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### POLICY FORUM: PEER-REVIEWED ARTICLE

#### Why Assuring the Quality of Antimicrobials Is a Global Imperative

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##### Abstract

Poor-quality antimicrobial medicines continue to proliferate across supply chains, threatening patients' health and safety, especially in low- and middle-income regions. This article discusses consequences and risks of antimicrobial resistance and other ways in which antimicrobial medicines can be of poor quality and recommends regulatory and policy reforms to help maintain supply chain resilience and quality of antimicrobial medicines.

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##### Introduction

The World Health Organization (WHO) has declared antimicrobial resistance (AMR) one of the top global public health threats facing humanity.<sup>1</sup> In the United States, more than 2.8 million antibiotic-resistant infections occur each year, resulting in more than 35 000 deaths,<sup>2</sup> and a recent study estimated that nearly 5 million people died worldwide in 2019 due to causes associated with AMR, with over 1 million deaths directly attributable to AMR.<sup>3,4</sup>

Poor-quality antimicrobials continue to proliferate across the medicines supply chain, threatening patient health and possibly increasing the incidence of AMR.<sup>5,6</sup> A 2017 WHO study estimated that approximately 1 in 10 medicines in **low- and middle-income countries** (LMICs) are substandard or falsified (SF),<sup>5</sup> with more recent estimates suggesting that approximately 17% of the global antibiotic supply may be SF.<sup>6</sup> SF antimicrobials can lead to failure in patient outcomes and substantial economic costs. The WHO estimated that between 72 430 and 169 271 excess child pneumonia deaths are due to SF antibiotic use.<sup>5</sup> Another national-level modeling study estimated that poor-quality antimalarials were responsible for over 12 000 deaths of children under 5 years of age and more than \$890 million in costs annually in Nigeria.<sup>7</sup> Incorporating antimalarial resistance, the model estimated that, in Nigeria, annual deaths among patients under 5 years of age would increase by 7700 and that annual costs would increase by another \$839 million.<sup>7</sup> Consequently, it is a moral imperative for countries to work together to sustain a supply of effective, quality-assured antimicrobials that is

both resilient to supply chain disruptions and that patients around the world can access in an equitable manner.

### **What Are Substandard Medicines?**

While misuse and overuse of antimicrobial medicines are major drivers of AMR,<sup>8</sup> another often-overlooked cause of AMR is the presence of SF antimicrobials. Substandard medicines are products authorized for use that fail to meet quality standards or their specifications, or both.<sup>5</sup> For example, in substandard antimicrobial formulations, the active pharmaceutical ingredient (API)—the biologically active component of a drug—may be present in a lesser dose than is required to treat the infection.<sup>6</sup> Poor-quality excipients, impurities, or degradation can also affect the medicine's solubility, bioavailability, and antimicrobial activity. Falsified medicines deliberately or fraudulently misrepresent their identity, composition, or source.<sup>5</sup> In the case of substandard antibiotics, antimicrobial characteristics and antimicrobials' subsequent interactions with bacteria can result in bacteria becoming altered, leading to AMR development.

### **Why Antimicrobial Quality Matters Everywhere**

In the United States, legislative proposals are under consideration and public-private partnerships have been formed to provide investments to ensure the availability of quality medicines.<sup>9,10,11,12</sup> However, the problem of medicine quality must be viewed through a multidisciplinary global lens, which includes evidence-based research on the impact of poor-quality antimicrobials on AMR.

Experimental research from the United States Pharmacopeia's Quality Institute, which sponsors independent research to inform policy decisions, helps build the evidence base that poor-quality antibiotics can drive bacteria to become multidrug resistant.<sup>13</sup> One such study found that exposure to low levels of API (in ciprofloxacin) led to multidrug resistance development that was below the clinical cut-off for resistance—which means resistance may go unreported or undetected until it is a significant problem.<sup>14</sup> Low-level resistance can serve to establish a reservoir of bacteria primed for further development of resistance.<sup>14</sup> This finding has important policy implications, as early emergence of resistance, especially in locations with high incidence of SF antibiotics, might be missed in current surveillance strategies. Research has also shown that exposure to impurities and degradation products—unwanted chemicals or by-products that can develop during the manufacturing, transportation, and storage of drugs—can promote AMR and interfere with content assays that aim to measure the quantity of API in a medicine.<sup>15,16</sup> Maintaining good storage and distribution practices along the medicines supply chain is also critical for maintaining quality medicines.

Tackling medicinal quality is critical to achieving universal health coverage (UHC), which the United Nations (UN) has identified as a global target. Sustainable Development Goal (SDG) 3.8 seeks to “achieve universal health coverage, including financial risk protection, access to quality essential health-care services, and access to safe, effective, quality and affordable essential medicines and vaccines for all.”<sup>17,18</sup> While access to quality medicines is mentioned under SDG 3.8, medicine quality itself is not one of the indicators of progress towards UHC.<sup>19</sup> This is a blind spot. The UN Interagency Coordination Group on Antimicrobial Resistance highlights the need for UHC schemes to promote not only access to quality-assured medicines but also appropriate use of antimicrobials to reduce AMR.<sup>20</sup>

Prior to the emergence of SARS-CoV-2, the virus that causes coronavirus disease (COVID-19) and that led to the ensuing global pandemic, AMR was one of the world's most concerning public health issues. As emergency declarations end and the threat of severe disease, hospitalization, or death from COVID-19 continues to decline, AMR has the potential to become the next major public health emergency. However, apathy toward discovery of new antibiotics in high-income countries persists.<sup>21</sup> Many pharmaceutical companies have stopped investing in research and development of antibiotics due to low financial projections. Increased funding for academic institutions and smaller start-ups to develop new antibiotics is promising though somewhat fragmented; however, scientific discovery is inherently slow, and getting a product onto the market requires substantial clinical work.<sup>22</sup> Thus, it is critical to maintain the quality of the antibiotics that we currently utilize. Additionally, medicine quality is rarely studied in high-income countries, where a lack of published SF prevalence data, despite documented recalls of poor-quality products, has led to gaps in our knowledge.<sup>23</sup> The COVID-19 pandemic has demonstrated that infectious diseases and supply chain disruptions are not isolated and can rapidly spread across the globe. Addressing the issue of medicine quality and AMR requires global investment and collaborative work at the local, regional, national, and global levels that relies on shared and effective communication, collaboration, and coordination.

### **Supply Resilience and Quality Assurance**

Several factors contribute to supply chain vulnerabilities that can exacerbate the proliferation of SF medicines. Increasingly common shortages of antimicrobials—including antibiotics like amoxicillin—and consequent increase in demand can create an incentive for actors to introduce SF products into the supply chain.<sup>24</sup> While LMICs experience drug shortages most acutely, the consequences, especially for AMR development, are global. Additionally, API manufacturing is geographically concentrated in a few locations, and concerns over antibiotic API quality have been another source of **vulnerability in the supply chain**, especially with the increase of extreme weather events that can cause product degradation or cut off supply.<sup>25,26</sup> However, attributing poor medicine quality to origin of manufacture, without evidence, should be avoided.

Global stakeholders, such as policy makers, national regulatory authorities, and public health authorities, have a responsibility to ensure equitable access to quality-assured antibiotics, especially by vulnerable populations. Medicine shortages and the proliferation of unauthorized sellers in many places undermine this goal. In many LMICs, people seeking medical treatment may access medicines from unlicensed outlets associated with poor-quality medicines and practices.<sup>19,27,28</sup> There would be less economic incentive to produce poor-quality antimicrobials if patients were ensured access to quality-assured antimicrobials.

### **Increased Efforts to Incorporate Quality Dimensions in National Action Plans**

For effective AMR stewardship, countries need to develop and implement a national strategy to combat AMR that integrates medicine quality. In 2015, the World Health Assembly encouraged member states to develop individual national action plans (NAPs) to fight AMR.<sup>29</sup> Since that time, many countries have developed NAPs, and several have incorporated quality dimensions in their plans. A review of publicly available NAPs in 2018 found that 27 of 41 NAPs included medicine quality.<sup>30</sup> Applying the cornerstone WHO “prevent, detect and respond” framework,<sup>5</sup> NAPs have outlined medicine quality activities, including implementing good manufacturing practices; coordinating quality control; **establishing national surveillance**; strengthening laboratory systems;

implementing a single drug regulatory system across human, animal, and aquaculture sectors; and removing SF medicines from the market.<sup>30,31</sup>

Additional work is necessary to convey the importance of AMR NAPs and their inclusion of quality considerations. It is also imperative that the global community continue to provide financial and technical resources to develop and implement national AMR strategies. Since resistance knows no borders, resistance in one country will remain a problem globally.

### **Global Call to Action**

Given the negative effects of poor-quality antimicrobials on AMR and public health, sustaining a resilient supply of quality antimicrobials is a global health imperative. Policy makers, regulators, manufacturers, distributors, and other stakeholders should build and maintain a resilient supply of quality-assured antimicrobials. These efforts are difficult and expensive and will require international cooperation and continued capital investment. We recommend 3 specific policy and regulatory reforms.

1. Prioritizing the building of resiliency into the global antimicrobial supply chain, including by fostering broader geographic distribution (less concentration) and more sources of API production.
2. Building capabilities among global stakeholders (eg, national regulatory agencies) to reduce the proliferation of poor-quality antimicrobials and to ensure access to effective antimicrobials by taking these steps:
  - a. Adhering to science-based public quality standards.
  - b. Increasing the use of AMR surveillance tools and strategies to track the emergence of resistance and provide targeted action.
  - c. Increasing the development of proactive risk-based tools and risk-based testing for quality along multiple points of the supply chain.<sup>32,33</sup>
  - d. Developing and strengthening quality assurance of local and regional API and finished product manufacturing by providing incentives in order to diversify the supply chain and build capacity.
  - e. Increasing information sharing and transparency through regulatory reliance and recognition agreements among national regulatory authorities to help facilitate bilateral cooperation.
3. Implementing steps to increase funding to incentivize research and development on the next generation of products while assuring the quality of the current antimicrobial armamentarium.

### **Conclusion**

Antimicrobials are lifesaving drugs that all countries need to protect the health of their populations. It is necessary to continue to raise awareness of the role that poor-quality medicines play in AMR. The global community should provide additional financial and technical resources as countries continue to implement AMR NAPs. Importantly, securing a resilient supply of antimicrobials made with quality APIs and excipients is imperative to ensuring that patients have access to effective therapies.

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