Policy position

USP Global Public Policy Position:

Addressing Antimicrobial Resistance

ISSUE: Antimicrobial resistance (AMR)—a growing public health threat—occurs when antibiotics, antivirals, antifungals, and other lifesaving antimicrobial drugs can no longer effectively treat bacteria and other microbes.[1] In the United States, more than 2.8 million antibiotic-resistant infections occur each year, resulting in more than 35,000 deaths.[2] Around the world, an estimated 700,000 people die each year due to AMR.[3] Without global action, AMR could lead to 10 million deaths a year by 2050.[4] Poor-quality medicines contribute to the emergence and spread of AMR, yet the prevalence of substandard and falsified medicines remains a persistent, and preventable challenge in many parts of the world.

Position

USP supports comprehensive policies and programs to address AMR, including building capabilities among global stakeholders to reduce the proliferation of poor-quality medicines and advocating and implementing strategies and practices to assure medicine quality and the stewardship of quality-assured antimicrobials. USP supports policies and approaches that:

1. **Strengthen regulatory systems to improve surveillance of poor-quality medicines.** This can include the establishment of country-level quality management systems to monitor for substandard medicines, and promotion of current good manufacturing practices (cGMPs) and current good distribution practices (cGDPs) to ensure antimicrobial medicines quality. Building capabilities for quality assurance to combat AMR threats, including surveillance for AMR and medicines quality, and application of pharmacopeial standards to ensure quality and safety, can improve access to quality-assured antimicrobial medicines.
2. **Raise awareness** around the link between poor-quality medicines and AMR, elevating the issue for policymakers, practitioners, and patients. Policymakers, particularly in low- and middle-income countries (LMICs), should understand that poor-quality medicines contribute to the emergence and spread of AMR and the resulting economic impact.

3. **Apply the "One Health" approach** as a holistic way to address human, animal, and environmental health in the context of AMR and medicines quality. Widespread and unchecked use of antibiotics in agricultural settings, particularly among livestock, where antibiotics are often used to promote growth rather than to treat illness, has exacerbated the AMR crisis. The One Health approach requires coordination and collaboration across multiple sectors, including health care, environment, agriculture, and industry to ensure the appropriate use of quality antimicrobial medicines.
4. **Advance stewardship of quality antimicrobial medicines** through curbing antibiotic over-prescribing and improving appropriate use by requiring diagnostic testing to inform whether antimicrobials are suitable and to identify an appropriate antimicrobial for treatment. Strategies can include encouraging patient adherence to treatment, dissuading against self-treatment without the guidance of a healthcare provider, and enhancing awareness on proper disposal of unused antimicrobials.
5. **Invest in medicines quality while incentivizing new medicines.** The inability to recover high investment costs and establish a market share has deterred the development of new antibiotics. National and international policy approaches to advance incentives and improve reimbursement for priority antibiotics should consider the impact of poor-quality medicines on current and future antimicrobial products.

I. What Is Antimicrobial Resistance?

AMR occurs when microorganisms adapt and become resistant to medicines intended to treat bacterial, viral, parasitic, and fungal infections. Some of these microorganisms can become resistant to multiple treatments and can evolve into what are popularly called "superbugs"—such as multi-resistant staphylococcus aureus (MRSA)—which fail to respond to multiple antibiotics and lead to prolonged illness and even death. Drivers of AMR include over-prescription and misuse of antibiotics, inadequate diagnostic testing to identify appropriate treatments, imperfect adherence to medication regimens, widespread use of antibiotics in agricultural settings for growth promotion, and the proliferation of poor-quality medicines.[5] Some organisms can also transfer resistant genes to other organisms, which can affect a wide range of antibiotic treatments, including other infections or diseases.[6]

Poor-quality medicines drive AMR primarily through exposing microorganisms in the body to sub-therapeutic doses of medicines—in other words, the medicine contains an insufficient amount of the active pharmaceutical ingredient. Sub-therapeutic doses can lead to AMR when drug concentrations in the body are too low to treat the infection effectively, but high enough to create a reproductive advantage for resistant strains by killing the more susceptible pathogens. This range of sub-therapeutic doses is often referred to as the "mutant selection window," and it has been studied in laboratory settings and living organisms.[7]

Low-level exposure may occur as a result of one or all of the following reasons:

- Treatment errors—incorrect or improper diagnosis, drug, dose, duration, or de-escalation (discontinuation of antibiotics or switching to one with a narrower spectrum), often referred to in clinical settings as the "5Ds."
- Imperfect adherence by patients to prescription and treatment guidelines.
- Exposure of patients to substandard medicines, including degraded products.

Research shows that low-level exposure to antibiotics causes mutations in bacteria; these changes lead to low-level resistance that can go undetected in a clinical setting. As a result, the bugs may survive treatment and develop higher-level resistance, leading to outbreaks of highly resistant infections. More importantly, bacteria that develop low-level resistance also may become resistant to multiple antibiotics, within and across classes of treatments, potentially rendering even new treatments ineffective. Bacteria exposed, in a laboratory setting, to sub-inhibitory concentrations of one antibiotic (i.e., ciprofloxacin) also demonstrated increased resistance to other antibiotics (namely, chloramphenicol, ampicillin, and tetracycline).[8] These treatments are among the last lines of defense against many bacterial infections, and this research underscores the importance of ensuring quality antibiotics are used at the right dose and following the appropriate treatment regimen.

Exposure to substandard medicines, which can occur when products are manufactured poorly or degrade due to improper storage conditions, can also engender resistance—and cross-resistance—to quality medicines.[9] Furthermore, resistant pathogen populations can outcompete wild-type microorganisms, thereby maximizing the spread of the resistant bugs and their genes throughout the ecosystem.[10] In other words, the pathogen that does not respond to treatment is stronger than the pathogen that

would be eliminated by the antimicrobial. While it was laboratory research that demonstrated this link, it echoes the emergence and spread of malaria-causing parasites documented in Southeast Asia.[11] These resistance patterns could spread globally, especially in Africa where malaria is endemic.

II. Why Should We Be Concerned?

AMR poses a significant threat to patients in the United States and around the world by endangering the successful treatment of common infections with existing therapies. Resistant strains of microorganisms can spread irrespective of borders or geography, overwhelming health systems. Since pathogens know no boundaries, AMR in one country or region presents a threat to others. The WHO has emphasized that, without urgent action, a post-antibiotic era is likely, wherein common infections and minor injuries can lead to prolonged illness and even death.[12]

Compounding the problem, few new antimicrobials are in the research and development pipeline. Furthermore, the COVID-19 crisis has increased the likelihood of supply chain disruptions that could lead to shortages, increased prices for antibiotics and other antimicrobials, and proliferation of poor-quality medicines—for therapies both related and unrelated to the novel coronavirus. The use of unproven antiviral treatments for COVID-19 may be ineffective in treating the virus and may lead to increased emergence and spread of resistance.

There is an urgent need to continue to raise awareness about the link between poor-quality medicines and AMR, particularly as efforts move from the global level to regions and countries. Without taking action to improve medicine quality and increase access to quality antimicrobials, other efforts to achieve universal health coverage and strengthen regulatory systems may be seriously undermined.

III. The Situation

The proliferation of substandard medicines as a significant driver of AMR is often overlooked, but very real. Poor-quality medicines can contribute to AMR by being partially or completely ineffective at treating illnesses and infections—providing enough exposure to surviving microbes to breed drug resistance.[13] Treating these "superbugs" can require more resources and time, and still be less successful than drug-susceptible strains. Allowing poor-quality medicines to prevail anywhere threatens the long-term viability of safe and effective drugs everywhere.

Key Facts

Scope and Scale

- In the United States, over 2.8 million antibiotic-resistant infections occur each year, resulting in more than 35,000 deaths.[14] Globally, an estimated 700,000 people die each year from AMR.[15]
- Without an immediate, collaborative response at the global level, AMR could lead to 10 million deaths a year by 2050.[16]

AMR & Poor-Quality Medicines

- In a study conducted in 2013 across 39 countries, the consumption of poor-quality antimalarials was associated with 120,000 deaths among children under five.[17]
- Poor-quality antimalarials have been responsible for over 12,000 child deaths and about $890 million in costs.[18]
- Antibiotics and antimalarials combined constitute 40% of substandard and falsified medicines.[19]
- A systematic review and meta-analysis estimated that 12.4% of antibiotics and 19.1% of antimalarials in LMICs were substandard or falsified.[20]
- In a study that tested the effect of a broad range of ciprofloxacin concentrations on antibiotic resistance development in Escherichia coli, researchers observed the emergence of stable, low-level multi-drug resistance.[21]

AMR Stewardship

- At least 30 percent of antibiotic prescriptions in the United States are unnecessary, according to a 2016 CDC study;[22] most unnecessary antibiotics are prescribed for respiratory conditions caused by viruses—including common colds, viral sore throats, bronchitis, and sinus and ear infections—which do not respond to antibiotics.[23]
- In many other countries, antibiotics and other antimicrobials can be obtained by consumers without the guidance of a healthcare provider or a diagnostic test.[24]
- Data from five countries suggest that about 7% of COVID-19 diagnoses are associated with bacterial infections, but 72% of COVID-19 patients received antibiotics without a clinical indication.[25]
- The use of real-time, rapid diagnostics such as rapid pathogen identification assays and biomarkers can help clinicians improve appropriate antibiotic use.[26]

Research & Development

- No major new types of antibiotics have been developed over the past 30 years.[27]
- The persistent threat of substandard medicines endangers the continued effectiveness of any new antimicrobials, including antibiotics, that may be in the pipeline.
- In 2019 WHO identified 32 antibiotics in clinical development that address the WHO list of priority pathogens, of which only six were classified as innovative.[28]

Inexpensive antimicrobial drugs in LMICs are frequently of poor quality, which not only put patients at risk of treatment failure but also encourage drug resistance, threatening population health for future generations.[29] Poor-quality antimicrobials contribute to drug-resistant tuberculosis in Africa, Asia, and other regions; threaten to undo once-successful malaria control programs in Latin America, Asia, and other regions; and spawn resistance to medicines used to treat bacterial infections as common as staphylococcus in many regions. A study by The Lancet Infections Disease Commission attributed over 58,000 neonate deaths in India to drug-resistant bacterial infections.[30]

The WHO Global Strategy for Containment of Antimicrobial Resistance recommends ensuring that only antimicrobials meeting international standards of quality, safety, and efficacy are granted marketing authorization.[31] WHO has also created a global monitoring system with data on incident reports that have identified hundreds of incidents of medicines of suspect quality.[32] In 2015, WHO called upon its Member States to develop AMR National Action Plans by 2017.[33] Many country plans have integrated medicines quality-assurance objectives, such as surveillance of AMR and medicines quality, prevention of substandard and falsified medicines, application of the "One Health" approach, and a systems-level approach to combat AMR threats.[34] While these initiatives follow recommendations of the Global Action Plan on Antimicrobial Resistance, there is still much progress to be made on implementation.

Access to and appropriate use of quality-assured antimicrobials is also critical to achieving universal health coverage.

The United Nations Interagency Coordinating Group (IACG) on AMR released a set of recommendations in April 2019 pressing for urgent action on AMR, including the importance of ensuring access to quality-assured antimicrobials, diagnostics, and vaccines as part of a strong health system. Specifically, the IACG called for tackling substandard and falsified medical products as part of AMR stewardship efforts, improving AMR surveillance, and enhancing supply chains through implementing track-and-trace systems.[35]

Access to and appropriate use of quality-assured antimicrobials is also critical to achieving universal health coverage. The 72nd World Health Assembly (WHA) passed a resolution on AMR in 2019, for which USP issued delivered a statement of support urging for continued attention to medicines quality in AMR stewardship.[36] The resolution called for increased surveillance of medicines quality and action to eliminate substandard and falsified antimicrobials through health systems strengthening, technical assistance, and capacity building.[37]

IV. Solutions and Approaches

Around the world, governments, industry, and civil society, as well as USP and its stakeholders, are implementing strategies and programs to combat AMR. USP supports the following policies and approaches to integrate quality assurance strategies into broader AMR efforts.

1. Build evidence and raise awareness.

Country health and finance ministries need more evidence about the impact of poor-quality medicines on public health and the return on investment in quality medicines. Policymakers and regulators working on AMR should continue to utilize existing and emerging evidence to urge decision-makers to incorporate quality into AMR National Action Plans and to allocate resources to implement these activities. National medicines regulatory agencies should be included in discussions around quality assurance and surveillance activities for AMR medicines.

As a global leader in promoting public health through public quality standards, capability building, and advocacy, USP supports research through its Quality Institute that broadens and deepens our understanding of how AMR has emerged and spread. Global advocacy initiatives such as the Medicines We Can Trust Campaign raise awareness of substandard and falsified medicines, including poor-quality antimicrobials.[38] Global and regional initiatives, such as the ReAct Network which was created to catalyze global engagement on antibiotic resistance through collaboration with a broad range of stakeholders, are also important contributors to this dialogue.[39]

2.Strengthen regulatory systems

Strong regulatory systems are needed to ensure that poor-quality medicines, including antimicrobials, do not reach patients. It is critical to invest in and build strong, sustainable quality systems including robust post-market quality surveillance, especially in LMICs. Building the local capabilities of manufacturers and regulators and introducing innovative safeguards (i.e., surveillance technologies) helps to mitigate substandard, falsified, and unapproved medicines, including antimicrobials. Surveillance programs identify substandard and falsified antibiotics and other medicines and take these products out of circulation. Public quality standards, including test specifications supported by acceptable procedures and reference materials, are key to the implementation of surveillance programs. Securing the global medicines supply chain through strengthening regulatory authority and bolstering quality assurance and adherence to public quality standards, will help ensure quality products and practices in LMICs.[40, 41]

Many countries have implemented or are considering ways to monitor bacterial resistance and medicines quality—through, for example, a national surveillance system. These strategies could include systematic and ongoing collection, analysis, and interpretation of data around AMR at national and local levels. Additionally, countries may invest to establish regional data-sharing networks and strengthen post-marketing drug quality monitoring systems and strengthening laboratory and reporting systems. These systems could align with existing global mechanisms such as WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS), which was launched in 2015 and provides countries with a standard approach to the collection, analysis, interpretation, and sharing of data and monitors existing and new national surveillance systems.[42]

With funding from the U.S. Agency for International Development (USAID) and implemented by a consortium of partners led by USP, the Promoting Quality of Medicines Plus (PQM+) program improves access to quality-assured priority medicines and helps to address the proliferation of poor-quality medical products in LMICs.[43]

3.Apply the "One Health" approach.

Increasingly, countries are starting to understand and address the connection between antimicrobial use among humans and animals. USP urges national stakeholders to consider the benefits of the One Health approach as

Public quality standards, including test specifications supported by acceptable procedures and reference materials, are key to the implementation of surveillance programs.

a comprehensive way to address human, animal, and environmental health in the context of AMR and medicines quality. The One Health approach acknowledges the interconnection of human, animal, and environmental health, including the potential transmission of resistant bacterial strains between species. Furthermore, responsible use of quality-assured medicines in both animals and humans—another tenet of the One Health approach, and recommended by the WHO and the U.S. Centers for Disease Control and Prevention—is essential to protect overall public health and to help ensure the continued effectiveness of antimicrobials.[44, 45] The holistic view offered by One Health is necessary to solve the AMR crisis. Regulators can coordinate their efforts to enforce quality standards of antimicrobial drugs for veterinary, human, and agricultural use. Implementation of a drug regulatory system aligned across humans and animals would also support a One Health strategy.[46]

4. Advance stewardship of quality antimicrobial medicines

Quality-assured medicines are a critical component to advancing antimicrobial stewardship. Misuse and overuse of antimicrobials remain the key drivers of AMR. As a result, efforts are needed to curb over-prescribing and improve appropriate use by requiring diagnostic testing to help clinicians identify an appropriate antimicrobial to treat a patient. More rapid, real-time diagnostic testing is needed to optimize the use of existing and new antimicrobials. According to the WHO, lack of access to quality antimicrobials remains a major issue. Antibiotic shortages affect countries across all levels of development, particularly within healthcare systems.[47] Strategies can also include encouraging patient adherence to treatment, dissuading against self-treatment with antimicrobials, and enhancing awareness on proper disposal of unused antimicrobials.

5.Invest in medicines quality while incentivizing new medicines.

A stagnant pipeline for new antibiotics threatens public health given the global spread of AMR. Recent trends, such as unpredictable market dynamics and inability to recover high investment costs, have deterred the development of new antimicrobial medicines, including antibiotics. National and international policy approaches to advance incentives and improve reimbursement for priority antibiotics should consider the impact of poor-quality medicines on the lifetime of current and future antimicrobial products. Ongoing research via the USP Quality Institute and other efforts suggests that resistance emerges when exposed to substandard antimicrobials and that resistance may spread across product classes. USP supports policies that will encourage a robust and diversified pipeline of new antimicrobial products in anticipation that resistance could spread faster and further than previously thought. While the global community and countries should continue to engage in collaborative action and investment in medicines quality for stewardship of existing antimicrobials, global funding mechanisms, and public-private partnerships can help incentivize new drugs for priority public health areas, while encouraging continued antimicrobial stewardship.

About USP

Founded in 1820, USP is an independent, nonprofit, science-based organization that safeguards the public's health globally by developing quality standards for medicines, dietary supplements, food ingredients, and healthcare quality. USP standards describe expectations and tests for identity, strength, quality, and purity; they assist industry in the development, manufacturing, and testing of medicines. USP standards have been used in more than 175 countries and are enforceable by the U.S. Food and Drug Administration (FDA) for medicines and their ingredients imported into or marketed in the United States. Standards in the USP compendia are developed by independent experts through a transparent and scientific process, with input from stakeholders and U.S. federal agencies such as FDA and the Centers for Disease Control and Prevention.

USP is implementing a comprehensive program to support the public health response to the COVID-19 pandemic. Our immediate work is focused on facilitating the supply of quality medicines across the global supply chain—especially for those medicines that treat symptoms associated with the virus—by working closely with regulators, manufacturers, and other stakeholders around the world. We are also engaging in middle- and long-term activities to assess vulnerabilities in the global supply chain for medicines, advocate for greater transparency and more diversity in the sources of medicines and their ingredients, and ultimately help build a more resilient supply chain.

To learn more about what USP is doing to help combat antimicrobial resistance through standards, capability building, and advocacy, please visit https://www.usp.org/our-impact/antimicrobial-resistance.

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