine, smart medicine inventory management, smart traceable packaging, and empowering local communities through health literacy.~~Streamlining medicine supply chains in developing nations has the potential to address PV-related impediments and improve medicine safety, thereby safeguarding human rights to health. However, challenges such as infrastructural limitations, resource constraints, disruption mitigation, data privacy and security, and opposition to change must be addressed. It is paramount that relevant stakeholders across medicine supply chain between governments, international organizations, pharmaceutical companies forge partnerships, to collaboratively develop tailored~~

~~solutions for successful realization of safe medicines that align with the unique needs of each developing nation.~~

[1] The terms medicines, pharmaceutical drugs, medications, and therapeutic interventions are used interchangeably in this article in accordance with medical dictionary definitions Stedman, T.L. (2006) *Stedman's medical dictionary.* 28th edn. Philadelphia: Lippincott Williams & Wilkins.

[2] In most instances, the terms drug safety and PV, both focusing on curbing ADRs/ADEs, are used interchangeably across the globe; the drug safety term being more prevalent in North America, whereas the PV term being more prevalent in Europe. Consecutively, we use these terms interchangeably in our research.

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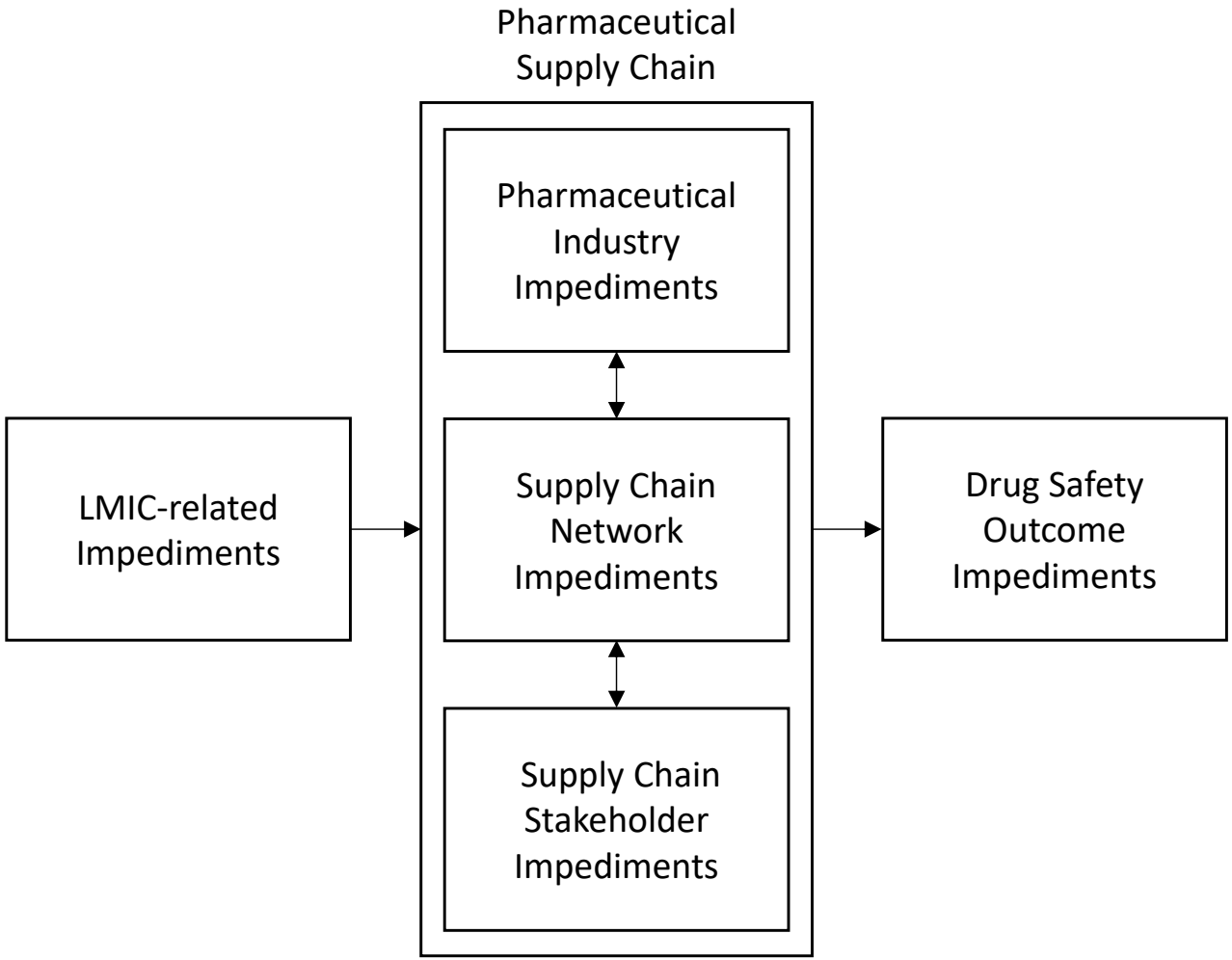
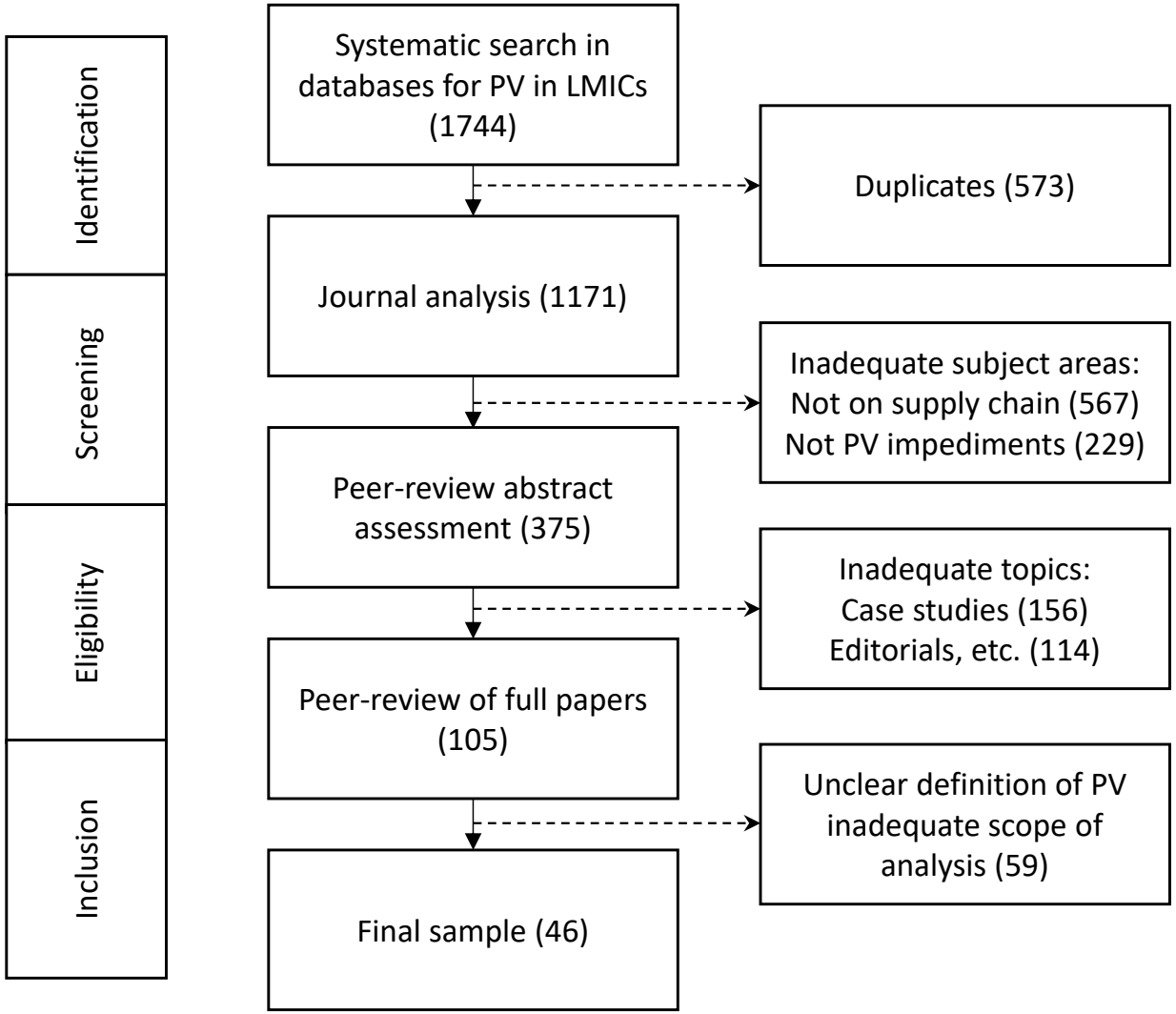
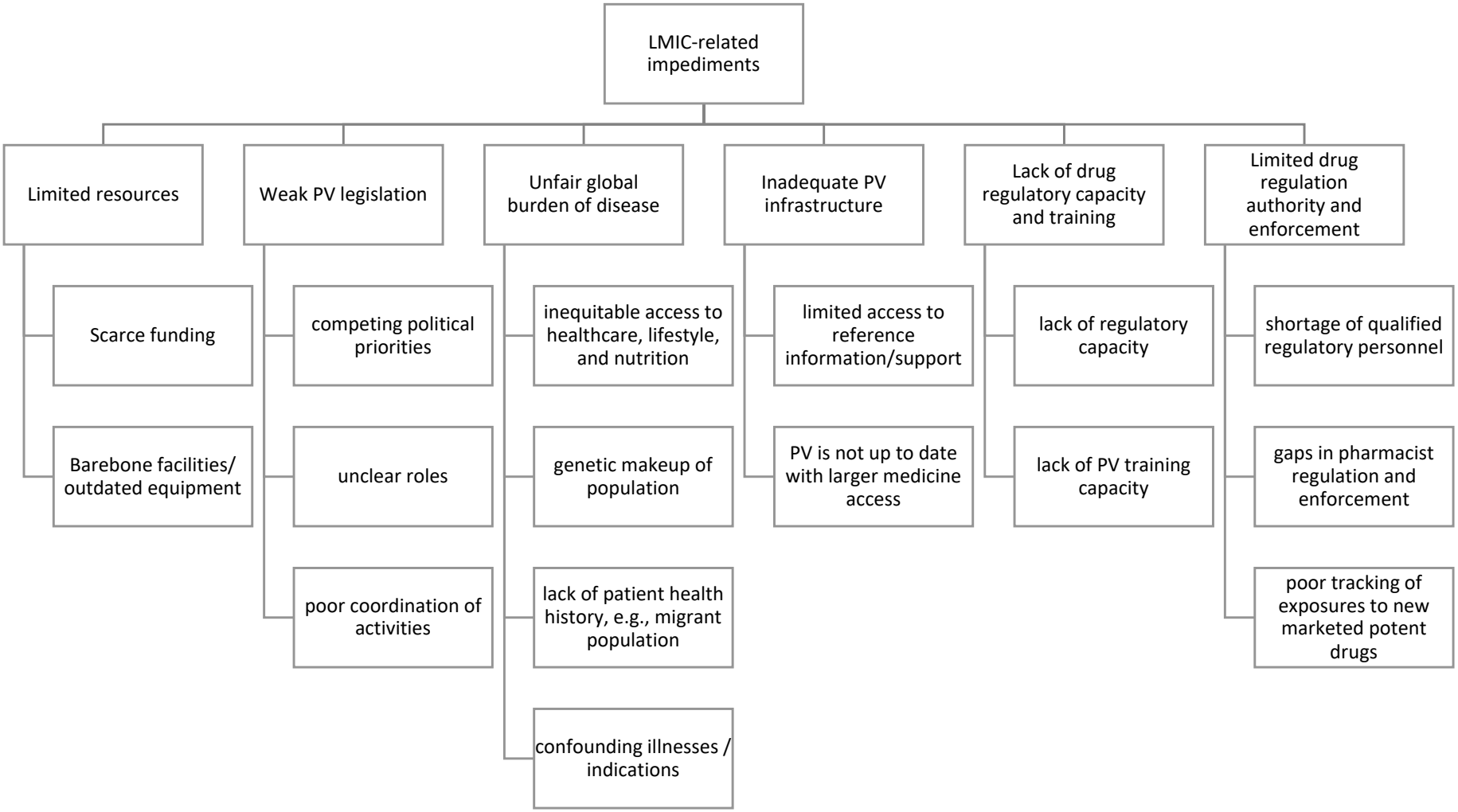
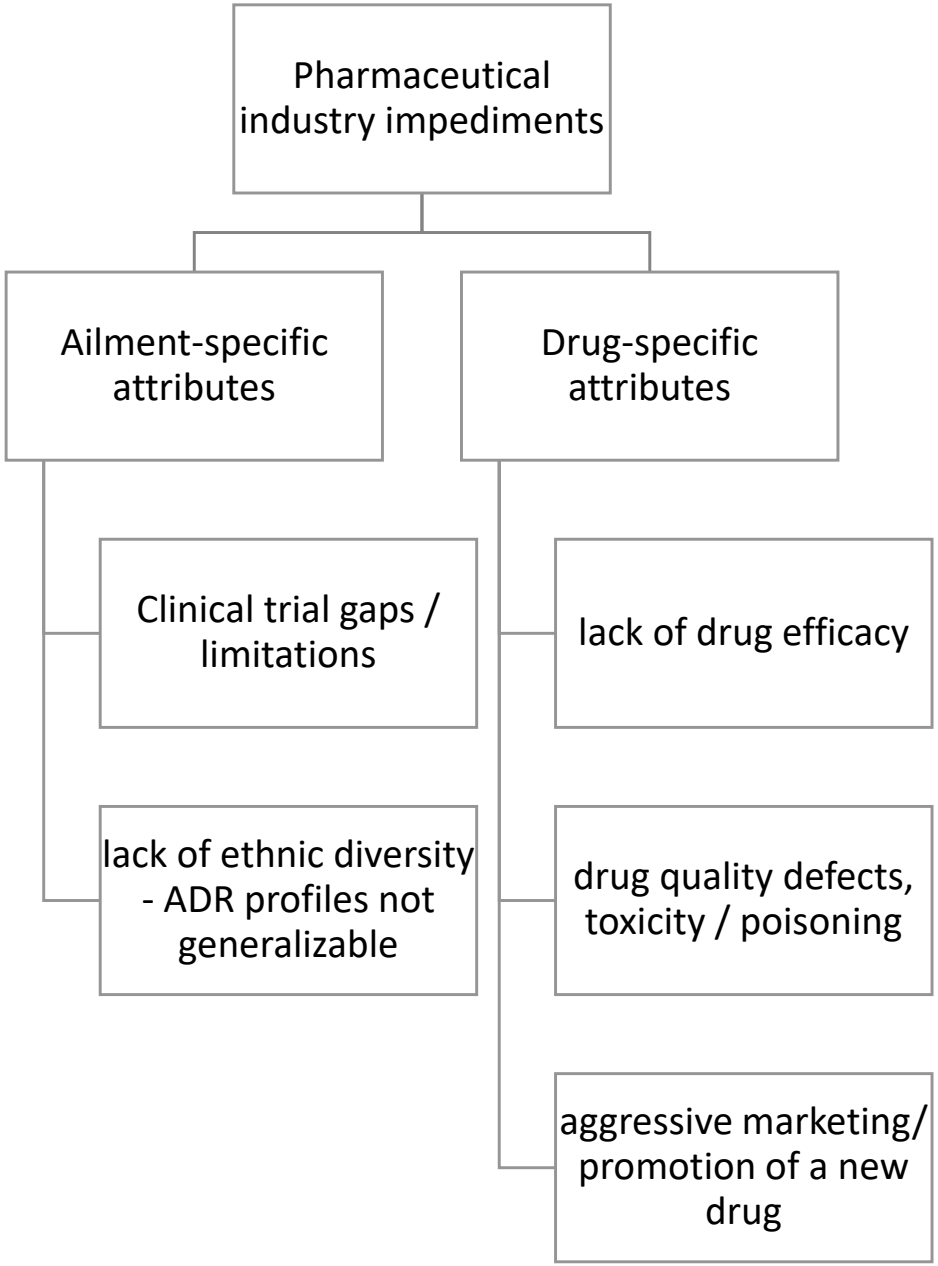
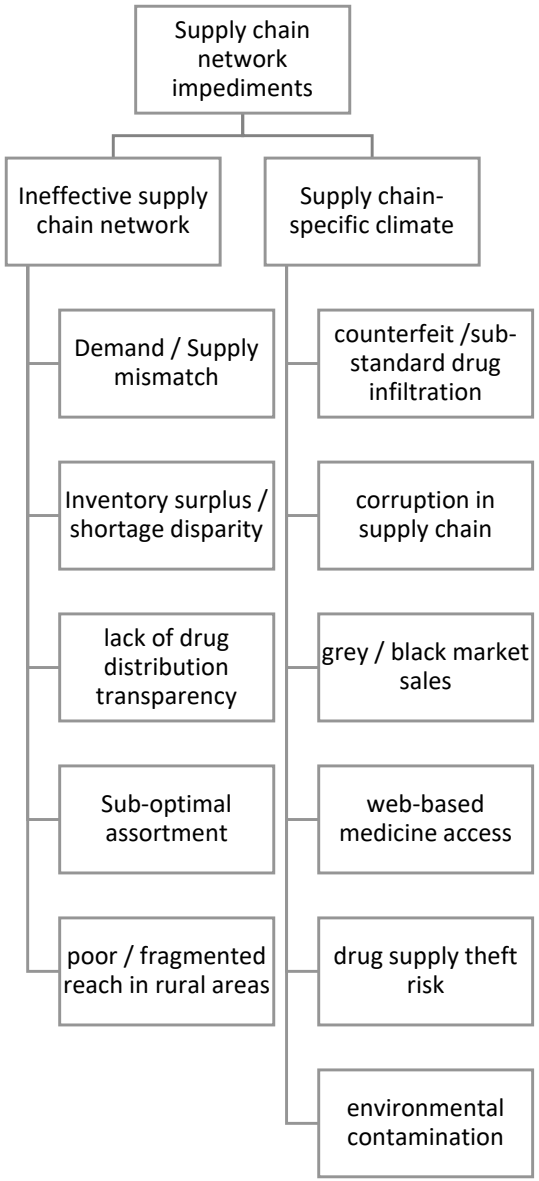
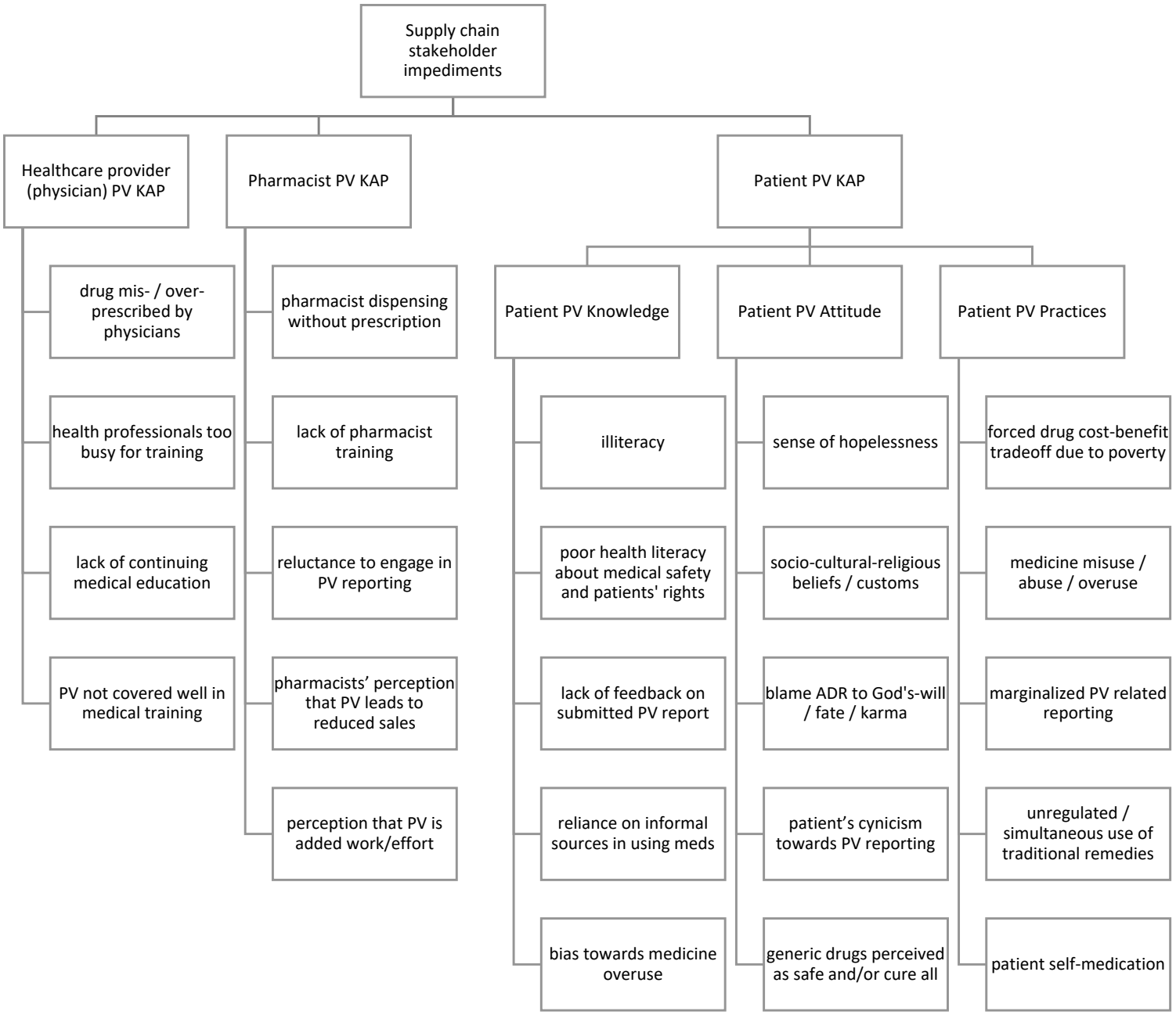

Pharmaceutical Supply Chain
Pharmaceutical Industry Impediments
LMIC-related Impediments
Supply Chain Network Impediments
Drug Safety Outcome Impediments
Supply Chain Stakeholder Impediments

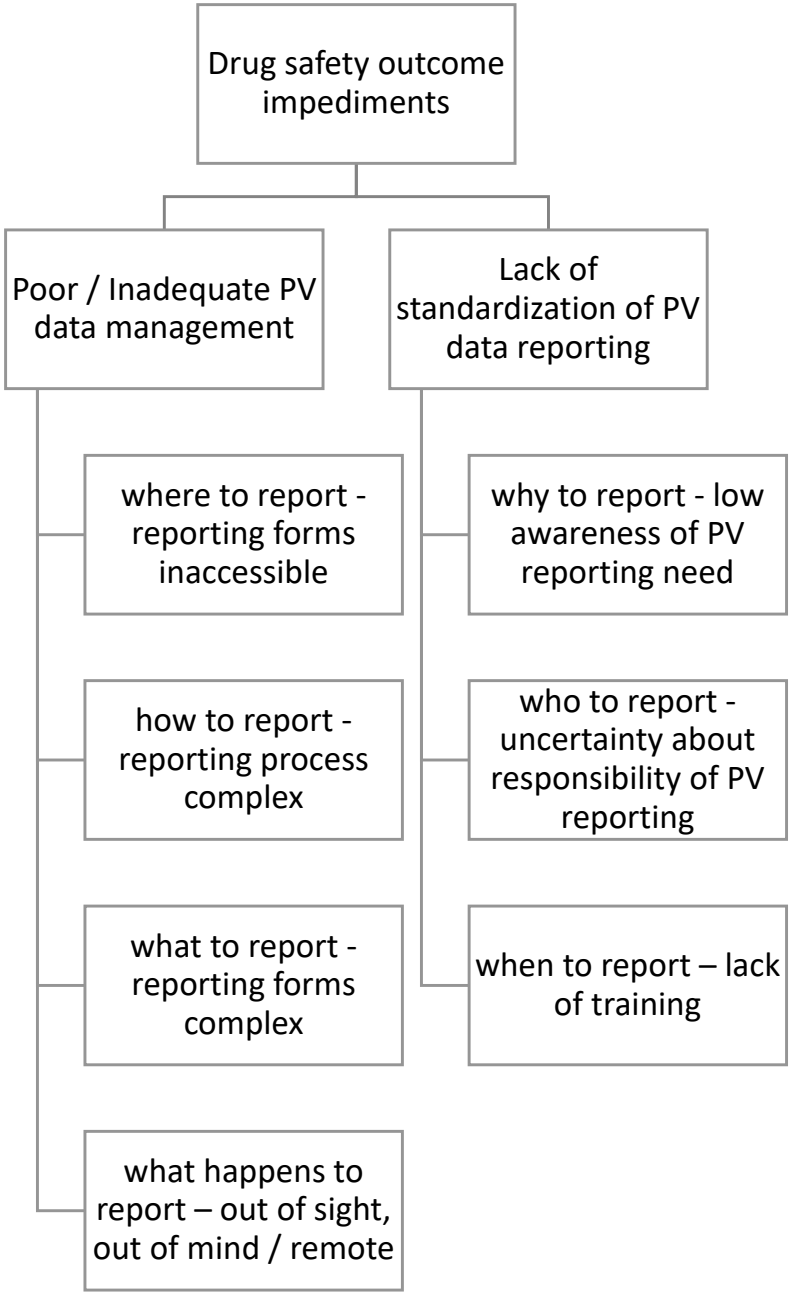

Identification
Screening
Eligibility
Inclusion
Systematic search in databases for PV in LMICs (1744)
Duplicates (573)
Journal analysis (1171)
Inadequate subject areas:
Not on supply chain (567)
Not PV impediments (229)
Peer-review abstract assessment (375)
Inadequate topics:
Case studies (156)
Editorials, etc. (114)
Peer-review of full papers (105)
Unclear definition of PV
inadequate scope of analysis (59)
Final sample (46)


LMIC-related impediments
Limited resources
Weak PV legislation
Unfair global burden of disease
Inadequate PV infrastructure
Lack of drug regulatory capacity and training
Limited drug regulation authority and enforcement
Scarce funding
Barebone facilities/ outdated equipment
competing political priorities
unclear roles
poor coordination of activities
inequitable access to healthcare, lifestyle, and nutrition
genetic makeup of population
lack of patient health history, e.g., migrant population
confounding illnesses / indications
limited access to reference information/support
PV is not up to date with larger medicine access
lack of regulatory capacity
lack of PV training capacity
shortage of qualified regulatory personnel
gaps in pharmacist regulation and enforcement
poor tracking of exposures to new marketed potent drugs


Pharmaceutical industry impediments
Ailment-specific attributes
Drug-specific attributes
Clinical trial gaps / limitations
lack of ethnic diversity - ADR profiles not generalizable
lack of drug efficacy
drug quality defects, toxicity / poisoning
aggressive marketing/ promotion of a new drug


Supply chain network impediments
Ineffective supply chain network
Supply chain-specific climate
Demand / Supply mismatch
Inventory surplus / shortage disparity
lack of drug distribution transparency
Sub-optimal assortment
poor / fragmented reach in rural areas
counterfeit /sub-standard drug infiltration
corruption in supply chain
grey / black market sales
web-based medicine access
drug supply theft risk
environmental contamination


Supply chain stakeholder impediments
Healthcare provider (physician) PV KAP
Pharmacist PV KAP
Patient PV KAP
drug mis- / over-prescribed by physicians
health professionals too busy for training
lack of continuing medical education
PV not covered well in medical training
pharmacist dispensing without prescription
lack of pharmacist training
reluctance to engage in PV reporting
pharmacists' perception that PV leads to reduced sales
perception that PV is added work/effort
Patient PV Knowledge
Patient PV Attitude
Patient PV Practices
illiteracy
poor health literacy about medical safety and patients' rights
lack of feedback on submitted PV report
reliance on informal sources in using meds
bias towards medicine overuse
sense of hopelessness
socio-cultural-religious beliefs / customs
blame ADR to God's-will / fate / karma
patient's cynicism towards PV reporting
generic drugs perceived as safe and/or cure all
forced drug cost-benefit tradeoff due to poverty
medicine misuse / abuse / overuse
marginalized PV related reporting
unregulated / simultaneous use of traditional remedies
patient self-medication


Drug safety outcome impediments
Poor / Inadequate PV data management
Lack of standardization of PV data reporting
where to report - reporting forms inaccessible
how to report - reporting process complex
what to report - reporting forms complex
what happens to report – out of sight, out of mind / remote
why to report - low awareness of PV reporting need
who to report - uncertainty about responsibility of PV reporting
when to report – lack of training