

# Combatting Antimicrobial Resistance



**ISSUE:** Antimicrobial resistance (AMR)—the threat of bacteria and other microbes becoming resistant to treatment by antibiotics and other lifesaving drugs<sup>1</sup> is a serious concern and public health threat. In the U.S., over 2 million people each year are infected with drug-resistant microbes, resulting in 23,000 deaths and over \$35 billion in costs.<sup>2,3</sup> Globally, an estimated 700,000 people die each year from antimicrobial resistance.<sup>4</sup>

## POSITION

**USP<sup>5</sup> supports a comprehensive public policy framework to combat AMR that focuses on reducing the threat of resistance posed by substandard medicines (one important cause) and advances stewardship of quality pharmaceutical products and practices.**

**Key elements include adoption of measures to eliminate the misuse and overuse of antimicrobial medicines for both human patients and animals; promoting appropriate selection of therapies; supporting patient adherence; reducing substandard medicines by following transparent quality standards; strengthening regulatory systems; preventing and controlling infections (especially healthcare-associated infections); and encouraging the development of new medicines.**

**1. Reduce medicine misuse and promote medication adherence.** According to the CDC, about a third of outpatient antibiotic prescriptions in the U.S. are unnecessary—some 47 million excess prescriptions each year.<sup>6</sup> The government<sup>7</sup> and private entities<sup>8</sup> have developed recommendations and reimbursement and accreditation policies that promote proper use. Strategies include educating patients about risks posed by overuse or misuse.<sup>9</sup> Prescribers must select appropriate medicines and durations of treatment, and patients must take medications correctly and completely

(adherence). Approaches to further these objectives include better labeling (including adoption of standards for easy-to-read-and-understand labels), appropriate counseling and follow-up, and leveraging technology (for example, apps) to provide information to patients and encourage adherence.<sup>10</sup>

**2. Advance effective infection control.** Best practices include immunization, safe food preparation, implementation of recognized infection prevention guidelines in the healthcare setting, including handwashing, and other infection control measures.<sup>11</sup> High priority settings include hospitals,<sup>12</sup> healthcare facilities,<sup>13</sup> nursing homes and day care centers,<sup>14</sup> and areas where food is prepared.<sup>15</sup>

**3. Take action against inappropriate use of antibiotics in livestock.** Three quarters of antibiotic sales in the U.S. are for use with livestock.<sup>16</sup> The usage is thought to be significantly higher in many low-and middle-income countries. Resistant bacteria have contaminated meat and spread to produce.<sup>17</sup> Sustainable practices<sup>18</sup> include judicious use of antibiotics, to the end of ensuring that therapies for multidrug resistant infections are preserved for human patients with serious illness. As with human use, antibiotics should only be used in livestock when medically necessary.<sup>19</sup>

**4. Ensure that antimicrobial medicines meet quality standards, and strengthen regulatory systems.** Substandard and falsified medicines can contribute to multi-drug resistant strains.<sup>20</sup> Quality standards of pharmacopeias around the world<sup>21</sup> help ensure the identity, strength, quality, and purity of a medicine, providing a measure to which to test—reducing AMR by helping to keep subpotent medicines out of the market. This objective can be further advanced by enhancing the capacity of regulatory authorities and manufacturers, especially in low-and middle-income countries, to help ensure safe and beneficial medicines, including antibiotics, and detect substandard and falsified products.



**5. Spur development of new antimicrobial medicines through incentives.** Government and the private sector can play a role in establishing new pipelines for antibiotics and other antimicrobials, including public-private partnerships, payment incentives, and expedited regulatory approval.<sup>22</sup> Implementing initiatives to reduce or slow the emergence of resistant pathogens (for example, building in quality surveillance early in the deployment of new antimicrobials), can extend the useful cycle of medicines, benefiting patients and creating more of a market incentive for the development of new treatments through assuring a longer revenue stream.

BACKGROUND

**I. What is AMR?**

AMR occurs when microorganisms adapt and become resistant to medicines intended to treat bacterial, viral, parasitic and fungal infections. The development of resistance is accelerated by medicine misuse and overuse in people and animals, improper prescribing, poor infection control practices, and the proliferation of poor quality medicines. When microorganisms become resistant to most treatments, causing highly fatal infections, they are sometimes popularly referred to as ‘superbugs.’ Some organisms also have the ability to transfer resistant genes to other organisms, which can affect antibiotic treatment of a wide range of infections and diseases.<sup>23</sup> Resistant strains can spread irrespective of borders or geography, overwhelming health systems.

AMR is caused, in part, by disease-causing microbes being exposed to sub-therapeutic doses of medicines. Sub-therapeutic doses can drive AMR when drug concentrations in the body are too low to effectively treat the infection, but are high enough to create a reproductive advantage for resistant strains by killing susceptible pathogens. This range of sub-therapeutic doses is often referred to as the “mutant selection window,” and it has been studied *in vitro*, *in vivo*, and *in silico*.<sup>24</sup>

There are several reasons why patients may take sub-therapeutic doses of medicines, including:

- Treatment errors by healthcare professionals (i.e., being prescribed an inappropriate medicine, dose, or duration of treatment).
- Non-adherence by patients to appropriate prescriptions/ treatment guidelines.

- A medicine not meeting its stated strength, etc. (e.g., intentional—a falsified medicine; or unintentional—a substandard medicine).

**II. Why Should We Be Concerned?**

AMR poses a significant threat to patients in the U.S. and around the world by endangering our ability to treat common infections with existing therapies. The World Health Organization (WHO) calls AMR a “**crisis that must be managed with the utmost urgency**” and warns that “**without urgent action we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill**”—an “**all-out**” effort is needed.<sup>25</sup>

Compounding the problem, few new antimicrobials are in the pipeline: over the last 30 years, no major new types of antibiotics have been developed.<sup>26</sup>

**III. AMR and Falsified and Substandard Medicines**

**A. Situation**

One causal component to AMR—low quality medicines—is often overlooked, but is very real. Falsified and substandard medicines can contribute to antimicrobial resistance by being partially or completely ineffective at treating illnesses and infections—providing enough exposure to surviving microbes to breed drug resistance.<sup>42</sup> Treating these ‘superbugs’ can be costlier, longer, and less successful than drug-susceptible strains. *Allowing poor quality drugs to prevail anywhere threatens the long-term effectiveness of efficacious drugs everywhere.*

**Facts**

**Globally:**

**By 2050, 10 million people** may die from causes attributable to AMR.<sup>27</sup>

Drug resistance affects a wide range of critical public health threats, including tuberculosis (TB),<sup>28</sup> malaria,<sup>29</sup> HIV,<sup>30</sup> gonorrhea,<sup>31</sup> and influenza.<sup>32</sup>

WHO has identified 12 resistant bacteria that pose the greatest risk to human health and for which there is an urgent need for new treatment<sup>33</sup>—some are so perilous they have been popularly dubbed “nightmare bacteria.”<sup>34</sup>

Many drugs do not work against the **deadliest strain of tuberculosis, Extensively drug-resistant-TB (XDR-TB)**, which is resistant to several first and second-line medicines. Curing the illness for those who are ultimately successful can take up to two years, and the drugs prescribed can cause severe and permanent side effects.<sup>35</sup>

#### IN THE UNITED STATES:

The CDC has identified **18 drug-resistant infections** that currently pose large threats to public health—frequently acquired in healthcare settings—including MRSA (methicillin-resistant *Staphylococcus aureus*), Drug-Resistant Non-Typhoidal Salmonella, Strep (drug-resistant *Streptococcus pneumoniae*), and drug-resistant TB.<sup>36</sup> In the U.S. MRSA **kills more people every year than emphysema, HIV/AIDS, Parkinson’s disease, and homicide, combined.**<sup>37</sup> Vulnerable populations such as the elderly<sup>38</sup> and children<sup>39</sup> are particularly at risk.

**One in five visits to the emergency room** in the U.S. is due to adverse effects from antibiotics, which the CDC has partially attributed to antimicrobial resistance.<sup>40</sup>

A lethal fungus, *Candida auris*, has been identified in at least 61 people in the United States, is considered highly dangerous, and is feared to pose a **“catastrophic threat”** to the public.<sup>41</sup>

Medicines can be **substandard** (not meeting quality, labeling, or other requirements) for a variety of reasons, including product degradation due to weak supply chains; or improper practices or missteps occurring during manufacturing (e.g., failure to follow Good Manufacturing Practices (GMPs)), packaging, labeling, transportation, and/or storage (including failure to follow Good Distribution Practices (GDPs)).

**Falsified** medicines can be motivated by the desire for improper gain. They may be contaminated or intentionally adulterated with a hidden or substituted and possibly cheaper ingredient (economically-motivated adulteration), contain the wrong amount or no active ingredient, and/or be deliberately mislabeled with respect to identity and/or source. Falsified medicines may look identical to authentic products, which makes them difficult to detect. The financial incentives to enter the criminal falsified market are high—coordinated action across governments, sectors, and agencies is critical to reduce the size of this market and reduce its harmful effects on public health.

The impact of poor quality antimicrobials is already being felt around the world: contributing to drug-resistant tuberculosis in Africa, Asia, and other regions; threatening to undo

many once-successful malaria control programs in Latin America, Asia, and other regions; and spawning resistance to medicines used to treat bacterial infections as common as staphylococcus in many regions, including India, where a study by The Lancet Infections Disease Commission attributed over 58,000 neonate deaths to drug resistant bacterial infections.<sup>43</sup>

In a 2013 report, “Countering the Problem of Falsified and Substandard Drugs”<sup>44</sup>, the National Academy of Medicine highlighted the contribution of poor quality medicines to AMR, noting that “a considerable body of research indicates that inexpensive antimicrobial drugs in low- and middle-income countries are frequently poor quality. This not only puts patients at risk, but encourages drug resistance, thereby threatening population health for future generations.”

Fully half of the recommendations in a report by the Center for Global Development’s Drug Resistance Working Group<sup>45</sup> are related to drug quality. Among them, secure the drug supply chain to ensure quality products and practices and strengthen national drug regulatory authorities in low-and middle-income countries.

The WHO Global Strategy for Containment of Antimicrobial Resistance<sup>46</sup> includes a recommendation to “ensure that only antimicrobials meeting international standards of quality, safety and efficacy are granted marketing authorization.”<sup>47</sup> WHO has also created a global monitoring system with data on incident reports that has identified hundreds of incidents of medicines of suspect quality.<sup>48</sup>

## B. Global Approaches

Around the world, governments and stakeholders are implementing approaches to minimize AMR induced by falsified and substandard medicines, through strengthening the supply chain and ensuring access to medicines of assured quality.<sup>49</sup> This includes:

### 1. Compliance with Quality Standards

Standards for quality help manufacturers of medicines, including antimicrobials, ensure their products are safe and reliable for patients and consumers in the U.S. and around the world. Pharmacopeial<sup>50</sup> quality standards (e.g., those of USP and other pharmacopeias) cover the entire lifecycle of medicines, from production to consumption, including:

- The quality of raw materials used to make drugs, including active pharmaceutical ingredients and excipients (the nonactive part of the medicine)



- The manufacture of finished products
- General standards that ensure the proper dosage, control of impurities, toxins, etc. (including for compounded preparations)

## 2. Quality Assurance Programs, Regulatory System Strengthening, and Surveillance

It is critical to invest in and build strong, sustainable quality systems including robust post-market quality surveillance, especially in low- and middle-income countries. Building the local capacity of manufacturers and regulators and introducing innovative safeguards (i.e., surveillance technologies) helps to eliminate falsified, substandard and unapproved medicines, including substandard antimicrobials. Surveillance programs identify substandard and falsified antibiotics and other medicines and take these products out of circulation. Publicly available test specifications supported by acceptable procedures and reference materials are key to the implementation of surveillance programs.

The United States Agency for International Development (USAID) funds and USP administers<sup>51</sup> an effort to improve the supply and availability of quality-assured essential medicines by strengthening regulatory systems and building manufacturing capacity in low-and middle-income countries, including building product quality surveillance systems and helping to detect substandard and falsified products. Other initiatives exist through the WHO,<sup>52</sup> the World Bank,<sup>53</sup> and other organizations.

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## USP's Role

USP is an independent, nonprofit, science-based organization founded in 1820 that safeguards the public's health globally by developing quality standards for medicines, dietary supplements, food ingredients, and healthcare quality. USP standards describe specifications and tests for identity, strength, quality, and purity.

USP's standards are enforceable by the U.S. FDA for medicines and their ingredients imported into or marketed in the United States, and have been used in more than 140 countries globally. Such standards also assist industry in the development, manufacturing, and testing of medicines.

USP standards are developed through independent experts<sup>54</sup> in a transparent scientific process with input from

stakeholders and Federal agencies such as FDA and Centers for Disease Control and Prevention (CDC).

USP participates in and helps to advance cross-sector partnerships that support pharmaceutical quality and build regulatory and surveillance capacity. USP offers programs in under-resourced countries to help combat substandard and falsified drugs and fight antimicrobial resistance (AMR). USP supports the AMR response through its existing work in creating standards, strengthening capabilities, and building an evidence base (including better understanding links between medicines quality and AMR): the organization has almost 700 anti-infective standards, including for antibiotics, antifungals, antimicrobials, antiparasitics, and antivirals.

**The Promoting the Quality of Medicines (PQM)<sup>55</sup>** program is a United States Agency for International Development (USAID) funded initiative implemented by USP, working with medicines regulatory authorities, manufacturers, quality control professions and others in over 35 countries across 4 continents to improve public health by building local capacity to ensure quality medicines.

### **Regulatory System Building and Strengthening & Working with Manufacturers to Increase the Supply of Quality Medicines:**

USP supports the development of local, sustainable quality assurance systems by helping local governments, regulators and manufacturers in low-and middle-income countries to ensure quality medicines, including antibiotics—offering education, outreach, and technical assistance. USP offers these services in partnership with, among others: USAID, national regulatory authorities, WHO, the Global Fund, the World Bank, and the New Partnership for Africa's Development (NEPAD). USP works closely with manufacturers to improve compliance with applicable standards and facilitate approvals for new antimicrobial drugs.

**Surveillance:** USP establishes and supports countries to build capacity for surveillance programs in Africa, Asia and South America to identify substandard and falsified antibiotics and other medicines and take these products out of circulation. As part of that effort, USP also maintains the Medicines Quality Database, a free, publicly available tool that monitors the quality of drugs in over 30 low-and middle-income countries and evaluates the capabilities of medicine quality screening technologies; the organization is engaged in work around large-scale sampling and statistical analysis.

**Quality in the Supply Chain:** To help secure medicine quality throughout the entire lifecycle and across the supply chain,

integrate knowledge and best practices, and promote international cooperation and communication, USP is piloting an effort with the Asia Pacific Economic Cooperation (APEC), a regional economic forum—supporting a Center of Excellence within APEC that is raising awareness about quality and making tools available to improve quality.

**Awareness:** USP is a longstanding proponent of raising awareness and taking action to improve quality along the pharmaceutical supply chain. USP is committed to funding research to better understand and strengthen the knowledge base on the link between poor-quality medicines and AMR. Recognizing the key role that quality standards play in improving public health outcomes, USP is steadfast in its commitment to be a leading advocate for the use of quality standards throughout the world.

**Convening:** USP works to convene stakeholders—for example, bringing together representatives of NGOs and others at the 2017 World Health Assembly to identify the role of medicine quality in AMR. USP also recently convened stakeholders in India to identify options to improve medicine quality that surfaced issues related to AMR in TB.

**Healthcare Quality Standards:** to assist healthcare professionals in the delivery of optimal patient care, USP establishes standards for labeling and physical environments that promote safe medication use (e.g., procurement, prescribing, transcribing, order entry, preparation, dispensing, administration, and monitoring of medications) and also help ensure the safety and quality of compounded preparations.

**Medication Adherence:** to help increase medication adherence, USP has developed and is promoting public standards for prescription container labels that are easy to read; simple to understand; highlight important information; and are standardized so patients know where to look. Such approaches help avoid medication errors and benefit populations including seniors and the sight-disabled: 77 million Americans currently have difficulty reading or understanding labels.

**To learn more** about what USP is doing to help prevent substandard and falsified medicines, including developing standards that help combat antimicrobial resistance, please go to [usp.org/global-health-programs](http://usp.org/global-health-programs).

[drugresistance/pdf/ar-threats-2013-508.pdf](https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf).

- 3 According to the CDC, lost productivity may cost \$35 billion annually in the U.S. due to AMR-related poor health (CDC, Antibiotic Resistance Threats in the United States, above); additionally, by 2050, 6.2% of global production (US\$14.2 trillion) could be lost because of AMR (Bate, Roger. Antimicrobial resistance: How substandard medicines contribute, American Enterprise Institute, 2015, <https://www.aei.org/wp-content/uploads/2015/11/Antimicrobial-resistance.pdf>).
- 4 World Health Organization (WHO), Antimicrobial Resistance Global Report on Surveillance. (2014), [http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1).
- 5 USP is an independent public health organization established in 1820. USP develops transparent standards of quality for medicines, dietary supplements and foods, working with a network of independent experts. USP collaborates with the U.S. Food and Drug Administration (FDA) and other Federal agencies; USP standards for drug quality have been recognized in Federal law since 1906 and are enforceable by FDA.
- 6 CDC: 1 in 3 antibiotic prescriptions unnecessary, <https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html>, relating data published in the Journal of the American Medical Association by CDC in collaboration with the Pew Charitable Trusts and other public health and medical experts.
- 7 The CDC has developed recommendations for antibiotic stewardship in various environments, including healthcare, hospitals, nursing homes, and outpatient settings: “Management of Multi-Drug Resistant Organisms in Healthcare Settings,” <https://www.cdc.gov/hicpac/pdf/MDRO/MDROGuideline2006.pdf>; “Core Elements of Hospital Antibiotic Stewardship Programs,” <https://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>; “Core Elements of Antibiotic Stewardship for Nursing Homes,” <https://www.cdc.gov/longtermcare/pdfs/core-elements-antibiotic-stewardship.pdf>; and “Core Elements of Outpatient Antibiotic Stewardship,” [https://www.cdc.gov/getsmart/community/pdfs/16\\_268900-a\\_coreelementsoutpatient\\_508.pdf](https://www.cdc.gov/getsmart/community/pdfs/16_268900-a_coreelementsoutpatient_508.pdf). Additionally, the Centers for Medicare and Medicaid Services (CMS) has proposed a requirement for antibiotic stewardship and infection prevention and control programs in hospitals, <https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-06-13.html> and has finalized a similar rule for long-term care facilities, <https://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2016-Press-releases-items/2016-09-28.html>.
- 8 The Joint Commission, an independent not-for-profit organization, has issued Medication Management Standards requiring antibiotic stewardship programs for accreditation of hospitals, critical access hospitals, and nursing care centers, [http://www.jointcommission.org/assets/1/6/HAP-CAH\\_Antimicrobial\\_Prepub.pdf](http://www.jointcommission.org/assets/1/6/HAP-CAH_Antimicrobial_Prepub.pdf). The National Quality Forum, a nonprofit organization that sets standards related to healthcare quality, has issued recommendations and best practices for antibiotic stewardship programs in acute care, [http://www.qualityforum.org/Publications/2016/05/National\\_Quality\\_Partners\\_Playbook\\_Antibiotic\\_Stewardship\\_in\\_Acute\\_Care.aspx](http://www.qualityforum.org/Publications/2016/05/National_Quality_Partners_Playbook_Antibiotic_Stewardship_in_Acute_Care.aspx). The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America have published evidence-based, voluntary guidelines for implementing and measuring antibiotic stewardship interventions in inpatient populations, <http://www.empr.com/news/idsashea-release-new-antibiotic-stewardship-guidelines/article/489919/>.
- 9 O’Neill, Jim. Safe, Secure and Controlled: Managing the Supply Chain of Antimicrobials. (November 2015).
- 10 FDA, Are You Taking Medication as Prescribed? <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm164616.htm>; see: the National Institutes of Health (NIH), Medication Adherence: Resources for Patients, <https://www.niddk.nih.gov/health-information/health-communication-programs/indep/health-care-professionals/medication-adherence/resources-patients/Pages/index.aspx>; CDC, Effective Interventions, HIV Prevention that Works, <https://effectiveinterventions.cdc.gov/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence.aspx>; NIH, Smartphone medication apps: Potential benefits to patients and providers, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3919626/>; American Pharmacists Association, Medication adherence: there’s an app for that, <https://www.pharmacist.com/medication-adherence-there%E2%80%99s-app>.
- 11 CDC, see above on Antibiotic Resistance Threats.
- 12 See, e.g., Spread from the Sink to the Patient: in situ Study Using Green Fluorescent Protein (GFP) Expressing- Escherichia coli to Model Bacterial Dispersion from Hand Washing Sink Trap Reservoirs (2017), <http://aem.asm.org/content/early/2017/02/13/AEM.03327-16.abstract?sid=2417007e-8cba-4bdc-bb88-3f1524f0ad80>
- 13 WHO, Tackling Antimicrobial Resistance, supporting national measures to address infection prevention and control and water sanitation and hygiene in healthcare settings, [http://www.who.int/water\\_sanitation\\_health/facilities/amr-ipc-wash-flyer-nov16.pdf?ua=1](http://www.who.int/water_sanitation_health/facilities/amr-ipc-wash-flyer-nov16.pdf?ua=1)
- 14 CDC, Antibiotic Resistance in Nursing Homes and Day Care Centers, <https://www.cdc.gov/healthcommunication/toolstemplates/entertainment/tips/antibioticresistance.html>
- 15 Servsafe, National Restaurant Association, <https://www.servsafe.com/home> (2017).
- 16 New York Times op-ed, “We Will Miss Antibiotics When They’re Gone,” <https://www.nytimes.com/2017/01/18/opinion/how-to-avoid-a-post-antibiotic-world.html?emc=edit>

1 Centers for Disease Control and Prevention (CDC), About Antimicrobial Resistance, <https://www.cdc.gov/drugresistance/about.html>.

2 CDC, Antibiotic Resistance Threats in the United States (2013), <https://www.cdc.gov/>



tnt\_20170119&nid=52256776&ntemail0=y

17 CDC, About Antimicrobial Resistance, <https://www.cdc.gov/drugresistance/about.html>

18 Food and Agriculture Organization of the United Nations, Sustainable Agricultural Practices, <http://www.fao.org/agriculture/crops/thematic-sitemap/theme/spi/soil-biodiversity/agriculture-and-soil-biodiversity/sustainable-agricultural-practices/en/>

19 Pew Antibiotic Resistance Project, <http://www.pewtrusts.org/en/projects/antibiotic-resistance-project/about/antibiotic-use-in-food-animals>

20 Antimicrobial resistance: What does medicine quality have to do with it? Paper prepared by Dr. Elizabeth Pisani, Visiting Senior Research Fellow, Policy Institute, King's College London and Director of Ternyata Ltd., September 22, 2015, <https://amr-review.org/sites/default/files/ElizabethPisaniMedicinesQualitypaper.pdf>.

21 E.g., USP, [www.usp.org](http://www.usp.org); the European Pharmacopoeia (EP), <https://www.edqm.eu/en/european-pharmacopoeia-background-50.html>; British Pharmacopoeia (BP), <https://www.pharmacopoeia.com/>; Japanese Pharmacopoeia (JP), <http://www.pmda.go.jp/english/rs-sb-std/standards-development/ip/0005.html>, and other world pharmacopoeias.

22 See Report to the President on Combatting Antibiotic Resistance, Executive Office of the President, President's Council of Advisors on Science and Technology, September 2014, [https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast\\_amr\\_sept\\_2014\\_final.pdf](https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast_amr_sept_2014_final.pdf); the Report also recommended direct Federal funding of advanced research and development for earlier stage commercial programs. The 2012 "Generating Antibiotic Incentives Now Act" (GAIN), included as part of Title VIII of Public Law 112-144, the Food and Drug Administration Safety and Innovation Act (FDASIA), provided manufacturers an extended, exclusivity period to sell newly-approved antibiotics. The recently-enacted 21st Century Cures Act also created an approval pathway for antimicrobials to treat a serious or life-threatening infection in a population of patients with unmet needs. H.R. 34 (21st Century Cures Act), as enacted (2016), Sec. 3042. Commentators have recommended greater targeting of incentives to high-priority health needs, and enhanced global collaboration, see: Repairing the Broken Market for Antibiotic Innovation, Outterson, K. (2015-02-01). Health affairs (Millwood, Va.), 34(2), 277-285.doi:10.1377/hlthaff.2014.1003, <http://drive-ab.eu/wp-content/uploads/2014/09/Health-Aff-2015-Outterson-277-85.pdf>; see also, Antimicrobial Resistance, a light at the end of the tunnel? The Lancet, Vol. 389, February 25, 2017, [http://thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)30512-3/fulltext](http://thelancet.com/journals/lancet/article/PIIS0140-6736(17)30512-3/fulltext).

23 WHO, Global action plan on antimicrobial resistance (2015), [http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf).

24 Pisani, note above.

25 WHO, Global action plan on antimicrobial resistance, note above, see Foreword; see also WHO infographic on Antimicrobial Resistance Global Report on Surveillance (2014), <http://www.who.int/drugresistance/publications/infographic-antimicrobial-resistance-20140430.pdf?ua=1>; European Commission, Antimicrobial Resistance, [http://ec.europa.eu/dgs/health\\_food-safety/amr/index\\_en.htm](http://ec.europa.eu/dgs/health_food-safety/amr/index_en.htm) (characterizing AMR as "a serious threat to public health worldwide").

26 Antibiotic Resistance- a major global threat, [http://www.futuretimeline.net/blog/2014/05/1.htm#WLR0b2\\_yu70](http://www.futuretimeline.net/blog/2014/05/1.htm#WLR0b2_yu70), also noting the above WHO Global Report on Surveillance.

27 O'Neill, Jim, Antimicrobial Resistance: Tackling a Crisis for the health and wealth of nations (December 2014); O'Neill, Jim, Safe, Secure, and Controlled: Managing the Supply Chain of antimicrobials (November 2015).

28 CDC, Fact Sheet, Drug Resistant TB, <https://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm>

29 WHO, "Eliminating Malaria in the Greater Mekong Subregion," <http://apps.who.int/iris/bitstream/10665/251668/1/WHO-HTM-GMP-2016.12-eng.pdf?ua=1>

30 WHO, Development of the Global Action Plan on HIV Drug Resistance, 2017-2021, <http://www.who.int/hiv/drugresistance/hivdr-action-plan-2017-2021/en/>

31 CDC, Antibiotic resistance threatens gonorrhea treatment, <https://www.cdc.gov/nchstp/newsroom/2016/gonorrhea-treatment-press-release.html>

32 University of Minnesota, Center for Infectious Disease Research and Policy, Drug Resistant Flu Viruses Cause Growing Concern, <http://www.cidrap.umn.edu/news-perspective/2008/10/drug-resistant-flu-viruses-cause-growing-concern>

33 WHO, Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics, [http://www.who.int/medicines/publications/WHO-PPL-Short-Summary\\_25Feb-ET\\_NM\\_WHO.pdf?ua=1](http://www.who.int/medicines/publications/WHO-PPL-Short-Summary_25Feb-ET_NM_WHO.pdf?ua=1); WHO also recently published a new classification of antibiotics that aims to fight antibiotic resistance, with penicillin-type drugs recommended as the first line of defense, and others only for use when absolutely necessary; Reuters, Health News, WHO ranks antibiotics in a bid to counter drug resistance, June 6, 2017; <http://www.reuters.com/article/us-who-medicines-idUSKBN18XIT3>; the new "essential medicines" list includes 39 antibiotics for 21 common syndromes, categorized into three groups: "Access," "Watch," and "Reserve."

34 ABC News: WHO Superbug List: Enemy No. 1 Is Bug That Plagues Soldiers, <http://www.nbcnews.com/health/health-news/who-s-superbug-list-enemy-no-1-bug-plagues-soldiers-n726311>.

35 New York Times, January 31, 2017, Global Health, "Deadly Tuberculosis Strain is Spread Directly."

36 CDC, Antibiotic/Antimicrobial Resistance, Biggest Threats, [https://www.cdc.gov/drugresistance/biggest\\_threats.html](https://www.cdc.gov/drugresistance/biggest_threats.html).

37 Robert Wood Johnson Foundation, Antibiotic Resistance, <http://www.rwjf.org/en/library/research/2015/05/antibiotic-resistance.html> (2015).

38 Taking stock of infections and antibiotic resistance in the elderly and long-term care facilities: A survey of existing and upcoming challenges, Eur J Microbiol Immunol (Bp). 2011 Sep; 1(3): 190-197, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906614/>

39 Washington Post, Dangerous antibiotic infections on the rise for children in the U.S., study finds, [https://www.washingtonpost.com/news/to-your-health/wp/2017/02/25/dangerous-antibiotic-resistant-infections-on-the-rise-for-children-in-the-u-s-study-finds/?utm\\_term=.d96d5ddad832](https://www.washingtonpost.com/news/to-your-health/wp/2017/02/25/dangerous-antibiotic-resistant-infections-on-the-rise-for-children-in-the-u-s-study-finds/?utm_term=.d96d5ddad832)

40 CDC, Antibiotic Resistance Threats in the United States, <https://www.cdc.gov/drugresistance/threat-report-2013/index.html> (2013).

41 STAT News, 'Catastrophic threat': CDC chief fears a deadly superbug's spread, April 21, 2017, <https://www.statnews.com/2017/04/21/superbug-cdc-fungus-candida-auris/>.

42 Bate, Roger, note above.

43 The Lancet Global Health, Antimicrobial resistance—a threat to neonate survival (2016), [http://www.thelancet.com/pdfs/journals/langlo/PIIS2214-109X\(16\)30221-2.pdf](http://www.thelancet.com/pdfs/journals/langlo/PIIS2214-109X(16)30221-2.pdf).

44 National Academies, Countering the Problem of False and Substandard Drugs (2013), [http://www.nap.edu/catalog.php?record\\_id=18272](http://www.nap.edu/catalog.php?record_id=18272).

45 Center for Global Development, the Race Against Drug Resistance (2010), <https://www.cgdev.org/publication/race-against-drug-resistance>.

46 WHO Global Strategy Recommendations, [http://www.who.int/drugresistance/WHO\\_Global\\_Strategy\\_Recommendations/en/index4.html](http://www.who.int/drugresistance/WHO_Global_Strategy_Recommendations/en/index4.html).

47 Id., Recommendation 5.5.

48 The WHO Global Surveillance and Monitoring System for SSFFC (substandard/spurious/falsely-labelled/falsified/counterfeit) medical products was launched in West Africa in July 2013; since then over 400 regulatory personnel have been trained in its use from 126 Member States and almost 1300 SSFFC medical products reported, <http://www.who.int/medicines/regulation/ssffc/surveillance/en/>.

49 O'Neill, Jim, Safe, Secure, and Controlled: Managing the Supply Chain of antimicrobials (November 2015).

50 See What is a Pharmacopoeia, <https://www.youtube.com/embed/i4Trcw0fAZY?rel=0>

51 USP administers, with funding from USAID, the Promoting the Quality of Medicines Program; Promoting the Quality of Medicines (PQM) FY 2016 Annual Report, Submitted to the United States Agency for International Development (USAID) January 2017 (an initiative funded by USAID and implemented by USP), [http://pdf.usaid.gov/pdf\\_docs/pa00mk28.pdf](http://pdf.usaid.gov/pdf_docs/pa00mk28.pdf). USP also receives support from the WHO and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (the Global Fund) to detect and combat substandard and falsified medicines.

52 WHO, <http://www.who.int/medicines/regulation/ssffc/capacity-building/en/>

53 World Bank, <http://projects.worldbank.org/P075056/food-drugs-capacity-building-project?lang=en&tab=overview>

54 <http://www.usp.org/expert-committees/compounding-expert-committee-work-plan>

55 <http://www.usp-pqm.org/>

56 <http://www.usp.org/global-health-programs/medicines-quality-database-mqdb>

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