Combating Antimicrobial Resistance in 2015

Back to the Future, and Beyond

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Summary

Antimicrobial resistance (AMR) lagged behind biodefense as a U.S. policy priority following the 2001 terrorist attacks. That has recently changed, as evidenced by President Barack Obama’s 2014 Executive Order on Combating Antibiotic-Resistant Bacteria and the subsequent U.S. National Action Plan outlining a whole-of-government approach to addressing antibiotic resistance. AMR has concurrently become a global priority, most notably at the World Health Organization and the Group of Seven (G7) in 2015. Despite recent progress, however, the United States still needs to formulate and articulate an overarching policy on economic incentives and business models that will stimulate research and development of new antibiotics while encouraging conservation and appropriate access globally.

Antimicrobial Resistance in 2015

2015 was a pivotal year for the world community in confronting the global public health threat of antimicrobial resistance. For historical context, 15 years ago was the last time there was similar national and global political commitment to combating AMR. The U.S. government Interagency Task Force on Antimicrobial Resistance (ITFAR)² was established in 1999 and released its Public Health Action Plan in 2001, with more than 80 action items for government agencies. Similarly, the World Health Organization (WHO) issued a Global Strategy for Containment of Antimicrobial Resistance³ in 2001, after a two-year consultation process. The official launch event for the WHO Global Strategy was scheduled for September 11, 2001.

As a result of the fear generated by the 2001 terrorist attacks and anthrax mailings in the United States, political and scientific attention quickly turned from antimicrobial resistance to bioterrorism and other man-made threats. Consequently, AMR was not prominent on the national or global policy agenda for more than a decade. Work ably continued at the level of technical or implementing agencies, including funding of antibacterial research by the National Institute of Allergy and Infectious Diseases (NIAID), monitoring of resistance in the civilian and military populations by the Centers for Disease Control and

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Prevention (CDC) and the Department of Defense (DoD), and regulation of antibacterial drug development by the Food and Drug Administration (FDA). While programs persisted, AMR initiatives did not receive as much funding or attention as other government priorities. Meanwhile, the prevalence of antibiotic-resistant strains in hospital and community settings escalated, and the development of antibiotics slowed as pharmaceutical companies found it more profitable to develop drugs in other disease areas.

Gradually, as the threat of AMR became more apparent, the tide began to turn and some of the research investments that had been poured into biodefense were leveraged for additional benefits. The Biomedical Advanced Research and Development Authority (BARDA) was created by Congress in 2006 to promote the late-stage development of drugs, vaccines, and diagnostics for chemical, biological, radiological, and nuclear threats, pandemic influenza, and emerging infectious diseases. Five years after the anthrax attacks, there was still a fear of bioterrorism but an increasing recognition that naturally evolving biological threats also posed a danger to the nation and the world. As concern over AMR increased, BARDA’s Broad Spectrum Antimicrobials program was launched in 2010 to advance the development of antibiotics and antivirals.

In response to the rising urgency of AMR, there is once again converging a national and global political will to identify and implement solutions. There is a greater awareness of AMR outside of the health and agricultural sectors and at higher levels of government. President Obama elevated AMR as both a public health and national security priority and issued an Executive Order directing federal agencies to develop a five-year National Action Plan to Combat Antibiotic-Resistant Bacteria (CARB), which was released in March 2015. The CARB Action Plan specifies measurable outcomes for one-year, three-year and five-year timeframes and was followed by the development of a similar National Action Plan focused on Multidrug-Resistant Tuberculosis (MDR-TB), released by the administration in December 2015.

Internationally, several organizations and collaborative bodies developed policy documents that emphasized the need for coordinated action. WHO member states approved a Global Action Plan on Antimicrobial Resistance in May 2015, outlining policy recommendations to address AMR and urging each country to develop its own national action plan of prioritized initiatives within two years. There is an increasing awareness that a multisectoral “One Health” approach (i.e., one that includes perspectives from the human health, animal health, and environmental sectors) is needed to tackle the complex AMR problem. WHO, the United Nations (UN) Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE) have committed to coordinate organizational recommendations on

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AMR through the tripartite collaboration. Accordingly, FAO⁸ and OIE⁹ each adopted a resolution on AMR in mid-2015, and both were actively engaged in the creation of the WHO Global Action Plan.

Led by Germany in 2015, the G7 designated AMR as a health priority, culminating in a commitment by G7 leaders to develop and share their national action plans, advance research and development of new antimicrobials, vaccines, and diagnostics, and enhance efforts to reduce the inappropriate use of antimicrobials. G7 health ministers subsequently met in October 2015 to initiate implementation of the leaders’ commitment, including publishing a compilation of best practices that could serve as models for countries developing their own AMR initiatives. As Japan assumes G7 leadership for 2016, Japanese officials are examining how to engage on AMR and other global health priorities. Looking ahead over the next year, it is very likely that the problem of antimicrobial resistance will again surface on the agenda of the G7 Summit, the Group of 20 (G20) Summit, the UN General Assembly (UNGA), and other international fora. In order to move from well-meaning policy statements to implementation, there needs to be sustained high-level political leadership, identification of national priorities, new forms of financing, and a commitment to working across national, regional, and sectoral boundaries to effect solutions.

From Policy to Implementation

International cooperation is required to effectively address the global phenomenon of antimicrobial resistance. International collaboration can take many forms, and different variations will be needed to resolve aspects of the AMR challenge.¹⁰ At the most basic level, an initial agreement on common norms, principles, and goals is a prerequisite for embarking on more elaborate forms of international cooperation, and this has largely been achieved through the litany of AMR policy documents described in the previous section. Second, after mutual goals have been established, groups of countries can create mechanisms to facilitate information sharing among members and simple coordination of members’ decisionmaking. Collaborative decisionmaking is the third level in a hierarchy of international cooperation and is often achieved through pooled financing and joint strategies. Finally, the most urgent and complex crises may require binding international agreements to resolve, such as the Montreal Protocol on Substances that Deplete the Ozone Layer, a 1987 treaty that phased out the use of products containing ozone-depleting chemicals.¹¹ Layered onto the described menu of available options is the question of whether implementation of a particular set of actions requires a truly global consensus, a regional coalition, or another self-identified grouping of countries.

The United States has already been active in a number of international AMR coalitions that are aimed at the first two levels of international collaboration (i.e., policy setting, shared communication, and coordination). The U.S.-EU Transatlantic Task Force on Antimicrobial Resistance (TATFAR) was established

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in 2011 to provide a forum for U.S. and EU technical agencies with antimicrobial resistance programs to exchange information, share best practices, and embark on joint activities. For example, the U.S. CDC and the European CDC coordinated annual public awareness campaigns on AMR. In November 2015, the WHO joined in and spearheaded the first World Antibiotic Awareness Week. TATFAR is entering its fifth year and recently expanded its membership to include Canada and Norway. TATFAR members tout the collaboration as a model of how to operationalize recent calls for international coordination to combat AMR.

Antimicrobial resistance is also a focus of the Global Health Security Agenda (GHSA), a collective of nearly 50 countries that have joined together with the purpose of improving global capacity to prevent, detect, and respond to infectious disease threats. A significant component of the program is a commitment by several countries to provide financial resources and direct technical assistance for capacity building in low- and middle-income countries. Launched in February 2014, GHSA is organized around 11 action packages, each with a specific focus such as AMR. Each action package is led by a few self-selected countries who have agreed to share their expertise and experience in the area with other interested countries. Countries in the AMR action package share information on their program activities in other countries to help ensure coordination of technical assistance to countries requesting support. The U.S. government has committed to assisting at least 30 countries implement all 11 action packages over the next five years and, in July 2015, announced that it will invest more than $1 billion in these efforts.

While communication, coordination, and regional partnerships can target some aspects of the AMR problem, some experts maintain that more extensively coordinated international actions are needed to address the thorniest issues. For example, Ardal et al.\textsuperscript{12} argue that effective global AMR surveillance can be achieved by establishing mechanisms for sharing national surveillance results internationally and through coordination of national and regional laboratory capacity. Similarly, improved infection control can be achieved by communicating evidence of the most effective interventions and coordinating technical and financial assistance to countries as needed (e.g., through GHSA). On the other hand, policies to limit the use of antimicrobials in humans and animals will require strong regulations, coordinated global targets, and perhaps legally binding agreements, such as occurred with the Montreal Protocol on Substances that Deplete the Ozone Layer.

The Review on Antimicrobial Resistance, chaired by economist Lord Jim O’Neill, was commissioned by Prime Minister David Cameron of the United Kingdom in 2014 to investigate drivers of antimicrobial resistance and propose solutions to be implemented through international collaboration. The Review has examined several areas to date, including research and development (R&D) of new antibiotics, diagnostics, and use of antibiotics in agriculture. O’Neill and the Review team have proposed preliminary solutions and are actively pursuing international consensus building for proposals they deem require collaborative decisionmaking by large coalitions such as the G20, or binding agreements through international organizations such as the United Nations. One such focus area is antibiotics R&D.

\textsuperscript{12} Ardal et al., “International cooperation to improve access to and sustain effectiveness of antimicrobials.”
Global Research and Development of Antibiotics: Stimulating Innovation, Conservation, and Access

Antibiotic development slowed over the years due to scientific, regulatory, and market challenges. Economic incentives can be deployed to stimulate antibiotic development, but in order to slow the inevitable rise of resistance to any new drugs, it is critical that incentives be combined with mechanisms to encourage appropriate use. It is also important to consider ways to promote access particularly in low and middle-income countries, where more deaths occur due to the lack of antibiotics than to antibiotic resistance.13

In December 2015, CSIS held a private roundtable of AMR experts to discuss the merits of proposals from the Review on AMR,14 Chatham House,15 and other groups that present economic incentives and alternative business models designed to stimulate antibiotic development while maintaining conservation and appropriate access. Much of the current discussion on alternative business models centers on ways that antibiotics revenue can be delinked from antibiotics sales volume. In other words, instead of a pharmaceutical company generating revenue through the traditional unit sales of antibiotics, which creates an incentive for increased antibiotics use, the company may garner revenue for an antibiotic through an alternative arrangement such as an annual license fee negotiated at a national level or a series of payments received upon achievement of specific milestones.

A mixture of push and pull economic incentives are needed to stimulate AMR product development. The Review on AMR has proposed a global AMR Innovation Fund for early stage research on antimicrobials, diagnostics, vaccines, and alternative therapeutics. O’Neill and his team argue that an estimated $2 billion over five years could be raised from industry contributions. The Review also proposes that a delinkage commercial model be implemented through a new international body similar to GAVI, the Vaccine Alliance. The body could be linked to an existing multilateral entity and would raise funding commitments from governments and large nongovernmental organizations. A developer of a new antibiotic that meets specified clinical criteria would be granted a lump-sum payment or a series of milestone payments upon regulatory approval. The payments could be linked to additional conditions, such as stewardship actions, global access, and post-approval clinical development. O’Neill believes that buy-in from a critical mass of countries, such as the G20, is key to implementing this model. He is advocating that the G20 engage on AMR under the leadership of China in 2016.

While there is still fervent discussion over the appropriate mechanisms to implement a delinkage business model, there seems to be a growing international consensus that a paradigm shift is needed. A few companies have expressed support for favorite models (e.g., GlaxoSmithKline for a fixed payment

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model), but industry also recognizes that particular models may be better suited for specific countries and health systems. At the January 2016 World Economic Forum in Davos, a coalition of more than 80 pharmaceutical, biotechnology, and diagnostic companies released a declaration calling on governments to commit to and fund alternative business models for antibiotics and pledging to work with governments, health insurers, health care providers and other stakeholders to examine the feasibility of various models for a given country’s health system.17

As industry is declaring its position, many governments are also intensely exploring economic policies on antibiotics. The United Kingdom, which has already demonstrated its leadership as the lead of the GHSA AMR action package and through the work of the Review on AMR, is again in the forefront. The United Kingdom is working with leading pharmaceutical companies to explore the feasibility of a licensing fee model for its single-payer health system.18 Similarly, European countries are coalescing around delinkage business models. The European Union, through a public-private partnership with the European Federation of Pharmaceutical Industries and Associations (EFPIA), has funded DRIVE-AB,19 a project to investigate alternative business models for antibiotic development that are nevertheless consistent with responsible antibiotic use.

The United States Should Formulate and Articulate a Cohesive Policy on Economic Incentives and New Business Models for Antibiotics

With all the enthusiastic global debate regarding economic incentives and alternative business models to stimulate antibiotics R&D, what is the position of the U.S. government? Despite recent progress in articulating a broad and relatively comprehensive National Action Plan, there is still no clear and coherent U.S. policy that specifically addresses antibiotics incentives and business models. If the current state of indecision persists, the United States risks getting left behind as other countries move forward with collaborative decisionmaking and implementation of new business models for antibiotic development.

While there is not currently an overarching U.S. policy, departments and agencies have for a few years been involved in deliberations on economic incentives and alternative business models for antibiotics. The FDA, through the Brookings Council on Antibacterial Drug Development, in 2013 sought external expert input on delinkage business models for antibiotics. The U.S. Department of Health and Human Services commissioned a 2014 study to assess the impact of different market incentives on antibiotic development and to model the potential value to society of a given new antibiotic.20 Under the CARB National Action Plan, BARDA and NIAID have proposed to establish a “biopharmaceutical incubator(s),” a new mechanism

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19 Driving reinvestment in R&D for antibiotics and advocating their responsible use (DRIVE-AB); see http://drive-ab.eu.
designed to support early stage product development efforts with funding, technical resources, and business expertise.

Reminiscent of AMR work after 2001, U.S. government agencies are endeavoring to address the gaps in market incentives for antibiotics development, but high-level White House leadership and prioritization are needed to accelerate efforts. Indeed, objective 4.5 of the CARB National Action Plan describes an interagency working group convened by the Office of Science and Technology Policy (OSTP) and the National Security Council (NSC) staff of the Executive Office of the President and tasked with analyzing potential economic incentives. The Plan further notes that “efforts to attract more private investment will reflect the recommendations of the CARB Economic Incentives Working Group.” According to an update at the September 2015 meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, the Economic Working Group’s report was submitted to OSTP, but it remains to be seen whether any of the recommendations will be implemented.

The United States will participate in several international fora in 2016 where AMR will likely be on the agenda and where the challenge of antibiotics development will be tackled, including the G7, G20, and UNGA meetings. The U.S. government may be reluctant to commit to a new global mechanism for antibiotic development. But regardless of specific position, the United States needs to have a consensus policy on economic incentives and alternative business models in order to be a leader in international discussions. Without having a clearly formulated and articulated policy on these matters, the United States risks being a largely silent and ineffective player in upcoming international settings.

**Recommendations**

1) The White House should consider the recommendations of the CARB Economic Incentives Working Group and map out a strategy for implementation through supporting legislative action, new funding authorities, and administrative action.

2) Delinkage business models are consistent with U.S. goals to improve stewardship of new and existing antibiotic agents. Building on the work of the CARB Economic Incentives Working Group, the White House should direct the interagency to examine the feasibility of implementing a delinkage business model at the national level, in close consultation with pharmaceutical companies, health care insurers, physicians, and patient groups.

3) Finally, the United States should formulate a position on whether and how to implement a global alternative business model for antibiotics development and sales, such as that proposed by the Review on AMR.
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