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**Highlights**

- Global challenge of antibiotic shortages requires urgent and coordinated responses
- Scarcity of antibiotics is exacerbated by manufacturing obstacles, supply chain vulnerabilities, and regulation barriers.
- This shortage severely impacts patient care and public health worldwide, worsening antibiotic resistance
- Addressing this crisis requires a multifaceted approach, strengthening supply chains, encouraging local production, and market entry incentives.

**Antibiotic shortages: An overview by the Alliance for the Prudent  
Use of Antibiotics (APUA)**

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ABSTRACT

*Background.* Antibiotics have been among the drugs most affected by shortages over the last two decades, with harmful consequences that may persist over years. This position paper was designed by the Alliance for the Prudent Use of Antibiotics (APUA), an international multidisciplinary consortium of experts dedicated to combating antimicrobial resistance.

*Methods.* We performed a narrative review to examine the main causes and impacts of antibiotics shortages, and to identify the solutions that may be proposed to prevent and mitigate this public health threat.

*Results.* The main causes of antibiotic shortages are failure to comply with good manufacturing practices, regulatory issues, unavailability of essential components, unanticipated discontinuation of production by a major supplier, unexpected surges in demand, and other logistical challenges. The main consequences include delays in appropriate treatment administration, overuse of broad-spectrum antibiotics with an increased risk of resistance, reduced efficacy, and increased toxicity due to sub-optimal antibiotics use, increased costs, medication errors, and prolonged or repeated hospital stays. Proposed potential solutions for antibiotic shortages include multidisciplinary international initiatives to foster market entry rewards, specific solutions for low-and-middle income countries (LMICs), strengthening supply chains, encouraging local production, implementing market entry incentives and facilitating the registration process for novel antibiotics and vaccines.

*Conclusions.* Antibiotics shortage severely impacts patient care and public health worldwide. The sustainability of both current and future antibiotics depends on the implementation of effective global health strategies and ongoing financial commitment. Immediate and decisive action is necessary to protect global health for future

generations.

## HIGHLIGHTS

- Global challenge of antibiotic shortages requires urgent and coordinated responses
- Scarcity of antibiotics is exacerbated by manufacturing obstacles, supply chain vulnerabilities, and regulation barriers.
- This shortage severely impacts patient care and public health worldwide, worsening antibiotic resistance
- Addressing this crisis requires a multifaceted approach, strengthening supply chains, encouraging local production, and market entry incentives.

### **1. Introduction**

According to the 2017 World Health Organization (WHO) technical definitions of shortages and stockouts of medicines and vaccines, two perspectives must be considered when defining drug shortages and stockouts. On the supply side, a shortage occurs “when the supply of medicines, health products, and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs.” On the demand-side, a shortage occurs “when demand exceeds supply at any point in the supply chain and may ultimately create a stock-out at the point of appropriate service delivery to the patient if the cause of the shortage cannot be resolved in a timely manner relative to the clinical needs of the patient

(<https://www.who.int/publications/m/item/WHO-EMP-IAU-2017.03>).”

It is crucial to distinguish common short supplies from major shortages. Short supplies are exceedingly frequent and involve drugs for which hospital pharmacists are usually able to find an equivalent product from another company. While these situations represent a considerable burden of work for hospital pharmacists, most physicians are unaware of them, and the consequences for patients are generally limited. Conversely, shortages that result in complete unavailability of a necessary product, often at the national level, have significant consequences for both physicians and patients. Although many studies have demonstrated an increasing trend in drug shortages and shown that antimicrobial drugs and vaccines are the most impacted, there is limited information available to precisely quantify the extent of this phenomenon. Moreover, most of these studies have been conducted from a hospital pharmacist's perspective, with limited assessment of clinical impacts (1).

Over the last two decades, antibiotics have been disproportionately affected by drug shortages compared to other drugs, for multiple reasons that will be detailed in this paper. The deleterious effects of shortages across all drug classes depend on the inability to treat patients according to the guidelines. These consequences may be minor (eg. the need to switch to another antihypertensive drug from the same class), moderate (eg. lack of access to a non-essential drug), or life-threatening (eg. no access to vasopressor agents in patients with septic or cardiogenic shock). In addition, shortages of antimicrobial agents may compromise basic antimicrobial stewardship (AMS) principles, as patients may end up being treated with a broader-spectrum antibiotic due to the unavailability of the optimal narrow-spectrum agent (2). Finally, the ongoing emergence of antibacterial resistance implies a continuous need for innovative

antibiotics to tackle extensively drug-resistant bacteria. This evolving landscape complicates the procurement of necessary antibiotics in many countries. Notably, the potential return-to-investment for antibiotics is among the lowest of all drug classes for several reasons including; i) most antibiotic treatments are prescribed for short durations, and recommended durations tend to decrease over time, resulting in lower potential sales compared to treatments for chronic diseases, which are often prescribed for life, ii) unlike other drugs that retain their intrinsic activity over time, antibiotics may lose a large part of their indications because of the emergence of antibacterial resistance.

The APUA is a not-for-profit organization founded in 1981 with the mission to maximize the effectiveness of antimicrobial treatment by promoting appropriate antimicrobial use and combating drug resistance. In 2019, APUA merged with the AMS group of the International Society of Antimicrobial Chemotherapy (ISAC). This position paper was initiated and decided upon by the APUA members who possess recognized expertise in the field, with professionals from all continents. The recommendations provided are based on a comprehensive review of the most recent and relevant literature on the subject and supported by the collective expertise of the board members. We aim to elucidate the causes, consequences, and potential solutions for the emerging concern of antibiotic shortage, and to advocate for the implementation of preventive measures worldwide.

## **2. Causes of shortage of old and novel antibiotics**

Antibiotic shortages can be broadly categorized into two key areas: the lack of access to existing antibiotics and the lack of access to novel antibiotics designed for drug-

resistant organisms. While the approaches to addressing these issues differ, they are deeply interrelated, affecting the global availability of antibiotics. Table 1 summarizes the main causes of antibiotics shortage.

### *2.1 Shortage of old antibiotics*

The shortage of old antibiotics, which have been long available on the market, is primarily driven by several factors. Compliance with good manufacturing practices and regulatory delays are significant contributors. These requirements, while essential for ensuring drug safety and efficacy, can lead to production delays and disruptions. Additionally, shortages often arise from the unavailability of essential components of the final product, whether the active pharmaceutical ingredient (API) or other inactive but still necessary components. Another critical issue is the discontinuation of antibiotics production by major manufacturers. When a key player exits the market, the supply chain is disrupted, leading to shortages. Transportation issues also play a role; even when antibiotics are produced and available: logistical challenges can prevent them from reaching the market. An unexpected surge in demand, as seen during the COVID-19 pandemic, can also strain supplies, leading to shortages. For instance, a study by the Food and drug administration (FDA) economists examining 163 drugs that faced shortages between 2013 and 2017 found that 62% of these shortages were linked to manufacturing or product quality issues (3). Antimicrobial agents were among the most affected by these disruptions (4).

#### *2.1.1 Manufacturing and regulatory issues*

The most frequently used antibacterial agents,  $\beta$ -lactams, are synthesized from

*Penicillium* spp. cultures. The production of 6-aminipenicillanic acid (6-APA), one key component of penicillin, is heavily dependent on Chinese and Indian suppliers due to their ability to produce it for global consumption at a low cost. However, strict regulations in some countries like Japan, limit the use of 6-APA refined in certain regions, further complicating supply chains, as only Chinese companies were able to meet the criteria requested by the Japanese drug regulatory agency. In addition, consideration for side chain manufacturing, which may at times involve dealing with explosive materials during the process might be very costly. Production costs are lower in China compared to most other countries, related to the expenses associated with hazard avoidance and environmental measures.

As a result, most of the global antibiotic production has shifted over the years to countries with lower production costs such as India and China. To generate profits, API manufacturers in these countries must produce large volumes. However, despite reasonable market demand, many antibiotic products remain dependent on a small number of API manufacturers due to quality issues related to production and availability of manufacturing facilities. Consequently, production is vulnerable to shortages if accidents occur or if facilities are shut down for quality issues or other problems that halt the production of APIs for antibiotics. For example, in 2017, the global supply of piperacillin/tazobactam was interrupted due to a fire at the sole API supplier. Similarly, a serious shortage of cefazolin occurred in Japan in March 2019 following manufacturing issues at the site of a key supplier (5). In January of that year, a major pharmaceutical company, which held roughly 60% of the Japanese market, announced the cessation of its cefazolin production due to a contamination by foreign substances at its Italian factory and the unavailability of the raw material needed for cefazolin

production from Chinese companies. Another example is India, a key global supplier of generic antibiotics, which has faced regulatory actions from the FDA and European Medicines Agency (EMA) for non-compliance with Good Manufacturing Practices (GMP). In 2023, inspections at IPCA Laboratories revealed deficiencies, resulting in production suspension and worsening critical drug shortages.

### *2.1.2 Economic limitations*

The antimicrobial market is unstable due to generally low profit margins, a limited market size for stakeholders, and a fragile supply antimicrobial chain often lacking transparency. Procurement processes frequently award contracts to the company offering the lowest price, which is unsustainable. Margins on generic drugs are already slim, and this practice may eventually lead to even fewer bidders. Lower prices result in reduced revenues and profits for manufacturers, prompting them to shift production to drugs with higher profitability potential. This sequence of events further reduces profitability, particularly for off-patent pharmaceutical products. Another reason contributing to undermine the supply of older antibiotics is the low return on investment and limited market size, leading to few participants in the production and supply chain.

## *2.2 Shortage of novel antibiotics*

The issue of novel antimicrobials shortages can be divided into two key areas: i) development; ii) production and distribution.

### *2.2.1 Development*

The challenges in developing innovative antimicrobials have been widely documented. Many issues have been raised, such as the difficulty in discovering

antimicrobials with novel mechanisms of action and the challenges associated with enrolling patients with multidrug-resistant (MDR) bacterial infections into clinical trials, each of which is discussed in detail in several insightful reviews. The cost of developing new drugs has significantly escalated over the past decade, deterring the pharmaceutical industry from investing in new antimicrobial agents, which are typically prescribed for short durations, unlike most new drugs developed for non-communicable chronic diseases. Moreover, investments in the development of novel antimicrobials are further undermined by the low profitability of this drug class. Even if pharmaceutical companies succeed in the research and development of novel broad-spectrum antimicrobials, they may not expect to generate significant profits based on 'usage or sales volume' as antimicrobials against MDR bacteria will be categorized as 'reserve' drugs, intended for use only in MDR infections. To make matters worse, the rapid evolution of resistance in MDR Gram-negative bacteria further shortens the lifetime of antimicrobials targeting these pathogens. Consequently, several large well established pharmaceutical companies have either withdrawn from the area of antimicrobial agents development or are divesting from these therapeutic areas.

### *2.2.2 Production and distribution*

Even if a novel antimicrobial is developed in some high-income countries, it may not be immediately available for use in the rest of the world. For example, the number of antimicrobials approved in Japan between 2010 and 2019 was lower than in Western countries, ranking among the second lowest in the 14 countries surveyed in a recent study (6). The authors of the study identified two key issues: 'unapproved drugs' which were approved in other countries but not in Japan, and 'lag' (delay), where drugs

took longer time to be approved in Japan than in other countries. The study also highlighted serious limitations on commercial launch and patient access in high-income countries (6). A large number of antibacterials approved since 2010 are not available in many high-income countries due to a combination of delayed marketing authorization submission and approval, delayed commercial launch after marketing approval, and market withdrawals due to bankruptcy. Interestingly, in several less wealthy European countries such as Greece, Romania, and Spain, the number of new antimicrobials available during that period was higher than in Canada or Japan. Plausible explanations include the consolidated marketing approval process through the EMA, as compared to the need to separately apply to drug regulatory agencies in Canada and Japan, as well as the potential requirement for additional clinical studies in Japan. As such, patient access to new antibacterials is limited, not only in low- and middle-income countries (LMICs), as previously reported, but also in some high-income countries such as Canada, Japan, and others.

### **3. Impact of antibiotic shortages**

Antibiotic shortages directly impact clinical outcomes. Understanding these impacts is essential, as antibiotics are often irreplaceable in medical treatment. This section explores the consequences of these shortages on patient care and the broader healthcare system. Table 2 summarizes the consequences of these shortages.

#### *3.1 Impact of antibiotic shortages on clinical outcomes*

Shortages of medications, including antibiotics, are a complex global issue that significantly impact individual patients directly affected (7). Although high quality studies are scarce, the available evidence highlights the reported effects on clinical

outcomes, including increased patient mortality, adverse drug reactions, and medication errors. Economic consequences, such as increased out-of-pocket costs, and negative impacts on patient care experiences, including a rise in patient complaints, have also been noted. (7). Assessing the impact of antibiotic shortages on patient outcomes is of utmost importance because antibiotics are non-interchangeable, potentially life-saving, and - despite this, are among the most frequently affected by shortages (8). Evidence of this issue is more prevalent in high-income countries, compared to LMICs. Knowledge on this topic is mainly provided through surveys, such as those conducted by the European Association of Hospital Pharmacists (9), drug shortages statistics reported by the American Society of Health System Pharmacists, and studies performed by infectious diseases physicians in the US (10). These data increasingly highlight the impacts of antibiotic shortages on treatment delays, the overuse of broad-spectrum antibiotics; suboptimal use of substitutions which are less effective, more costly, or associated with increased toxicity, increased medication errors, and increased risk of hospital readmissions. For instance, pharmacists in Spain, Greece and Serbia, reported delays in treatment initiation and the transfer of patients to other facilities where the necessary drugs were more available. (11).

### *3.2 Challenges in LMICs*

In LMICs, where the demand is higher due to a greater burden of infectious diseases, the shortage of both novel and old antibiotics is exacerbated by challenges such as the lack of registration, lengthy submission processes and weak regulatory capacity. (12). Indeed, LMICs have limited capacity to invest in systems for monitoring and prevention of shortages. Despite the lack of awareness of antibiotic shortages

reported in the policy agendas, LMICs are more likely to experience severe consequences due to the lack of reliable access to alternative antibiotics in the context of high patient loads, poor infection control practices, a scarcity of diagnostic facilities, the availability of over-the-counter antibiotics, and substandard drug quality (13,14). A convenient sample survey of 28 LMICs indicated that many of the “forgotten” antibiotics such as polymyxins, aztreonam and fosfomycin are not approved in the majority of these countries (15). Some anecdotal evidence describes multi-faceted challenges in the daily practices, including insufficient control and monitoring related to shortages (16).

### *3.3. Management and communication challenges*

Effective management of antibiotic shortages requires early communication and close monitoring. However, this has not been adequately addressed due to factors such as the lack of time, high workloads, miscommunication among healthcare teams, insufficient information to assess the effectiveness of alternatives, and inappropriate hospital monitoring systems and internal procedures, further exacerbating the impacts on patient outcomes (17). Without proper communication and management of drug shortages, a domino effect may be triggered where the shortage of a commonly used antibiotic agent leads to increased use of a substitute, which may then also become scarce (18). Countries have rarely developed their own redundancy plans resulting in a limited understanding of which antibiotics may have increased demand due to shortages. This can create cascading shortages as unexpectedly high demand for substitute antibiotics depletes global stocks, raising equity concerns when remaining supplies are sold to countries willing and able to pay higher prices.

### 3.4 Implications on healthcare systems and global health

Antibiotic shortages tend to have an immediate and widespread impact on antibiotic prescribing patterns. For example, after the U.S. Food and Drug Administration (FDA) declared a shortage of amoxicillin powder for liquid suspension in 2022-2023, prescriptions of amoxicillin decreased while those of amoxicillin-clavulanate and cefdinir increased in children with uncomplicated acute otitis media (19). Notably, no significant changes were observed in the management of patients without antibiotics and prescriptions for other antibiotics. Similarly, cefepime shortage following its withdrawal from the Swiss market in January 2007 shifted the consumption patterns towards piperacillin-tazobactam and meropenem (18). In Japan, serious shortages of cefazolin were associated with increased use of broader-spectrum beta-lactams and clindamycin in hospitals (20). Such shifts inevitably impact the development and spread of antibiotic resistance and adverse events such as *Clostridioides difficile* infections.

Although it does not strictly fall within the definition of shortages, the currently limited pipeline of new antibiotics exacerbates the challenge of managing antibiotic resistant bacterial infections, posing a significant threat to global health. The declining number of drug candidates in phase-III trials from 2013 to 2022 is an ongoing concern (21). As expressed in the latest report by WHO on antibacterial agents in clinical and preclinical development, there will be insufficient antibiotics to address the critical priority of MDR Gram-negative pathogens including *A. baumannii* and *P. aeruginosa* in the coming years (22). This situation, coupled with the lack of access to old antibiotics and poor AMS programs in many countries could lead to a threatening post-antibiotic

era where common infections become untreatable (23). This further outlines the need to develop strategies for the prevention of antibiotics shortages, as one of the consequences of these shortages is an increase in antibiotic resistance.

Another significant consequence of antibiotic shortages resides in its broad impact on healthcare systems and public health policies. In fact, antibiotic shortages could induce intangible effects including disruptions and setbacks in current stewardship, education and professional development of healthcare professionals on appropriate antibiotic use. This is particularly concerning for junior physicians and pharmacists, whose perception and practices may be adversely affected. Studies have already reported the effects of inappropriate shifts in prescribing choices to broader-spectrum antibiotics as seen in the case of cefazolin shortages (19), as well as the concerns of physicians and pharmacists, who are often forced to choose suboptimal antibiotics in many situations (9)(10). Thus, beyond the direct impact on patients, antibiotic shortages can undermine the confidence of healthcare professionals and public trust in the healthcare system, if there are no effective and timely management, mitigation and communication systems at both national and global levels.

#### **4. Potential solutions**

Addressing the shortage of antibiotics requires innovative strategies to incentivize pharmaceutical companies and improve access, especially in LMICs. This section outlines various approaches that could help mitigate this global health challenge (table *4.1 Market entry rewards*)

To address antimicrobial shortage, it is crucial to create incentives for pharmaceutical companies to develop new antibiotics. One of the effective approaches

would be the proposed PASTEUR Act, which aims to provide a delinked pull incentive to promote antimicrobial innovation for critical new drugs (24,25). This market entry rewards strategy generally ensures that companies can achieve adequate revenues without the need to sell a large amount of the product. There are two main models for this. In the fully delinked model, the developer's revenue is entirely independent of the amount of antibiotics sold. This approach would encourage product affordability and discourage inappropriate use because the pricing and distribution of antibiotics would be managed by the supplier, rather than being driven by market demand. The European Parliament and some US states have already suggested this model to its member states (24,25). In the partially delinked model, the developer's revenue is a mix of the reward payment and sales income. These 2 models are promising, but require international cooperation to share the financial burden and create viable ways to fund the substantial pharmaceutical companies' rewards. Therefore, implementing these models would be challenging particularly in LMICs.

#### *4.2 Proposed solutions for LMICs*

##### *4.2.1 Enhancing data collection on antimicrobial use and resistance*

In LMICs, fostering collaborations between the governments, Ministries of Health (MOHs) and international organizations such as WHO global-antimicrobial-resistance-surveillance-system (GLASS) and World organization for animal health (OIE) is essential to enhance data collection and support planning and budgeting. Developing mobile-based applications to maintain a centralized flow of information on antibiotic use and resistance across all sectors is a potential solution for surveillance (26). Moreover, efforts should be made to integrate healthcare workers from rural areas

into government meetings and decision-making processes. This will empower them and enhance inclusivity when collecting data and conducting surveillance.

#### *4.2.2 Voluntary licensing*

Another approach to address antimicrobial shortage in LMICs would be to encourage pharmaceutical corporations to establish terms for the entry of generic versions of antimicrobials from alternative suppliers, which can enhance access to essential medicine. This can be achieved by issuing appropriate voluntary licenses as was done with the provision of hepatitis C drugs in India, where medicines manufactured under voluntary licenses are given free of charge to patients at governmental clinics (27). Appropriate voluntary licenses can be secured through contractual obligations set by public and philanthropic funders of research and development or by governments exercising health safeguards embedded in global trade agreements.

#### *4.2.3 Local drug manufacturing*

Encouraging local drug manufacturing, particularly in LMICs, is another strategy to curtail drug shortages. To achieve an adequate process, the following should be established: international agreement and public-private partnerships to ensure appropriate regulations which would help the public sector to fill the gaps by building capacity for public sector antimicrobial production. A successful example is the mRNA COVID-19 vaccine production during the pandemic, where regional manufacturing hubs were implemented. These hubs could prioritize the essential antimicrobials at risk of shortage and manufacture API, shifting production dominance from monopolization,

and introducing competitive prices which would ultimately lead to cost reduction. However, to ensure equal and sustainable access to less profitable antimicrobials, balanced geographic distribution, multiple manufacturing players, and resilient models not vulnerable to supply chain disruptions should be implemented. Strategic planning efforts are especially needed in LMICs which currently lag behind high-income countries.

#### *4.2.4 Scalable stewardship programs*

AMS ensures that only patients who need antibiotics receive them, which may contribute to prevention and mitigation of antibiotics shortages. As more international awareness and collaboration are directed towards AMS, significant work remains to be done in LMICs. Training community pharmacists is as crucial as physicians training, since the former play a significant role in managing and dispensing antimicrobials. This approach has been successfully applied in several African countries (28,29). However, education alone is insufficient and should be supplemented with regulations and continuous feedback, as demonstrated by many successful examples from China, where antibiotic prescription rates were reduced when education interventions were combined with compulsory administrative regulations with financial incentives (30). Additionally, there is emphasis on the need for new stewardship models in LMICs to effectively introduce and use new antibiotics (31). For instance, point-of-care diagnostics, designed for LMICs, can improve diagnostic access by ensuring cost-effectiveness, availability, training, and maintenance (32). However, one must be vigilant when implementing new stewardship programs, as suboptimal AMS programs can inadvertently contribute to antibiotic shortages through inappropriate use of antibiotics, particularly when this

involves excessive prescription of the same antibiotic. This issue often arises when prescribers have limited awareness in this field. To address this challenge, efforts are being undertaken by organizations such as the WHO and Médecins Sans Frontières (MSF) particularly in LMICs to implement effective stewardship programs and provide education to stakeholders involved in these initiatives in collaboration with health authorities. Moreover, an effective stewardship program cannot be implemented without a robust infection prevention and control (IPC) program, as the two go hand in hand.

#### *4.3 Facilitating the registration process of new antibiotics*

One major reason behind the lack of access to antibiotics is their limited registration process in many countries, which is considered a crucial initial step for drug introduction. Filing submissions to different regulatory bodies can be lengthy and challenging which results in prolonged waiting times for regulatory approval. To address these challenges, several bodies have been recommended to facilitate the national registration of antibiotics. These include the WHO collaborative Registration Procedure, the African Medicines Regulatory Harmonization (AMRH) program, and the African Medicines Agency (AMA) (31). High-income countries are already in the process of regulating registration through the Transatlantic Taskforce on Antimicrobial Resistance (TAFTAR) and the International Coalition of Medicines Regulatory Authorities (ICMRA). Regulatory bodies from LMICs should be included in these authorities to standardize the process and enhance collaboration. LMICs can also create a process for a category of essential antibiotics for serious and life-threatening infections and seek expedited approval within the regulatory framework. These initiatives were already explored by the Global Antibiotic Research and Development Partnership (GARDP) and WHO by developing the SECURE Model (33). A model

proposed a hub-and-spoke approach where new and expansive drugs can be made available even in LMICs but the use is controlled and centralized in one place (31). Although facilitating the registration of new antibiotics may seem an appealing solution, each country must tailor its approach to its specific epidemiology and resistance patterns. Intelligent regulation is crucial to prevent the emergence of resistance while preserving diversity in treatment options.

#### 4.4 Vaccines

Vaccination can reduce infections and contribute to herd immunity, all leading to a decreased need for antibiotics. One example to highlight the connection between vaccination and reduced antibiotic use (34) is maternal vaccination which has been estimated to prevent around 3.6 antimicrobial prescription courses per 100 infants in high-income countries and 5.1 courses per 100 infants in LMICs (35,36). Moreover, there is a need to expedite research progress in vaccine development against the WHO's priority pathogens list (22,37,38), among which only *S. pneumoniae* has a licensed vaccine. Challenges in developing vaccines for other pathogens include low general population infection incidence, multiple pathogens causing similar syndromes, and difficulties in conducting large efficacy trials with standardized clinical endpoints in critically ill patients (39,40).

#### 4.5 Role of WHO

The WHO as the leading global health authority, is well-positioned to address antibiotic shortages and their consequences on public health. To tackle this issue, the WHO could establish a global surveillance system to actively monitor shortages and their impacts, drawing on models like the GLASS program for AMR. Additionally,

creating a dedicated office to investigate the root causes of shortages and propose actionable solutions for both LMICs and HICs could ensure targeted and realistic interventions. WHO could also collaborate with NGOs such as MSF to implement educational programs and build capacity among stakeholders, including healthcare providers and policymakers, to prevent and manage shortages effectively. Additionally, the WHO can advocate for international collaborations by pooling resources, sharing supply chain data, supporting regional stockpiles, and promoting public-private partnerships to ensure continuous production and availability of antibiotics. Adapting successful models, such as the Global Fund's approach for antiretrovirals, could help maintain steady antibiotic supplies. Together with active surveillance, dedicated oversight, and regulatory reforms, these initiatives can significantly mitigate the global impact of antibiotic shortages.

## **5. Conclusions**

The global challenge of antibiotic shortages is complex and requires urgent and coordinated responses. The scarcity of old and new antibiotics is exacerbated by manufacturing obstacles, supply chain vulnerabilities, and regulation barriers. Despite the general agreement that antibiotic shortages severely impact patient care and public health worldwide, leading to higher mortality rates and worsening antibiotic resistance (41, 42), there remains a lack of robust studies with pharmaco-economic data, to convincingly demonstrate to stakeholders that this issue must be aggressively addressed (43). Addressing this crisis required a multifaceted approach, including strengthening supply chains, encouraging local production, and implementing market entry incentives.

In LMICs, increased efforts and international collaborations are needed due to a higher burden of infection diseases. While there is progress in developing new antibiotics and expanding vaccination programs, robust global health policies and sustained financial investment are essential to ensure the continuity of both existing and new antibiotics. Without adequate measures, the world risks entering a post-antibiotic era, where common infections could once again become lethal. Urgent action is imperative to safeguard global health for future generations.

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**Table 1.** Main causes of antibiotic shortages

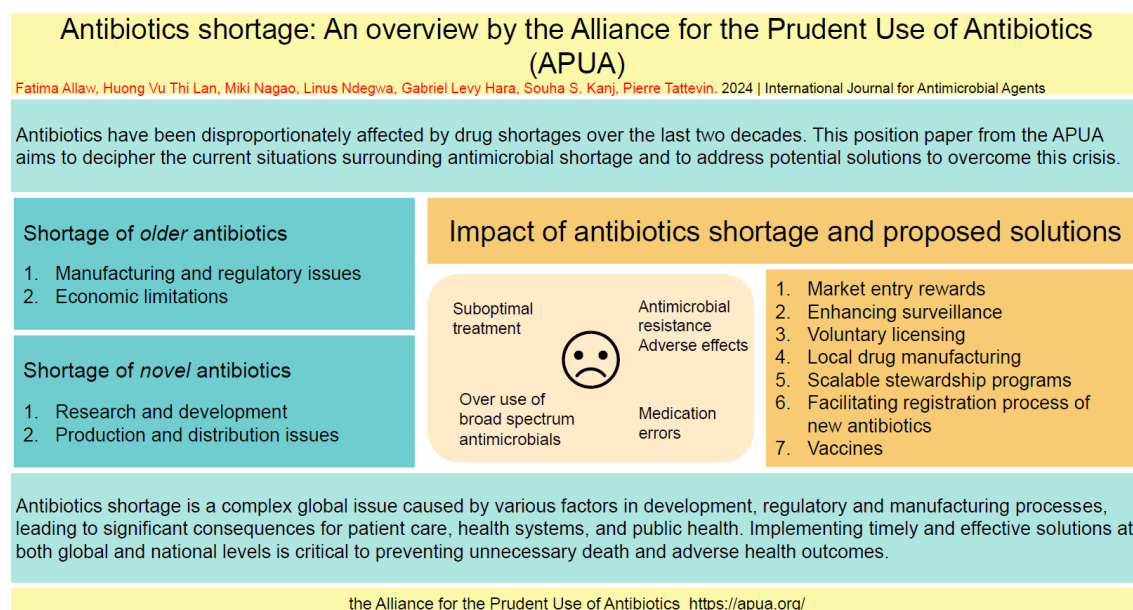
<b>Old antibiotics</b>
Failure to comply with good manufacturing practices
Regulatory delays
Unavailability of essential components, primarily active pharmaceutical ingredients
Unanticipated discontinuation of production by a major contributor
Logistical challenges (transportation issues, etc.)
Unexpected surge in demand (eg. the COVID crisis; changes in international guidelines; the 'domino' effect)
<b>Novel antibiotics</b>
Development (complexity of large clinical trials on multidrug-resistant infections; expected low return on investment)
Production and distribution (delayed access in low-and-middle income countries due to high cost, delayed marketing authorization)

**Table 2.** Consequences of antibiotic shortages

Consequences	Examples
Delays in appropriate treatment administration	Difficulties to build an effective treatment against carbapenemase-producing gram-negative bacteria (eg. shortages of colistin, fosfomycin, tigecycline, etc) Delays in treatment initiation due to patients transfer to another facility
Overuse of broad-spectrum antibiotics	Ceftriaxone instead of intravenous penicillin G for neurosyphilis Carbapenems in case of cefepime shortage
Reduced efficacy	Cefalexin instead of fluoroquinolones for pyelonephritis Use of sub-optimal alternatives in case of carbapenem shortages Shortages of polymyxins lead to use of combined therapy with meropenem, sulbactam or gentamicin, despite poor synergistic profile Cefazolin shortages may increase the risk of surgical site infections
Increased toxicity	Vancomycin instead of linezolid to treat <i>Enterococcus</i> spp bacteremia in patients with higher risk for renal failure. Clindamycin instead of metronidazole to treat anaerobic infections.
Use of more expensive drugs	Amoxicillin/clavulanate instead of amoxicillin Fluoroquinolones instead of nitrofurantoin for cystitis Significant increase in piperacillin-tazobactam and meropenem use after cefepime withdrawal
Prolonged length of stay	Unavailability of antibiotics necessary for oral switch
Medication errors	Use of agents unfamiliar to physicians, pharmacists and nurses
Increased hospital readmissions	Recurrent sepsis associated with suboptimal treatment
Antibiotic resistance and adverse events	Increased use of piperacillin-tazobactam and meropenem linked to decrease in susceptibility of <i>P. aeruginosa</i> Use of alternative agents (levofloxacin) was associated with increases in <i>Clostridioides difficile</i> infections

**Table 3.** Potential solutions

<b>Market entry rewards</b>	PASTEUR Act (delinked pull incentive to promote antimicrobial innovation) - model 1: developer's revenue entirely independent of the quantity of novel antibiotics used - model 2: developer's revenue is a mix of reward payment and sales income
<b>Solutions for low-and-middle income countries (LMICs)</b>	- Enhancing data collection on antimicrobial use and resistance (to better anticipate, and adapt resources allocations to the local needs) - Voluntary licensing (convention between pharmaceutical corporations, and alternative suppliers, for early production of low-cost generic drugs specific for LMICs) - Local drug manufacturing with public-private partnerships - Development and implementation of antimicrobial stewardship and infection prevention and control programs
<b>Facilitating the registration process for novel antibiotics</b>	Several promising initiatives - World Health Organization (WHO) collaborative Registration Procedure - African Medicines Regulatory Harmonization (AMRH) program - African Medicines Agency (AMA) - Transatlantic Taskforce on Antimicrobial Resistance (TAFTAR) - International Coalition of Medicines Regulatory Authorities (ICMRA) - SECURE Model by Global Antibiotic Research and Development Partnership (GARDP) and WHO
<b>Vaccines</b>	Vaccination can reduce infections and contribute to herd immunity, all leading to a decreased need for antibiotics.

**Graphical abstract**

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