Antimicrobial Resistance: Urgent Need for Responsible and Sustainable R&D Incentives
Support HR 6294: REVAMP Act of 2018

Consensus AMR is a Critical Public Health Threat requiring immediate and significant action

- AMR has emerged as one of the most significant threats to biodefense and public health security. Other important efforts can assist like stewardship and diagnostic innovation, new antibiotics, vaccines and other innovations are urgently needed now and the demand will only grow as resistance overtakes our current supply; however, there are relatively few in development. Over the past two decades, there has been a considerable decline in the number of companies conducting antibiotic R&D due to the significant scientific, regulatory, and economic challenges. These challenges have been addressed thoroughly for over a decade. See Appendix A, below.
- In the U.S., 2 million people get serious antibiotic-resistant infections each year. In total, the economic burden created by antibiotic resistance in the U.S. is estimated at $55 billion, with $20 billion in medical costs and $35 billion in lost productivity/wages from excess hospital stays. By 2050, KPMG estimates that North America could see a 0.73% - 3.7% drop in GDP under a range of different AMR scenarios.[i]
- Without novel treatments antimicrobial resistance will reduce the effectiveness of treatments for infectious diseases and jeopardizes health care gains to society that rely on the ability to effectively treat and prevent bacterial infections, such as organ transplantation, cancer chemotherapy, caesarian sections, and major surgery.
- By 2050, the deaths attributable to AMR could be higher than cancer[ii].

A Strengthened Pipeline is Necessary

- Market entry rewards have been proffered recently by numerous groups of leading experts, including Chatham House, [iii] DRIVE-AB, The Review on Antimicrobial Resistance, the German Global Union for Antibiotics Research and Development, and the Duke-Margolis Center for Health Policy.[iv] Market entry awards in addition have support from leading stakeholders such as the Infectious Diseases Society for America.[v] Such have been designed to provide supplemental revenue for successful development of antimicrobials targeting a prioritized pathogen, and removes the need for volume-based sales models.
- According to Pew Charitable Trusts it has been decades since a truly new innovative class of antibiotics has made it to market.
- A 2017 report by the World Health Organization found only 8 products in development are classed as innovative treatments that will add value to the current antibiotic treatment arsenal.[vi]
- In June 2018 the United Nations published a discussion paper calling on governments to develop incentives that are sustainable and able to support appropriate use of antibiotics.[vii]
- In the past 18 months alone 4 large pharmaceutical companies have exited antibiotic development due to the market challenges.

REVAMP Requires HHS to Define an Extremely Limited Set of Pathogens Based on Urgent Medical Needs

- HHS will form a Committee that includes officials from the FDA, CDC, and other public health and medical officials to develop a limited list of critical need antimicrobial priorities, based in part on the current CDC list, which is far more restrictive than the existing Qualifying Infectious Disease Product designation.
- The list require priority given to products that are novel first-in-class, possess a novel mechanism of action, or treat a vulnerable population such as children

REVAMP Incentivizes Research and Development for All Solutions and Requires Support of Development of Diagnostics

- REVAMP incentivizes innovation beyond only antibiotics, but all products that meet FDA-defined criteria are eligible.
- A company that receives an incentive should work with diagnostic companies to support the timely development of beneficial, innovative diagnostics.

Conveyance Awards Have a Manageable Impact on the Patient and Health Systems

- REVAMP does not require any upfront government funding and unlike other Market Entry Awards will not require a new tax—such as a tax on antibiotic prescriptions, or annual appropriations.
- REVAMP only rewards an antimicrobial company upon licensure of a novel, critical need product and provides appropriate guardrails for recipient manufacturers.
- The U.S. health system is structured in a manner that distributes the cost burden across the entire health sector. It is not accurate to state that patients will incur the entire cost burden. Relative to the cost burden noted above for infections, the impact of the incentive on health care costs will be minimal.
- REVAMP includes provisions to ensure limited impact on the ability of a generic company to launch a new product and also allowing payers ample time to plan for the additional exclusivity.
    - Exclusivity extension cannot be applied to any product with less than 2 years of exclusivity remaining.

REVAMP Includes Provisions to Require Companies to Support Product Stewardship and Surveillance

- Critical need antimicrobial companies will be required to perform above and beyond existing standards:
    - Identify, track and make publicly available antimicrobial resistance occurrence and trends for the drug;
    - Require appropriate use of the drug, including but not limited to appropriate promotional practices, education to encourage correct use, surveillance/monitoring, and stewardship.
    - Develop education and communications strategies for the purpose of educating HCPs about the drug and its appropriate use.

Appendix A: Synopsis of Key Reports, 2010-2018

Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance. Center for Disease Dynamic, Economics & Policy. 2010[1]

- Report from a two-year study by researchers at Resources for the Future, the University of Chicago, the National Institutes of Health, and Emory University that objectively evaluates a range of policy options for dealing with antibiotic resistance. It recognizes the "conflict between the interest of individual decisionmakers and the interest of society as a whole, now and in the future," and supports incentive-based policy solutions to both reduce demand as well as address supply. In regards to encouraging additional R&D, the report considers merits and concerns of various incentives, including tax policy changes, patent changes and wildcard patent extensions.

Policies and incentives for promoting innovation in antibiotic research. London School of Economics. 2010.[2]

- Provides a thorough assessment of the background and causes of antimicrobial resistance and examines the severe economic challenges to the marketplace. It considers a variety of push and pull incentives to stimulate antimicrobial R&D and concludes an urgent need for an "European strategy to address this lack of new antibiotics." It suggests a 'kick-start' targeted R&D and to expect decreasing marginal returns to development investment. The report examines the array of push and pull incentives, focusing on the latter's advantages, and considers a hybrid approach in a 'call-option' model to be promising.

New Business Models for Sustainable Antibiotics. Chatham House. February 2014[3]

- Outlines growing threat of AMR and describes inadequate market incentives to invest in research and commercialization. Current commercial model fails because: it encourages firms to market their drugs aggressively during the exclusivity period and in particular when patent expiration looms, driving resistance through overuse and misuse; proper stewardship controls prevent the drug from being used; and the low price of new treatments caused by downward generic pricing pressure. Delinkage model suggested to reduce commercial risk for companies by addressing market inefficiencies, while encouraging disease prevention and conservation of new antibiotics.

[1] https://www.cddep.org/wp-content/uploads/2017/06/etc_full_6-1.pdf
[2] https://www.lse.ac.uk/LSEHealthAndSocialCare/impacts/LSEHealthNews/News%20Attachments/Policies%20and%20incentives%20report.pdf
[3] https://www.chathamhouse.org/sites/default/files/public/Research/Global%20Health/0214SustainableAntibiotics.pdf

Analytical Framework for Examining the Value of Antimicrobial Products. HHS-ASPE, as prepared by Eastern Research Group. April 2014[4]

- Office of the Assistant Secretary for Planning and Evaluation outlines the value of antibacterial products and assesses various incentives in response to growing crisis. Reports determines very low average private returns for six classes of infections, ranging from -$4.5 million for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) to $37.4 million for community acquired bacterial pneumonia (CABP). All of the infections fall well below the $100 million the net present value "identified by industry and other experts as the ENPV threshold commonly used in decisions whether to enter pre-clinical trials." While privately unprofitable, products determined to provide high value to society, with estimates ranging from $486.6 million for acute bacterial otitis media (ABOM) to $1.217 billion for HABP/VABP. The report considers four categories of incentives and provides helpful evaluative criteria but fundamentally states, "The gap between the current private and public values of drug development suggest that incentives are desirable to stimulate the development of (new) drugs."

President's Council of Advisors on Science and Technology. Reporting to the President on Combating Antibiotic Resistance. September 2014[5]

The PCAST states that changes to antibiotic clinical trials is not sufficient to move the needle with respect to commercial interest. Furthermore, the report states, "[T]here is no way to sustain a robust pipeline of antibiotic development without a major influx of private investment. This will require substantially changing the economics of drug development." The report discusses transferable exclusivity vouchers, delinkage models, higher reimbursement payments, and antibiotic usage fee as ways to reward drug development. An award of $800 million to $1 billion might be required. The advantages of a transferable exclusivity vouchers include leaving innovation up to the free market, not requiring direct appropriations, and spreading the cost of incentivizing development.

Tackling Drug-Resistant Infection Globally: Final Report and Recommendations. United Kingdom, Review on Antimicrobial Resistance. May 2016[6]

- The report provides an updated and detailed evaluation of the brewing AMR crisis and predicts significant economic malaise and morbidity/mortality consequences of AMR. In regards to development incentives it hones in on market entry awards and determines valuation needs to be between $800 million to $1.3 billion. The reward would need to be guided towards urgently needed antibiotics, should be free from political risk, linked to a product's value to society, should come soon after a product reaches the market, should come with guardrails, leave control in the developer's hands, and should be administered at a global level. "We believe this would provide the best of both worlds, encouraging the private sector to innovate while ensuring research priorities are aligned to public need," the

[4] https://aspe.hhs.gov/report/analytical-framework-examining-value-antibacterial-products
[5] https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf
[6] https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

report said. "Such an approach will help stimulate the market for antibiotics, ensuring that there is better commercial reward for antibiotic development without relying on high prices or large sales volumes."

Breaking through the Wall: A call for concerted action on antibiotic research and development. Boston Consulting Group, prepared by Federal Ministry of Health, Germany. February 2017[7]

- The report calls for the creation of a pull incentive to make antibiotics a more attractive commercial proposition. Due to lack of profitability, many large companies are exiting the space. The report states, "This effect ripples down the value chain: big pharma retracts, small and medium-sized companies find fewer investors, basic research is reduced—the pipeline dries up." The report recommends a reward of at least $1 billion for each new high-need product to increase the net present value to a sufficient level.

Recommendations for Incentivizing the Development of Vaccines, Diagnostics, and Therapeutics to Combat Antibiotic-Resistance. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. September 2017[8]

- The report states recommended focused financial incentives to encourage the development of vaccines directed at pathogens that have high rates of AMR across the research and development continuum (from early to advanced development). The report could be provided in the form of pull incentives. Opportunities should be evaluated to expand federal support of grants for advanced development funding through BARDA and Department of Defense for promising vaccines focused on preventing AMR infections. Regarding therapeutics, the report called for a $1 to $2 billion market entry award and suggested paying for it through a transferable exclusivity vouchers.

Revitalizing the antibiotic pipeline. DRIVE-AB—Innovative Medicines Initiative. March 2018[9]

- The report states that public grants for new initiatives at pre-clinical and phase 1 stages are significant at around $550 million annually, this is estimated to produce merely four new classes of antibiotics in the next 30 years. On the flipside, DRIVE-AB forecasts that $1 billion invested in market entry per antibiotic has the potential to quadruple the amount of antibacterial products on the global market over the next 30 years. In addition to "push" and grant financing, the report recommends $200 million paid for the first market entry reward and $400 million after the second reward. Such payments are estimated to yield 18 antibiotics in 30 years post-implementation. Without these policies, increasing grant funding will not have a meaningful effect in generating private-sector R&D funding. Where fully delinked market entry rewards have consistent payer costs amidst decreasing post-approval costs for developers, partially delinked policies increase payer costs slightly.

[7] https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf
[8] https://www.hhs.gov/sites/default/files/paccarb-final-incentives-report-sept-2017.pdf
[9] http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf

DRIVE-AB recommends partially delinked policies to accelerate "Type B" antibiotic approvals to minimize the necessary market entry reward payment, with as much as 50 new approvals resulting from an $800 partially delinked market entry payment.

Workshops. Numerous workshops have been organized that have continued to discuss and consider the problems of AMR and address possible solutions.

- Brookings Institute. Incentives for Change: Addressing the Challenges in Antibacterial Drug Developments. February 27, 2013.[10]
- Chatham House-World Health Organization. Working Group on New Business Models for Antibiotics. May 13, 2014.[11]
- FDA-CDER. Facilitating Antibacterial Drug Development for Patients with Unmet Need and Developing Antibacterial Drugs that Target a Single Species. July 18-19, 2016.[12]
- Characteristics of the Market for Antibiotics. Meeting with US Department of Treasury, Office of Management and Budget et al. September 2016.

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[i] The Global Economic Impact of Anti-microbial Resistance, 2014. Available at: https://home.kpmg.com/content/dam/kpmg/pdf/2014/12/amr-report-final.pdf

[ii] Review on AMR, Tackling Drug-Resistant Infections Globally: Final report and recommendations, May 2016. Available at https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

[iii] Outterson K, Clift C, Gopinathan U, Morel C, Røttingen JA, So A).Towards a new global business model for antibiotics: delinking revenues from sales. Report from the Chatham House Working Group on New Antibiotic Business Models, Chatham House Centre for Global Health Security (London, Oct. 2015).

[iv] See synopsis below.

[v] https://www.healio.com/infectious-disease/antimicrobials/news/online/%7Be44fb88c-e1ad-4e43-b92b-1589076b97b3%7D/idsa-weighs-in-on-bill-for-pandemic-preparedness-funding

[vi] World Health Organization. Antibacterial Agents in Clinical Development: An analysis of the antibacterial clinical development pipeline, including tuberculosis. http://www.who.int/medicines/news/2017/world-running-out-antibiotics-WHO-report/en/ Accessed September 25, 2017.

[vii] Interagency AMR Coordinating Committee. Antimicrobial resistance: Invest in innovation and research, and boost R&D and access: IACG discussion paper http://www.who.int/antimicrobial-resistance/interagency-coordination-group/public-consultation-discussion-papers/en/. Accessed June 22, 2018.

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[10] https://www.brookings.edu/events/incentives-for-change-addressing-the-challenges-in-antibacterial-drug-development/

[11] http://www.who.int/phi/implementation/4_chatham_house_working_group_new_business_models_antibiotics.pdf

[12] https://www.fda.gov/Drugs/NewsEvents/ucm497650.htm