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Systematic review

A systematic review of antibiotic drug shortages and the strategies employed for managing these shortages

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ABSTRACT

Background: There is a need to examine the impact of increasingly prevalent antibiotic shortages on patient outcomes and on the emergence and spread of antimicrobial resistance.
Objectives: To: (1) assess patterns and causes of shortages; (2) investigate the effect of shortages on health systems and patient outcomes; and (3) identify strategies for forecasting and managing shortages.
Data sources: PubMed/MEDLINE, EMBASE, Scopus, and Web of Science.
Study eligibility criteria: Studies published in English from January 2000 to July 2023. Participants health care, policy, and strategic teams managing and responding to shortages. Patient populations (adults and children) affected by shortages.
Participants: Healthcare workers responding to and populations affected by antibiotic shortages.
Interventions: Strategies, policies, and mitigation options for managing and responding to antibiotic drug shortages.
Assessment of risk of bias: The methodological quality of included studies was reviewed using the most appropriate tool from Joanna Briggs institute critical appraisal tool for each study design.
Methods of data synthesis: Data synthesis was qualitative and quantitative using descriptive statistics.
Results: The final analysis included 74 studies (61/74, 82.4% high-income countries). Shortages were most reported for piperacillin-tazobactam (21/74, 28.4%), with most of the reported antibiotics being in the WHO Watch category (27/54, 51%). Frequent cause of shortages was disruption in manufacturing, such as supply of active pharmaceutical ingredients and raw materials. Clinical implications of shortages included increased length of hospital stay, treatment failure after using inferior alternative agents, and a negative impact on antimicrobial stewardship programmes (AMS). Robust economic impact analysis of shortages is unavailable. Successfully reported mitigation strategies were driven by AMS and infectious diseases teams in hospitals.

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Conclusions: Antibiotic shortages are directly or indirectly driven by economic viability and reliance on single source ingredients. The limited data on clinical outcomes indicates a mixed effect, with some infections becoming more difficult to treat, though there is no robust data on the impact of shortages on antimicrobial resistance. The mitigation strategies to manage shortages rely heavily on AMS teams. **Avaneesh Kumar Pandey, Clin Microbiol Infect 2025;31:345**

Introduction

The lack of access to safe and effective antibiotics is a threat to global health security and contributes to the emergence and spread of antimicrobial resistance (AMR) [1–3]. Increasingly common, shortages of antibiotics are an additional threat, hindering effective antimicrobial stewardship programmes (AMS) [4]. In a recent review of existing National Action Plans for AMR, we described the lack of clear objectives for responding to the need to ensure robust, stable, and quality assured antibiotics [5]. The threat of antibiotic drug shortages impacts low-income and middle-income countries (LMICs) and high-income countries (HICs) [6–8]. The COVID-19 pandemic has highlighted the fragility of existing supply chain systems and the risk of antibiotic agents being struck off the manufacturing priorities of pharmaceutical companies [9,10].

Early in the COVID-19 pandemic, azithromycin was suggested as a potential therapeutic option; however, evidence soon emerged indicating its lack of efficacy for COVID-19 [11]. Despite this, hoarding and inappropriate use led to its shortage in many countries [12]. In 2022, an unseasonal surge in Group A *Streptococcus* infection among children in the United Kingdom resulted in the deaths of 48 children. In response, health authorities reduced the prescription threshold for penicillin and amoxicillin, leading to a surge in demand [13,14], which increased wholesale prices and caused a demand-driven shortage. Although the issue of shortages is capturing the attention of policymakers with steps being taken to mitigate the impact in HICs, the mechanisms to report and take necessary steps to minimise their impact are not streamlined, particularly in LMICs.

Building on an initial review highlighting the scale of the problem of shortages and the need for sustainable approaches to better understanding their causes and consequences [4], we performed a systematic review to investigate the existing evidence for (1) patterns and causes of shortages; (2) the effects of shortages on supply systems, health systems, and patient outcomes; and (3) strategies for forecasting and managing shortages, including within AMS. This review represents the initial phase of a broader, comprehensive programme focused on identifying evidence-based solutions.

There are several websites predominantly based in HICs, such as the U.S. Food and Drug Administration (FDA) and the European medicines agency, that report on medicine shortages, such as antibiotics [15,16]. The academy of health systems pharmacists does have a resource page for drug shortages, which includes self-reporting by pharmacists. On this website, as of June 30, 2024, there were 39 active antimicrobial drug shortages reported in the United States [17]. Although these websites provide notice of a shortage and an expected end date, information is lacking with regards to mitigation strategies at health care system level or analysis of consequences of these shortages. Having reviewed the information available on these websites, we purposefully included peer-reviewed publications providing empirical findings on the causes and consequences of antibiotic shortages.

Methods

Study design

The systematic review was registered in Prospero [CRD42021296472]. Two reviewers independently performed the first search on PubMed/MEDLINE, EMBASE, Scopus, and Web of Science on 31 May 2022, with a subsequent search on 22 July 2023. The search strategy included indexing (MeSH) terms and text words for antibiotic agents and antibiotic supply chains, antibiotic prescribing, shortages of essential antibiotics, and medicine shortages, globally. The MEDLINE search strategy is available as supplementary files. This search strategy was adapted to match the syntax and subject headings appropriate for other databases.

The reference lists of included studies and related systematic reviews were also searched to identify additional relevant studies. Search results were exported and uploaded to Rayyan (a systematic review management system). Duplicates were manually cross-checked and removed.

Study inclusion and exclusion criteria

The search was limited to studies published since 1 January 2000, reflecting the period when supply chains and procurement systems began to change, with an increased reliance on single-supplier models, and the migration of active pharmaceutical ingredient (API) manufacturers to China and India. The results include articles published in English; in supplementary files, we have included the relevant articles that were not in English. We included studies that reported on antibiotic shortages and at least one of the following outcomes: causes of shortages, duration of shortages, clinical and economic impacts, and mitigation strategies. Antitubercular, antimalarial, anti-retroviral, other anti-viral agents, and antifungals were excluded, as were studies that mentioned antibiotic shortages without including data on rationale, management, or impact analysis of those shortages.

Data extraction (selection and coding)

We used Rayyan software for reviewing articles. Study selection was performed independently by pairs of reviewers. Discrepancies were resolved with moderation and input from a separate set of reviewers. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to map the selection process. The methodological quality of included studies was assessed using the most appropriate critical appraisal tool for each study design from the Joanna Briggs institute check lists [18]. The risk of bias was independently evaluated by two reviewers, and any disagreements were mutually resolved, with input from a third reviewer if necessary. Data were thematically analysed and coded under the relevant defined drivers and outcomes of shortages. Descriptive statistics were used to analyse the included studies.

Antibiotics were categorised by the WHO AWaRe [19] classification and the WHO essential medicines list [20]. Heterogeneity of the included studies precluded meta-analysis. Where possible, quantitative data from the studies along with thematic qualitative findings have been included.

Results

Descriptive statistics of the included evidence

Fig. 1 summarises the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of included studies. Table S1 in supplementary materials provides a full summary of the 74 publications in the systematic review of antibiotic shortages, categorised by study type. The details of the 12 non-English studies are also provided. Of the included publications in English, 61/74 (82%) were from HICs, majority (70%) being from North America and Europe (Table 1). Injectables were the most common formulation reported (85%). In 54 studies, where the population affected by the shortages was defined, 59% (32/54) reported adults and paediatric populations, 35% (19/54) only adults, and 9% (5/54) reported paediatric population exclusively. In Table S1, the reported impacts of shortages (antibiotic use, clinical, and economic) and any mitigation strategies are presented. Where sufficient empirical data were not provided, we have summarised the key findings.

Of the antibiotics reported, 37% (20/54) were in the Access, 51% (27/54) Watch, and 11% (6/54) in Reserve WHO categories. Agents most affected by shortages were piperacillin-tazobactam (TZP) (21/74, 28%), penicillin G (15/74, 20%), gentamicin (9/74, 12%), meropenem (9/74, 12%), cefazolin (11/74, 15%), and ampicillin (8/74, 11%) (Table 2). The duration of shortage was specified in 43 (58%) studies, with four studies reporting ongoing or unresolved shortages. The median reported duration was 232.5 days, ranging from a minimum of 31 days to a maximum of 8 years.

Table 1
Regions of the world and countries where shortages are reported in the papers included in the systematic review

Continents *N* (%)	Country name	No. of studies
America 32 (43)	United States	31
	Canada	1
Europe 18 (24)	Belgium	1
	Europe wide	4
	France	3
	Germany	1
	Hungary	1
	Italy	2
	Spain	5
	Switzerland	1
Asia 14 (19)	Japan	8
	Indonesia	1
	Pakistan	1
	India	2
	Saudi Arabia	1
	Jordan	1
Australia 2 (3)	Australia	1
	New Zealand	1
South America 3 (4)	Brazil	3
Africa 4 (5)	Malawi	2
	South Africa	1
	Ethiopia	1
Global 1 (1)	Global	1

The included studies ranged from quantitative before and after studies (48/74, 65%), surveys of health care professionals nationally, regionally, and globally (16/74, 22%), qualitative studies (6/74, 8%), and mixed methods studies (4/74, 5%).

The reasons behind antibiotic shortages varied, with the most common issues relating to a lack of supply of raw materials and

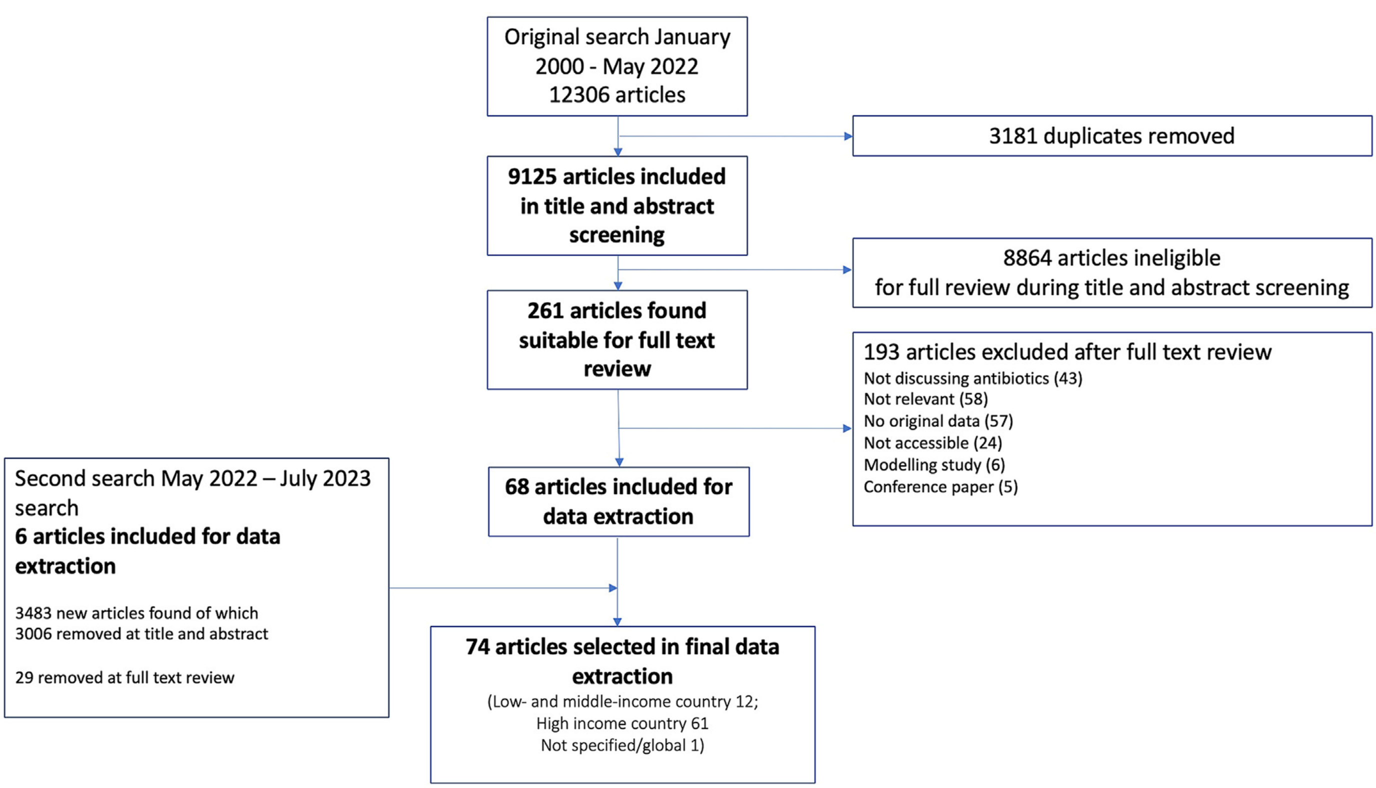

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included studies in the systematic review of antibiotic shortages and the strategies employed for managing these shortages.

Table 2
Antibiotics shortages reported in the published literature by WHO access, watch, reserve categories, and essential medicines list status

Class *N* (%)[a]	Name (*n* = 54)	No of studies reported the shortages (*n* = 74)	Aware (A) *n* = 20 (37%) Watch (W) *n* = 27 (51%) Reserve (R) *n* = 6 (11%)	Eml status essential (E) *n* = 37 (69) Not essential (NE) *n* = 17 (31)
Aminoglycoside: 13 (17)	Gentamicin	9	A	E
	Tobramycin	2	W	E
	Amikacin	1	A	E
	Kanamycin	1	W	E
Antimetabolites 4 (5)	Co-trimoxazole	1	A	NE
	Sulfamethoxazole-trimethoprim	3	A	E
Carbapenems 14 (19)	Meropenem	9	W	E
	Imipenem	4	W	E
	Doripenem	1	W	NE
Cephalosporins 35 (47)	Cefazolin	11	A	E
	Cefotaxime	5	W	E
	Ceftazidime	2	W	E
	Cefepime	5	W	NE
	Cefpodoxime	2	W	NE
	Cefixime	2	W	E
	Ceftolozane	1	R	E
	Cefpodoxime	1	W	NE
	Cefotiam	1	W	NE
	Cefmetazole	1	W	NE
	Cefalexin	1	A	E
	Ceftizoxime	1	W	NE
	Ceftriaxone	1	W	E
	Cefuroxime	1	W	E
Fluoroquinolones 6 (8)	Ciprofloxacin	5	W	E
	Levofloxacin	1	W	E
Glycopeptides 6 (8)	Vancomycin	6	W	E
Lincosamides 1 (1)	Clindamycin	1	A	E
Macrolides 8 (11)	Erythromycin	3	W	E
	Azithromycin	3	W	E
	Clarithromycin	2	W	E
Monobactam 6 (8)	Aztreonam	6	R	NE
Monoxycarbolic acid 2 (3)	Mupirocin	2	—	E
Nitroimidazole 3 (4)	Metronidazole	3	A	E
Oxazolidinones 1 (1)	Linezolid	1	R	E
Penicillin 68 (92)	BPG	15	A	E
	Amoxicillin	7	A	E
	Amoxicillin + clavulanic acid	2	A	E
	Piperacillin + Tazobactam	21	W	E
	Ampicillin	8	A	E
	Procaine penicillin	2	A	E
	Doxycycline	5	A	E
	Nafcillin	2	A	NE
	Ticarcillin	3	W	NE
	Sultamicillin	1	A	NE
	Cloxacillin	1	A	E
	Oxacillin	1	A	NE
Polymyxins 3 (4)	Colistin	3	R	E
Streptogramins 1 (1)	Dalfopristin	1	R	NE
Tetracycline 1 (1)	Minocycline	1	R	NE
Miscellaneous 7 (9)	Chloramphenicol	1	A	E
	Fusidic acid	2	W	NE
	Fosfomycin	3	W	E
	Spectinomycin	1	A	E

BPG, benzathine penicillin.

APIs (Table S1 and Table 3). The reliance on single source manufacturers for APIs was a recurring theme, as was the lack of financial incentive to produce low-cost antibiotics. This was linked to supply and demand misalignment. In addition, regulatory and quality assurance concerns raised by auditors and regulatory agencies, such as the FDA, were cited as reasons for shortages.

Reported impact of the shortage on antibiotic prescribing

Antibiotic shortages were associated with increased use of alternative broad-spectrum agents. leading to a knock-on effect, resulting in additional shortages due to the increased demand for the alternative agents. The shortage of the first-generation cephalosporin cefazolin had substantial implications for antibiotic use patterns, particularly in the treatment of methicillin sensitive *Staphylococcus aureus* bacteraemia, where cefazolin was the preferred choice in Japan. Notably, there was a decline in the percentage of patients receiving cefazolin for definitive therapy (53% vs. 82%, p 0.014), leading to increased use of penicillin during the shortage period when compared with before [21]. Increased use of broader spectrum antibiotics, including β-lactams and clindamycin, was reported during the cefazolin shortage in Japan [22,23]. A time-series model study highlighted a substantial increase in use of third-generation cephalosporins in surgical antibiotic prophylaxis in all surgical procedures (1.0–63.1%, $p < 0.001$) during the same period [24].

Table 3
Summary of the reported reasons for shortages by country economic status, AWaRe category and antibiotic class, the totals here are tallied for all included antibiotic shortages which had this data available in the papers

Reasons for shortages	Income status		AWaRe class			Antibiotic class					
	HIC (%)	LMIC (%)	Access (%)	Watch (%)	Reserve (%)	Penicillins, such as β-lactamase inhibitor combinations (%)	Cephalosporins (%)	Carbapenems (%)	Aminoglycosides (%)	Macrolides (%)	Others (%)
Manufacturing problems including lack of supply of API and raw material	19.64	25	45.83	42.42	35.71	44.89	45.45	37.5	35.71	45.00	41.94
Lack of economic viability to sell the product due to lack demand or high manufacturing costs	7.14	37.5	14.58	3.03	—	10.20	9.09	—	—	—	3.23
Failures in procurement and tendering	5.35	25	4.16	3.03	—	6.12	—	12.5	7.14	5.00	6.45
Withdrawn from market and discontinuation	8.92	—	12.5	15.15	21.42	10.20	12.12	12.5	21.43	15.00	16.13
Regulatory and quality related issues in manufacturing, such as failing mandatory audits by governmental bodies	8.92	—	6.25	12.12	14.28	10.20	12.12	12.5	14.29	15.00	12.90
Demand and supply mismatch	21.42	12.5	14.58	24.24	28.57	18.36	21.21	25	21.43	20.00	19.35
Denominator	56	8	48	33	14	49	33	8	14	20	31

API, active pharmaceutical ingredient; HIC, high-income country; LMIC, low-income and middle-income country.

The global shortage of TZP has been associated with increased use of alternative antibiotics [25], such as meropenem, cefepime, metronidazole, clindamycin, vancomycin, fluoroquinolones, and extended spectrum cephalosporins [26,27]. For specific infections, such as intra-abdominal infections, the use of cefepime and ceftriaxone increased by 190% and 57%, respectively, leading to a cefepime shortage in a hospital in the United States [28]. In another study from the United States that assessed the impact of the TZP shortage on existing stewardship efforts, meropenem use increased 110% in a tertiary care setting, with no observed changes in mortality, length, or cost of therapy [29]. High-risk antibiotic use significantly increased across 72 hospitals during the shortage, primarily due to increased use of cefepime [30].

The resulting treatment changes due to the ongoing benzathine penicillin (BPG) shortage have been associated with negative effect on prescribing patterns, potentially contributing to AMR [31]. During a penicillin G shortage in the United States, ampicillin over time completely replaced penicillin G for obstetric practice. Increase in the use of cephalosporins and fluoroquinolones or combinations of agents was reported during this shortage [32].

In surveys evaluating the impact of antibiotic shortages, a significant shift in antibiotic use was observed, with a notable increase in the use of broad-spectrum antibiotics [33]. Previous surveys in 1999 and 2000 highlighted the impact of shortages on treatment regimens, with varying degrees of influence reported. Dispensing second, third, and fourth generation antibiotics and employing broader spectrum agents were common practices during shortages [34].

Clinical and economic impact of antibiotic shortages

There is limited evidence on the clinical and microbiological impact of shortages (Table 4). Cefazolin emerged as an effective and safe alternative during shortages of oxacillin and cloxacillin for treating bloodstream and osteoarticular infections, without promoting methicillin-resistant *Staphylococcus aureus* or extended spectrum β lactamase-producing bacteria [35]. In one hospital in

Table 4
Summary of reported clinical and economic impact of shortages in the included studies in this review

Reported impact of antimicrobial shortages	Total no. of reported outcome measures (total = 69) (*n* [%])		
Clinical impact	Positive impact	Negative impact	No change
1. Delayed antibiotic therapy	—	5 (7.2)	1 (1.44)
2. Duration of hospital stay(s)	—	1 (1.44)	3 (4.34)
3. Duration of antibiotic treatment	—	1 (1.44)	2 (2.89)
4. Adverse drug reactions (no./severity)	1 (1.44)	4 (5.8)	3 (4.34)
5. Hospitalization (no./recurrent)	—	1 (1.44)	1 (1.44)
6. Incidence of *Clostridium difficile* infection	2 (2.89)	2 (2.89)	3 (4.34)
7. Use of alternative regimen and associated net impact on desired outcome	—	5 (7.2)	—
8. Treatment failure	—	5 (7.2)	1 (1.44)
9. Suboptimal therapy	—	6 (8.7)	—
10. Cancellation of care	—	2 (2.89)	—
Economic impact			
11. Overall treatment cost	—	1 (1.44)	1 (1.44)
12. Use of more expensive alternative	1 (1.44)	17 (24.63)	—
Total	4 (5.7)	50 (72.46)	15 (21.73)

the United States, a shortage of TZP was associated with a doubling in the rates of vancomycin-resistant enterococci (VRE) infection [27]. In addition, hospitals experiencing these shortages were found to have an increased risk of hospital-onset *Clostridioides difficile* infection (CDI), and those that switched to high-risk antibiotics during the shortage faced an even higher relative risk [30]. In contrast, findings from another study showed that VRE infection rates remained unchanged during the TZP shortage. However, rates of CDI colitis decreased, which was linked to a reduction in ceftriaxone use [25].

During BPG shortages, there was a 2.17-fold increased risk of a significant rise in congenital syphilis incidence [36], particularly in poorer neighbourhoods. A higher prevalence of congenital and gestational syphilis was observed among patients in Brazil [37]. In addition, prolonged hospitalization and excessive antibiotic use were noted in patients who should have received a single dose of BPG [31].

During cefazolin shortages, there was a significant increase in the risk of reoperation for deep surgical site infections within 30 days of spine surgery [38]. In addition, there was a collapse in AMS, therapy failures, and altered treatment durations [21,23]. After the resolution of the shortages, susceptibility to gram-negative pathogens for cefazolin improved [39], but there was an increase in ceftriaxone consumption [24].

Antibiotic shortages, such as meropenem, imipenem, and TZP, have been associated with a decreased hospital mortality rate during the shortage years, with no significant changes in length of stay or rates of CDI [40]. Shortages of gentamicin ocular formulation for neonatal ocular prophylaxis led to a higher rate of periocular ulcerative dermatitis [41]. In addition, shortages of gentamicin lock solution resulted in increased frequency of bacteraemia [42]. Fusidic acid shortages for methicillin-resistant *Staphylococcus aureus* infections led to the use of various alternative antibiotics, depending on antibiogram results [43]. Amoxicillin shortages in France and Spain, particularly paediatric formulations, posed a serious public health crisis [44].

The surveys on antibiotic shortages report on the use of more toxic agents, delayed treatment, prolonged hospitalization, slower clinical response, and long-term morbidity due to inadequate infection treatment [33]. Respondents reported coping strategies such as substituting equivalent or inferior drugs, delaying therapy, rationing drugs, observing more frequent medication errors, referrals to other hospitals, and switching to lower doses [45]. Adverse outcomes included suboptimal therapy, care cancellations, increased length of stay, readmissions, and nonadministration or delays in administering replacement medicines [46,47]. Over 80% of respondents noted adverse health outcomes due to shortages, leading to less effective, delayed, or even no treatment, and a decrease in patient trust in medications and pharmacists. Shortages also interfered with physicians' ability to prescribe freely [48].

During a carbapenem shortage, AMS teams increased consultations on meropenem use [27,29] The precise costs associated with increased AMS resources during such shortages are challenging to quantify but are considered to be substantial [49].

In addition to the indirect costs resulting from poor clinical outcomes due to antibiotic shortages, several studies report the direct economic burden. A Swiss study reported a significant increase in mean costs per 100 bed days: a 51% increase from \$259.1 to \$391.0 ($p < 0.05$) in hospitals without any cefepime supply [50]. Another study found that the cost of treating CDI rose from \$22 to \$2800 for a 10-day course, due to the substitution of fidaxomicin for vancomycin and metronidazole during the shortage [51]. Other studies have documented the direct economic burden on health care systems [52–55] with one survey reporting the need to make budgetary adjustments to manage antibiotic shortages [6].

Mitigation strategies reported in the included studies

The evidence on mitigation strategies for managing antibiotic shortages includes immediate and longer-term sustainable strategies to manage the impact of shortages on clinical and economic outcomes.

Immediate responses include the following: (1) recommendation of appropriate alternative antibiotics at the hospital level e.g. prolonged use of cefazolin during shortages of cloxacillin and oxacillin [35]; (2) implementation of innovative administration methods to optimize available resources e.g. introducing continuous infusion protocols for selected antibiotics like TZP, cefepime, and ceftazidime, to conserve limited small volume parenteral solutions [56]; (3) change in dosage regimen e.g. changing dose strength of cefepime from 2 g every 8 hours to 1 g every 6 hours [57]; and (4) substituting with alternative antibiotics according to local hospital and national empirical guidelines [32,50].

Studies also emphasize the need for systematic hospital-wide contingency plans, such as providing alternative recommendations for antibiotics such as TZP, intravenous amoxicillin/clavulanate and cefepime based on clinical indications [49]. Re-education initiatives and the adoption of alternative recommendations from the hospital formulary are essential components of effectively coping with shortages [43,58].

Sustainable long-term strategies included the role of government involvement and leveraging the resources of existing AMS and infectious diseases teams at the hospital level. The government's role included providing alternative agents, developing antibiotic policies and lists of approved antibiotics to guide prescribing practices during shortages [22–24,27,38]. One study reported that the government relaxed regulations to allow the import of medicines to address shortages [59]. The presence of AMS programmes was associated with a positive response to managing shortages, as these programmes actively track drug stocks, audit antibiotic use, and modify protocols to replace scarce antibiotics with alternatives [40]. AMS programmes also impose preauthorization from infectious diseases specialists to ensure judicious antibiotic use during shortages [25] and increase consultations and formulary restrictions [28,29]. There is a lack of economic analysis regarding the cost of redirecting AMS services to manage shortages. For example, one study from Japan attributed the cefazolin shortage to the collapse of the AMS programme [23].

Discussion

Antibiotic shortages pose a critical challenge to health care systems worldwide, with consequences extending far beyond simple lapses in drug availability [60]. These shortages impact clinical outcomes, economic stability, AMS strategies, and exacerbate AMR. Given these challenges, there is a need for robust data and sustainable strategies. This systematic review summarises the current evidence on the global causes and consequences of antibiotic shortages. Fig. 2 presents a case study of TZP shortages, illustrating the reasons for shortages, their clinical and economic impacts, and the mitigation strategies adopted. Although economic drivers and consequences remain understudied, they are a recurring theme, such as the market economy for antibiotic production, increased costs in laboratory services, changes in antibiotic use, selection of resistant bacteria causing drug-resistant infections in hospitals, and placing increased service burden on AMS teams.

The existing evidence suggests a complex interplay of factors contributing to shortages, from supply chain disruptions to regulatory obstacles, with significant variability between HICs and LMICs. The unavailability of essential antibiotics leads to the use of alternate antibiotics, which can result in suboptimal treatment, exacerbate

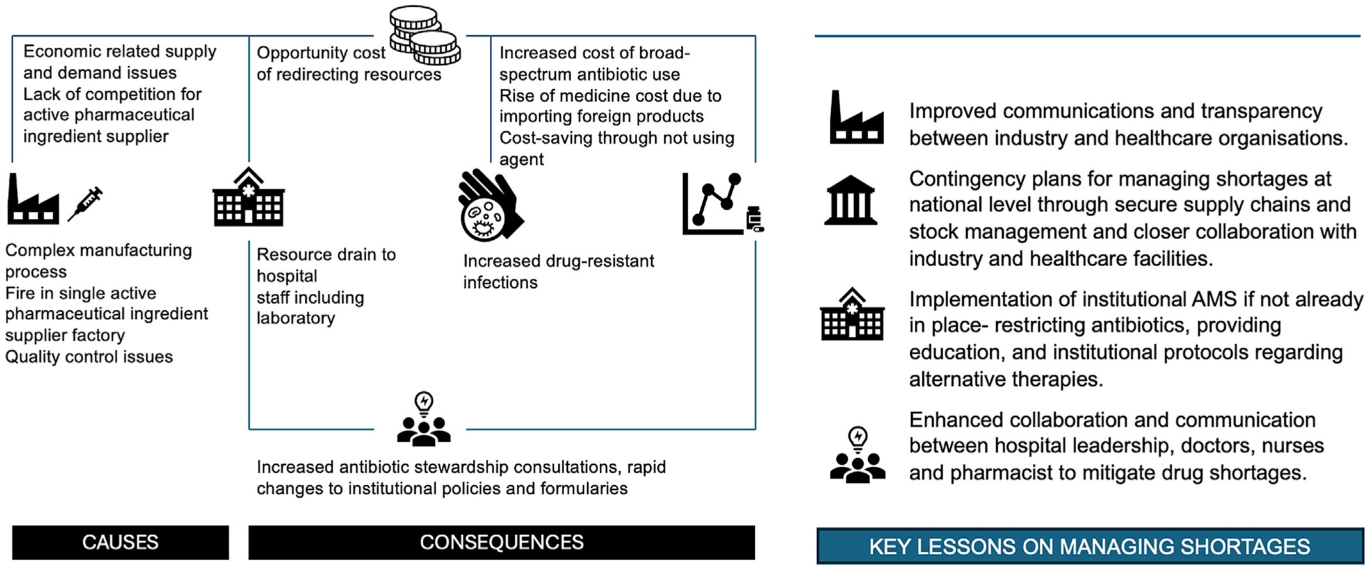

Fig. 2. Piperacillin-tazobactam shortages: a case study of causes, consequences, and recommendations for managing shortages. AMS, antimicrobial stewardship programmes.

existing shortages, and contribute to the development of AMR [61]. A report on shortages estimated the cost of one antibiotic shortage to be between € 20–30 million [62]. Antibiotic shortages may impact AMR through changes in prescribing patterns, leading to the use of suboptimal alternatives, and increasing reliance on more broad-spectrum antibiotics, as illustrated from the combined evidence on TZP in Fig. 2. In addition, shortages may increase the likelihood of substandard antibiotics entering the market [60]. In our review, the most reported antibiotics in shortage were those in the Access and Watch AWaRe categories. The shortages of these first-line antibiotics can have wider clinical and economic impact. The agents used as substitutes have been linked to a higher occurrence of hospital acquired infections such as CDI [25], VRE, and carbapenem-resistant *Enterobacteriaceae* [27].

In HICs, where most of the published evidence originates, the primary cause of shortages is the lack of availability of APIs, leading to the suspension or discontinuation of specific antibiotics. Factors contributing to the unavailability of APIs include batch contamination [22], fires at production facilities [29], shortages of raw material supplies required for API production [21,24], and global scarcities of APIs [45]. Additional factors contributing to shortages in HICs include the cessation of production [31] market withdrawal [42] of certain products and regulatory issues [63]. In LMICs, antibiotic shortages are frequently attributed to concerns about API quality, economic feasibility, and insufficient infrastructure for procurement and stock management. For example, in Brazil, shortages of BPG occurred after regulators revoked a quality certificate for an API supplier [36]. Research from African nations highlights that shortages are primarily due to inadequate funding for procurement, supply problems, insufficient infrastructure for procurement, management, storage, and real-time inventory management, along with reliance on foreign funding [64,65]. Thus, while HICs face challenges related to dependency on international API supplies, LMICs struggle with financial and infrastructural limitations.

The Australian government reported shortages of several antibiotics in 2022–2023 along with mitigation strategies adopted [66]. Similar evidence from LMICs is not available due to weak laboratory capacity, poor health system governance, inadequate health information systems, and limited resources. It is crucial to implement demand forecasting and preparedness systems for antibiotics, invest, and develop sustainable surveillance, and ensure appropriate data sharing with organisations like the WHO's global AMR surveillance system and world organisation for animal health surveillance [4]. Globally, WHO and the Global Antibiotic Research and Development Partnership are funding studies to further explore the causes of antibiotic shortages and potential mitigation strategies. In addition, organisations like the Swedish multi-sectorial platform PLATINEA [67] are focusing on optimising the use of existing antibiotics to ensure patients continue to have access to the effective treatments.

Based on the evidence from the included papers and the authors' expertise, Fig. 2 outlines several solutions for managing antibiotic shortages. Many of these solutions focus on supporting AMS teams at the institutional level, reflecting the existing evidence on their effectiveness. It is important that mitigation strategies are implemented both at country and hospital levels. At the hospital level, AMS programmes are essential for managing antibiotic shortages; however, these shortages can disrupt the effective functioning of AMS programmes [23], and increase the workload and costs [49,68]. Although shortages negatively impact AMS, it has also been reported that AMS is one of the effective strategies to manage shortages [69]. Griffith et al. [70] suggest that AMS pharmacists can play a crucial role in effectively communicating shortages, supervising their management, and quantifying the impact of AMS efforts. Beyond these institutional roles, a national strategy is essential for ensuring safe and reliable antibiotic supply chains. This strategy should also address the threat of AMR and consider the economic consequences of unstable supply chains, and the broader impact of shortages on health systems.

Limitations

While this review aimed to be comprehensive, it is limited by the geographical focus on HICs in the existing published literature, which may overlook the nuances and severity of antibiotic shortages in LMICs. Future research should address this gap by including more studies from LMICs, where the impacts of shortages may be more severe. In addition, there are several limitations in our methodological approach and scope. We focused on identifying evidence for the causes and consequences of shortages from the reported literature and did not include data from national websites such as WHO, centres for disease control, or the FDA. These sources are also biased because most of the websites reporting on shortages are concentrated in HICs. To mitigate the limited evidence, we included conference abstracts discussing the causes and consequences of shortages. Although this limited the level of data that we could collect and report, it did provide an overview of all the existing research that is being undertaken to understand the causes and clinical and economic consequences of antibiotic shortages. Relying solely on published studies provides a biased representation of the scale of the problem, as many more shortages occur than are reported in scientific literature.

Conclusions

Reasons for antibiotic shortages often are directly or indirectly related to economic viability and reliance on single source ingredients. The limited data on clinical and economic outcomes suggests that shortages impose a significant health and financial cost on systems, with no robust data on their impact on AMR. Mitigation strategies to manage shortages rely heavily on AMS teams. The economic analysis of antibiotic shortages and their impact on healthcare systems remains underexplored. Robust and contextualised economic analyses would enhance understanding of the broader economic implications and support the development of policies aimed at minimising these impacts.

Transparency declaration

Potential conflict of interest

E.C. has provided educational seminars and lectures on antimicrobial stewardship and received honoraria for this from Pfizer. The other authors declare that they have no conflicts of interest.

Author contributions

N.S. and E.C. acquired the funding. A.K.P., J.C., N.S., and E.C. developed the study design. A.K.P., J.C., V.N., A.G., O.M., T.T., N.S., and E.C. were responsible for data collection. A.K.P., J.C., O.M., N.S., and E.C. assisted with data interpretation. A.K.P., V.N., O.M., and E.C. wrote the first draft of the paper. All authors have critically read and commented on draft versions of the manuscript and approved the final version. N.S. and E.C. provided equal contribution.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.09.023.

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