

Review Article

Tackling Drug Shortages: An In-Depth Systematic Review Protocol

Reem Alraya , Mohammed Kanan , Ahmad k. Aljabri , Baiaan Alsaadi , Maryam M Althubiani , Sarah Alamri , Abdullah Alqarni , Yazeed Alenazi , Assaf Almutairi , Amani Alshehri , Nofa Alshammari 

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Abstract

Addressing global drug shortages demands proactive measures. Enhanced reporting, supply chain policies, and quality systems are crucial to minimize it. Notably, there's a lack of systematic review on the reasons of drug shortage. To fill this gap, our study will adhere to PRISMA guidelines for systematic reviews, conducting a thorough literature search across various databases using specific descriptors related to drug shortages. Articles will be screened for relevance, with eligibility assessed by two independent reviewers and disagreements resolved through consensus. Duplicates will be removed, and data will be extracted using a standardized form. Quality assessment will employ the Mixed Methods Appraisal Tool, with appraisals conducted independently by two reviewers and discrepancies resolved through consensus. A narrative synthesis approach will be used to synthesize findings, initially presenting results in tabular form before discussing and structuring them into themes. Drug shortages are caused by a range of factors, including issues with drug supply, demand, and regulatory challenges. These factors interact in complex ways, requiring comprehensive solutions to effectively address the scarcity of medicines.

Reem Alraya. Department of Pharmaceutical Care, First Health Cluster in Eastern Province, King Fahad Specialist Hospital, Dammam, Saudi Arabia. Reem.raya@kfsh.med.sa

Mohammed Kanan. Department of pharmaceutical care, Rafha Central Hospital, Northern Border Health Cluster, Kingdom of Saudi Arabia, Rafha . ii_kanan101@outlook.com

Ahmad k.Aljabri. Clinical Pharmacy Services, Pharmacy department, King Salman Bin Abdulaziz Medical City, Madinah Health Cluster,Madinah, Kingdom of Saudi Arabia, Akbaljabri@gmail.com

Baiaan Alsaadi. Clinical Pharmacy Services, Pharmacy department, King Salman Bin Abdulaziz Medical City, Madinah Health Cluster, Madinah, Kingdom of Saudi Arabia, Baiaana@moh.gov.sa

Maryam M Althubiani. Department of Clinical Services, Pharmaceutical Care Services, King Salman Medical City, MOH, Al Madinah Al Munawwarah, Saudi Arabia, mmalthobiany@moh.gov.sa

Sarah Alamri. Department of Pharmacy, King Faisal University, Al Hofuf 31982, Saudi Arabia. Sarah.f.amri@gmail.com

Abdullah Alqarni. Department of Pharmacy, Aldawaa Medical Services Co, Kingdom of Saudi Arabia, Riyadh, 13249.alqarni.ph@gmail.com

Yazeed Alenazi. Department of Pharmacy, Northern border university, Kingdom of Saudi Arabia, Rafha, 34217 Yz_saud@outlook.com

Assaf Almutairi. Department of public health, Rafha Central Hospital, Northern Border Health Cluster, Kingdom of Saudi Arabia, Rafha. assafaa@moh.gov.sa

Amani Alshehri . PharmD student, king Khalid University, Abha 62542 , Saudi Arabia. amani.a.alshehri.02@gmail.com

Nofa Alshammari. Department of Pharmacy, Security Forces Hospital, Riyadh, KSA. aalshammarin@gmail.com

INTRODUCTION

Patient's care and health management encompasses the use of medicines that are important for enhancing the well-being and the overall quality of life of patients¹. The access to medicines is deemed an intrinsic human right². Despite advances in production, delivery, and transportation technologies, medication shortages remain a significant global concern. This growing issue has become a major health challenge in recent times, highlighting that supply issues are more complex than anticipated³. In the past few years, there have been reports of deficits in medicinal and vaccination supplies across both high and low-income countries⁴. The repercussions for patients can be quite severe during the shortage duration⁵. The potential consequences of these can be fatal, alteration in treatment, subpar medical care, and therapeutic errors^{6,7,8}. The shortage of drugs continues to have significant negative impacts on both public health and the economy^{9,10}.

The World Health Organization (WHO) reports that about 33% of the global population is affected by drug shortages, leading to inadequate access to safe, reliable, effective, and high-quality medications^{2,11}. Drug shortages have become a widespread issue impacting people across all socio-economic levels. The shortage of drug has received a disproportionate attention in high-income countries when contrast to other regions¹². Several entities including government associations and agencies have devised diverse guidelines, programs and policies to tackle this occurrence¹³. Many countries have adopted various strategies to address drug shortages, tailored to factors such as financial resources, healthcare system strength, and prior research. These



approaches include improving reporting mechanisms, revising policies, creating drug shortage platforms, and accelerating drug approval processes^{14,15}. Managing drug shortages and procuring alternative medications can be costly, often totaling hundreds of millions of dollars annually for high-income countries (HICs)¹⁶. Contrary to HICs, Low- to middle-income countries (LMICs) face unique challenges contributing to drug shortages, including issues with product and manufacturer licensing, limited access to raw materials for local production, illegal drug trafficking, and government policies on taxes and regulations¹⁷. Unlike HICs, LMICs encounter multiple new factors contributing to the commencement of drug shortages¹⁸. There are some narrative, rapid or mini reviews on the drug shortage but according to best of our knowledge till date no systematic review is presented in the scientific knowledge about the reasons of drug shortage.

METHODS

Search strategy

The PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines will adhere for this review. A thorough literature search will be conducted across multiple databases including Cochrane, PubMed (Medline), PsycINFO, Google Scholar, Scopus, Science Direct, and Springer Links. The search utilizing descriptors such as “medicine shortage,” “medicine supply,” “drug shortage,” “cause of drug shortage,” “solutions to drug shortage,” “issues of drug shortage,” “problem of drug shortage,” “remedies of drug shortage,” “drug shortage dilemma,” “drug shortage in LMICs,” “drug shortage in HICs,” “difficulties in medicine availability,” and “matters of drug shortage.” will be applied.

Article selection and data collection

The title and abstract of each retrieved article will be assessed for relevance. In case of any ambiguity or uncertainty, the complete article will be investigated for relevance. The articles will then be further assessed according to inclusion and exclusion criteria.

Study selection

The studies identified through the literature search will be screened by two independent reviewers to assess their eligibility. Any disagreements will be resolved through consensus or by involving a third reviewer. After evaluating all the databases, the studies will be screened for duplications, which will then be deleted. The articles will also be excluded after screening the titles and abstracts.

Data extraction

Data will be extracted from the eligible studies using a standardized data extraction form. The data will include information on study references, designs, sample size, participant, research objectives, and outcome measures.

Quality assessment

The “Mixed Methods Appraisal Tool” will be used to appraise

the quality of the empirical studies, as it covers a variety of methodologies. Five core quality criteria for each of the following categories of study designs will be included: qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies, and mixed-method studies. Critical appraisals of the methodological quality and the risk of bias assessment of the included papers will be undertaken independently by two reviewers. A third reviewer will be consulted in cases of disagreement without reaching consensus.

Analysis

A narrative synthesis approach will be used to synthesize the findings of the included articles due to the heterogeneity of the studies in the review, with a range of methodologies. First, a preliminary synthesis will be conducted to search the studies and present results in a tabular form. Then, the results will be discussed by two reviewers and structured into themes. The studies included in the narrative synthesis will then be summarized within a framework. Themes and contextual factors like intervention, effectiveness of interventions and barriers will be synthesized.

RESULTS

The causes of drug shortages vary depending on the specific type of medication¹⁹. In general, the reasons behind drug shortages can be attributed to problems with the drug supply, demand, or regulatory factors^{20,21}.

DISCUSSION

Reasons

Drug shortages globally affect patient care and increase healthcare costs. Understanding the reasons behind these shortages is vital for developing effective strategies to address them. Concerns about drug supply, including technical issues, raw material shortages, logistical challenges, and economic factors, contribute to manufacturing halts. To mitigate these shortages, improvements in manufacturing, raw material sourcing, supply chain management, and regulatory processes are necessary²²⁻²⁶. HICs have made progress, but LMICs face financial issues affecting medicine quality and supply chain interruptions^{27,22}.

Production issues, particularly quality and competing priorities, contribute significantly to drug shortages. Studies in HICs like Canada, Finland, and Saudi Arabia emphasize manufacturing challenges as a major issue^{26,28,14}. In contrast, LMICs such as China and Pakistan encounter manufacturing challenges due to lower disease incidence, insufficient regulatory policies, and financial limitations^{18,29}. Quality issues are a major driver of drug shortages, stemming from factors such as microbial contamination, the presence of endotoxins, and violations of Good Manufacturing Practice (GMP) standards^{30,31}. Quality issues frequently result in voluntary recalls and contribute substantially to drug shortages^{19,26}.



Raw material shortages like ingredients and packaging materials can cause delays in drug manufacturing and worsening shortages³⁴⁻³⁷. Political instability, trade disputes, and environmental disasters can disrupt the critical components' supply chain, affecting essential medication production and availability^{5,38-43}. Low prices for generic drugs and cost-saving measures like plant consolidation can lead to drug shortages^{7,44-47}. Orphan drugs, with their small market sizes, are especially susceptible to shortages³³. LMICs often face shortages due to procurement processes and local drug purchasing practices⁴⁹⁻⁵³. Transportation challenges and supply chain issues exacerbate drug shortages. Weather, traffic, and disasters disrupt deliveries^{41,42}. Poor inventory management and supply chain coordination worsen shortages by creating imbalances between supply and demand^{19,44-46}.

Just-in-time inventory systems and demand fluctuations contribute to drug shortages^{20,33}. Marketing efforts and demand spikes during outbreaks contribute to shortages⁶¹⁻⁷¹. Single-supplier drug tendering can exacerbate shortages⁵¹. Regulatory factors including inflexible processes and communication gaps among stakeholders are significant contributors to drug shortages in LMICs^{2,63,95}. Strict enforcement of safety and efficacy standards can disrupt supply and demand, leading to drug shortages^{23,96}.

Remedies

During drug shortages, healthcare institutions could manage medicine stocks by optimal patient care. Several strategies can be employed to address this issue and mitigate its impact on patient outcomes. One approach is to implement prioritization criteria for allocating the limited medicine stock to specific patients. Modeling methods, decision-making process ensures the availability of highly demanding medication⁹⁷⁻¹⁰¹. Healthcare providers prioritize patients requiring immediate therapy^{22,90,92,98}. Additionally, accepting minor flaws in manufacturing can help alleviate shortages. Regulatory authorities like the FDA allow for the use of products with

minor defects, such as packaging or labeling issues, under strict supervision and proper handling protocols^{16,67,103-109}. This approach optimizes available resources while upholding safety standards and mitigating potential risks.

Extending the expiry dates of near-expiry drugs offers another solution to address shortages. Regulatory evaluation helps the medications safe and effective beyond their expiry date and ensures the availability of therapy treatments^{66,109-113}. Ensuring the redistribution of available drugs is key to solve issues. Manufacturers play a vital role in coordinating distribution, collaborating with stakeholders, and maintaining open communication to address shortages effectively^{114-116,20}.

Establishing an expert platform at the institution level facilitates proactive management of drug shortages. Multidisciplinary teams assess the impact of shortages, review alternative treatment strategies, and provide guidance on medication utilization, optimizing patient care even in challenging circumstances¹¹⁶⁻¹²⁰. Utilizing leftover drugs through strategic scheduling and techniques like the double syringe method minimizes waste and maximizes the use of available resources, particularly in chronic conditions like oncology and pediatrics^{117,121-124}.

CONCLUSION

Drug shortages pose a significant global challenge impacting patient care and healthcare costs. These shortages result from various factors, including production issues, regulatory constraints, and logistical challenges. HICs and LMICs face distinct obstacles in addressing shortages, with financial constraints being prominent in LMICs. Solutions entail improvements in manufacturing, supply chain management, and regulatory processes, alongside proactive measures like prioritization criteria for drug allocation and extension of expiry dates. Collaboration among stakeholders is key to managing drug shortages and ensures the access that improves patient outcomes.

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