

### POLICY UPDATE

APRIL 2017

*This is the fourth update in a [series](#) focusing on current policy issues regarding antimicrobial stewardship and the spread of drug-resistant infections. This update highlights recent major initiatives to combat antimicrobial resistance (AMR) involving industry leadership, global policy analysis, research funding, legislation, and strategic international collaboration. As always, we welcome feedback on any of the topics presented in this series. If you have comments or suggestions, you can reach the CIDRAP-ASP project team via Twitter at [@CIDRAP\\_ASP](#) or email at [asp-cid@umn.edu](mailto:asp-cid@umn.edu).*

### Global Action on Antimicrobial Resistance

Efforts to tackle the global threat of AMR have recently taken shape in a number of potentially far-reaching collaborative initiatives. In January 2016, industry leaders at the World Economic Forum publicly committed their support for action to combat AMR. In May, the AMR Review published its final comprehensive report and recommendations for global action. Formation of the new biopharmaceutical accelerator CARB-X was announced in July, and the UN General Assembly held a high-level meeting on AMR in September. In December, the US government enacted the 21st Century Cures Act, which included provisions for accelerating the development and approval of new antimicrobial drugs. A brief synopsis of each of these initiatives is provided below.

#### ***Davos Declaration and Industry Roadmap***

In January 2016, more than 90 pharmaceutical, biotechnology, and diagnostics companies and industry associations signaled for the first time their collective intent to align priorities and support global efforts to address the threat of AMR. On behalf of their companies and associations, senior leaders from some of the world's largest drug and diagnostic developers, including Merck, Johnson & Johnson, Pfizer, Sanofi, Novartis, and Roche, issued a joint declaration to that effect at the 2016 World Economic Forum in Davos, Switzerland. After the initial announcement, additional companies joined the declaration, bringing the total number of signatories to more than 100.

The [Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance](#) calls on governments to allocate funds needed to create a “sustainable and predictable market” for antibiotics, diagnostics, and vaccines. It supports collective action among governments, industry, and nongovernmental organizations to: (1) prevent infections and preserve the effectiveness of new and existing antibiotics (eg, by implementing antibiotic stewardship activities, enhancing integration of rapid diagnostics, and removing financial rewards for greater antibiotic prescribing); (2) improve financial and access-related predictability for industry and health systems to ensure sustainable investment in new antibiotics and diagnostics (eg, by delinking profit from sales and mitigating financial risks for developers and health systems while reducing investments in marketing); and (3) commit globally to coordinated action on antimicrobial stewardship, conservation of existing antimicrobials, enhanced hygiene, and the creation and use of commercial models for developing new antibiotics and diagnostics.

The declaration also highlights the industry's commitment to a set of core [principles](#):

- Work to reduce the development of AMR (eg, by reducing environmental pollution from antibiotic production, encouraging appropriate use of antibiotics, implementing infection control measures, and reducing unnecessary antibiotic use in livestock).
- Invest in the development of new innovative antibiotics, vaccines, alternative technologies, and diagnostics (eg, by supporting collaborative public-private research initiatives).
- Ensure affordable access to new and existing antibiotics globally (eg, through collaborative efforts such as the successful global public health programs to improve access to drugs for HIV, tuberculosis, and malaria).

In September 2016, 13 of the signatory companies issued a [roadmap](#), outlining objectives that they pledge to accomplish by 2020:

- Reduce the environmental impact of antibiotic production, including the development of a framework for assessing and managing antibiotic discharge into the environment.
- Help promote appropriate use of antibiotics and reduce uncontrolled antibiotic purchasing.
- Improve access to current and future antibiotics, vaccines, and diagnostics and reduce the availability of substandard or counterfeit products in high-risk markets.
- Support new public-private collaborations for research and development (R&D) of new antibiotics, vaccines, and diagnostics.

The companies also reiterated their support for a coordinated global effort to combat AMR, including establishment of a high-level coordinating mechanism to provide leadership, mobilize resources, and monitor progress (see Interagency Coordination Group on Antimicrobial Resistance, below).

### ***AMR Review***

The Review on Antimicrobial Resistance, an independent, comprehensive two-year project sponsored by the UK government and the Wellcome Trust, released a series of [interim papers](#) culminating in the landmark final [report](#), *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, published in May 2016. The review was chaired by economist Lord Jim O’Neill, who was charged with analyzing the global problem of rising drug resistance, particularly as an economic and security threat; explaining why action is needed to combat it; and identifying solutions, including ways to build global financial and political support.

The most widely cited aspect of the review is its forecast of severe consequences worldwide if action is not taken to reduce the spread of AMR: by 2050, 10 million lives per year and USD100 trillion in cumulative global economic production would be at risk because of infections that are resistant to antibiotic therapy, the experts predicted. O’Neill notes that this forecast may even underestimate the future impact of AMR, since the review’s predictive macroeconomic models did not take into account increased healthcare costs associated with drug-resistant infections or secondary effects, such as a reduction in joint replacement surgery, difficulties treating cancer, or greater risk of untreatable infection from cesarean sections and gut surgery. Low- and middle-income countries would likely bear a disproportionate burden from AMR in the future, but all countries would continue to be affected.

The review’s final report identifies a diverse set of recommendations to combat AMR globally by reducing demand for current antimicrobial drugs, developing new antimicrobials to treat drug-resistant infections, and building economic and political support for coordinated, international action:

1. **Education:** Deliver a global public awareness campaign aimed at patients, farmers, clinicians, veterinarians, and policymakers to reduce the unnecessary use or prescription of antimicrobials and strengthen support for policies that combat AMR.
2. **Prevention:** Improve hygiene, sanitation, access to clean water, and infection control in healthcare settings to prevent the spread of infections and thereby reduce the need for antimicrobials.
3. **Agriculture:** Reduce unnecessary use of antimicrobials in livestock and aquaculture (eg, for growth promotion), restrict the use of medically important antimicrobials in animals (particularly including last-line drugs for humans), and reduce environmental contamination with antibiotics from industrial and agricultural sewage or run-off.
4. **Surveillance:** Improve collection and reporting of data on antimicrobial consumption in humans and animals, levels of AMR, and biological factors in resistance.
5. **Diagnostics:** Promote the development (eg, through support for early-stage research) and widespread adoption of rapid diagnostic technology to guide appropriate use of antimicrobials.
6. **Vaccines:** Promote development (including early-stage research) and use of vaccines and alternative technologies to prevent infections, thereby reducing the need for antimicrobial treatment.
7. **Workforce:** Increase the numbers, pay, and recognition of infectious disease specialists, including physicians, nurses, pharmacists, microbiologists, and research scientists, working in AMR-related fields.
8. **Funding:** Establish a Global Innovation Fund of up to \$2 billion over 5 years to ensure sufficient private and public investment in research and development, including basic (“blue sky”) research, applied research (in areas such as pharmacology and diagnostics), and non-commercial research.
9. **Incentives:** Enhance market incentives to promote investment in the development of new classes of antimicrobials and the improvement of existing ones by establishing a system of market entry rewards (“pull incentives” that delink R&D rewards from sales volume) of \$1 billion per drug for effective treatments against resistant pathogens in areas of most urgent need.
10. **Global Action:** Build a coalition for global action through G20 and United Nations (UN) leadership to enable coordinated, effective action and sustained progress in combatting AMR.

## **CARB-X**

The 2015 US [National Action Plan on Combating Antibiotic-Resistant Bacteria \(CARB\)](#) called for the creation of a biopharmaceutical incubator, a consortium of academic, biotechnology, and pharmaceutical industry partners to promote innovation and stimulate the development of new antibiotics. The plan directed the Department of Health and Human Service's (HHS's) Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID) to develop a consortium within 3 years. At the June 2016 [Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria \(PACCARB\)](#) meeting, BARDA reported that multisectoral plans were under way to stoke the pipeline of antibiotics and diagnostics. The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, known as CARB-X, was officially launched in July 2016 ([Outterson 2016](#)).

[CARB-X](#) is one of the largest international public-private partnerships for the discovery and preclinical development of antimicrobial products. Its mission is to accelerate a diverse portfolio of innovative antibacterial products, including therapeutics, vaccines, diagnostics, and devices, into clinical development. Its initial priority is the development of treatments for gram-negative bacteria identified on the Centers for Disease Control and Prevention's [list of urgent or serious drug-resistant threats](#) or multidrug-resistant bacteria on the World Health Organization's (WHO) [list of priority pathogens](#).

In addition to \$30 million in first-year [funding](#) from [BARDA](#) and up to \$250 million over the first 5 years, CARB-X receives [matching funds](#) from Wellcome Trust (London) and the AMR Centre (Cheshire, UK) along with research, business, and technical support from NIAID, MassBio, California Life Sciences Institute, the Broad Institute, and RTI International. The partnership is headquartered at Boston University. A key feature is its ability to provide significant, non-dilutive funding and comprehensive business and drug development support services to research teams and biotechnology companies working on AMR.

CARB-X [announced](#) the first group of competitive research awards in March 2017. Eleven early-stage research projects will share up to \$48 million over 3 years. Three of the projects focus on new classes of antibiotics, four projects are aimed at alternative technologies (bifunctional immunotherapy, virulence modifiers, recombinant lysin proteins, and antibody-drug conjugates), and one project seeks to develop a rapid diagnostic tool (optical bacterial imaging). CARB-X's initial goal is to move up to 20 projects through preclinical and early clinical development, enabling private or public investment of the most promising candidates through late-stage development and regulatory approval. Additional awards are expected to be announced later in 2017.

### ***United Nations General Assembly Declaration and Follow-up***

Addressing a One Health issue for the first time in its history, the UN General Assembly (UNGA) convened a high-level meeting of heads of state in September 2016 to address the global issue of sustainable access to effective antimicrobials. The UNGA approved and ratified a resolution [[UN 2016](#)] acknowledging the importance of AMR as a public health threat and the urgent need to take strategic action at national, regional, and international levels to address it. The resolution called for a coordinated response to preserve the effectiveness of antimicrobials and enhance access to antimicrobials for those in need, using [WHO's 2015 global action plan](#) on AMR as the blueprint for these efforts.

Key tasks include raising awareness about AMR and access to effective antimicrobials; setting enforceable global and national targets for antimicrobial access, appropriate use, policies, and resistance rates; mobilizing financial support; and ensuring accountability and multisectoral coordination ([Jørgensen 2016](#); [Laxminarayan 2016](#)). In September 2016, the Center for Disease Dynamics, Economics & Policy formed a global alliance of human and animal health organizations, the Conscience of Antimicrobial Resistance Accountability, to monitor overall progress on the UNGA's resolution and evaluate AMR reduction efforts internationally ([CDDEP 2016](#)).

The UNGA resolution directed the establishment of an ad hoc interagency coordination group to oversee the global agenda and provide guidance for implementing national action plans to combat AMR. In March 2017, the UN secretary-general announced the establishment of the ad hoc [Interagency Coordination Group on Antimicrobial Resistance](#), which will be co-chaired by the UN deputy secretary-general and the WHO director-general.

## 21st Century Cures Act

In December 2016, President Obama signed into law the 21st Century Cures Act ([PL 114-255](#)), a massive piece of bipartisan legislation aimed at stimulating medical innovation and promoting a wide range of healthcare initiatives. The law authorizes more than \$6 billion over the next decade, subject to Congress's annual appropriation, for "innovation funds" within the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) to support activities such as brain research, precision medicine, the Cancer Moonshot, prevention and treatment of opioid addiction, mental health services, new regulatory approval processes for drugs and medical devices, and efforts to combat AMR. Key provisions of the law pertaining to antimicrobial stewardship and antimicrobial drug development include the following:

- **Antibacterial resistance monitoring:** requires HHS to (1) encourage federal healthcare facilities (eg, in the Departments of Defense and Veterans Affairs) to report on antimicrobial drug use, AMR, and antimicrobial stewardship programs; (2) publish annual data on AMR trends and stewardship programs; (3) provide guidance and other informational materials about antimicrobial stewardship for residential and ambulatory healthcare facilities; (4) assist states with their AMR prevention activities; and (5) establish a mechanism for facilities to report antimicrobial stewardship activities and evaluate drug resistance data, including data for drugs approved under the new limited population pathway (see below) (*Title III, Subtitle E, §3041*).
- **Susceptibility test interpretive criteria and testing devices:** requires the FDA to (1) identify updated antimicrobial susceptibility interpretive criteria ("breakpoint" data) to help guide appropriate antimicrobial use and (2) establish a public Web site and maintain updated listings of interpretive criteria standards for susceptibility testing and non-standard criteria relevant to premarket review (*Title III, Subtitle E, §3044*).
- **Limited population pathway for antibacterial and antifungal drugs:** creates a new FDA approval pathway for antibacterial or antifungal drugs if (1) the drug is intended to treat serious or life-threatening infections (eg, multidrug-resistant disease) in a limited population of high-risk patients and (2) the standards for new drug approval or biologics licensure are met. The determination of safety and efficacy of such a drug/biologic under this new pathway reflects the benefit-risk profile of the drug in the intended limited population. The label and prescribing information must indicate that the drug has been approved for use in a specific population of patients and that sponsors must submit promotional materials to FDA for review before dissemination (*Title III, Subtitle E, §3042*).
- **Prescribing authority:** does not restrict off-label prescription of drugs approved under the limited-population pathway (*Title III, Subtitle E, §3043*).
- **Novel clinical trial designs:** requires the FDA to issue guidance for incorporating adaptive and other novel trial designs into the development and review of new drugs and biological products (*Title III, Subtitle C, §3021*).
- **Real-world evidence:** requires the FDA to evaluate the potential use of "real world evidence" (defined as data on the use, benefits, or risks of a drug derived from sources other than

randomized clinical trials—eg data derived from ongoing safety surveillance, observational studies, claims, and patient-centered outcomes research) and to issue guidance for industry on the use of such evidence to support new drug approval or post-approval requirements. This provision is not intended to change the FDA's standards of evidence for approval or post-approval of drugs or biologics (*Title III, Subtitle C, §3022*).

## References

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