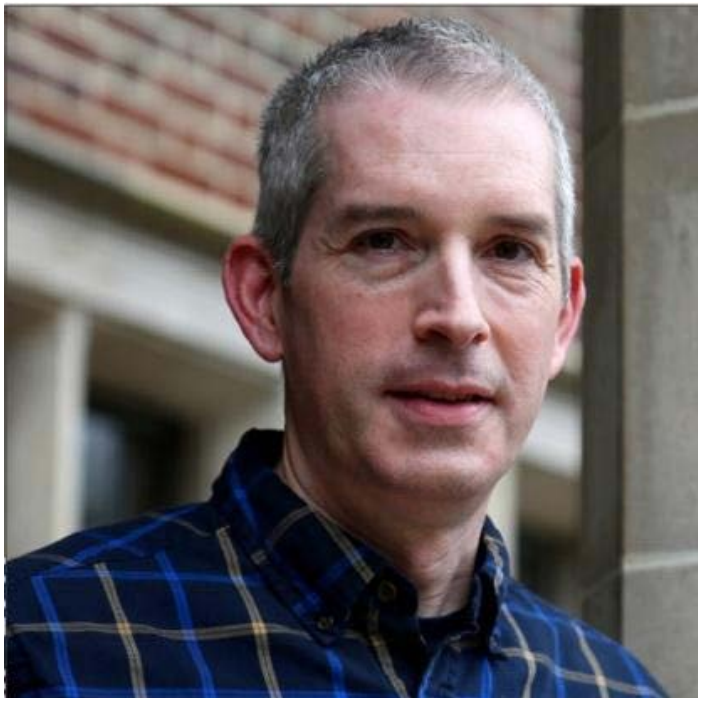
Objective Lens: The PASTEUR Act – Bipartisan Legislation to address the MDR Crisis

John L. McKillip
Managing Editor, Fine Focus, Professor, Microbiology, Ball State University



Infectious disease is currently the 2nd leading killer in the world, and 4th in the U.S. Globally, 17 million people die annually from bacterial infections (1). Yet relatively few have even heard of antibiotic-resistant bacteria or understand the implications for global health. As I mentioned in this contribution in our Spring 2020 issue (*Fine Focus* 6:6-8), no new classes of antibiotics have been developed to treat microbial infections in over 30 years, as pharmaceutical companies have instead pursued research and development of more lucrative drugs for non-infectious diseases. Most large pharmaceutical companies have ceased natural product (NP) discovery, leaving academic labs and small start-up companies to explore antimicrobial therapeutics (2). This crisis is well-known among experts but rarely brought to the attention of the general public.

Alexander Fleming's discovery of penicillin in 1928 was met with his own prediction that bacterial resistance to this "miracle drug" would soon be documented (3,4). In the 70+ years since penicillin was introduced, overuse and misuse of antibiotics have contributed to the problem of MDR bacterial infections, as has the widespread use of antibiotics in agriculture for prophylaxis and growth promotion (5). In fact, the CDC has reported that over 70% of antibiotics used in the U.S. are in production animal environments (6,7). Clinically, antibiotic stewardship and surveillance programs have shown limited success in addressing the MDR crisis (8). In recent years, both the CDC and the White House have outlined clear goals and objectives for directly addressing antibiotic resistance in order to slow the spread of MDR bacteria, while offering a timeline on collaborative international efforts required to make this happen by 2020 (5,6). Unfortunately, this Executive Order signed by President Barack Obama (#13676) has not been addressed, during which time MDR bacterial infections have worsened and become more frequently diagnosed (9,10). Incentivizing large pharmaceutical companies to resume new product discovery and development is an overdue action item; therefore, many scientists and members of the concerned general public may be wondering what, if any, initiatives are in play for operationalizing a solution to this pending crisis.

One solution being explored in our teaching and research laboratories also addresses another international need. In 2015, Singapore led in the global Program for International Student Assessment (PISA) rankings in math and science; the US ranked 38th in math and 24th in science, well behind developing countries including China and India (15,16). Addressing this dire need must come immediately by training new scientists with novel creative and authentic approaches. We are working to improve the quality and effectiveness of undergraduate education in STEM by transforming the focus of the laboratory section of our undergraduate microbiology class from a traditional model to a course-based undergraduate research experience (CURE) design, wherein students would isolate antibiotic-producing bacteria while learning the scientific method. The concept of implementing the CURE structure in laboratory science, as well as non-

science classes, has been well documented and successful in recent years (11-14). At their best, CURE models offer three distinct features: discovery, iteration, and collaboration, all of which are tied together into the goal of teaching undergraduates the process of doing science while working on an original research problem (14) – in our case, isolating and identifying antibiotic-producing bacteria. Using resources, expertise, and protocols modified from the Small World Initiative (SWI) (17), our goal is to isolate and identify multiple metabolites from naturally occurring bacteria in soil, freshwater, and agricultural specimens.

Transforming the undergraduate microbiology curriculum in this way is a completely new teaching and research direction for us, and will blend pedagogy and original research into an entirely different direction than at present. We offer that our CURE model epitomizes engaged student learning, focuses on students as future scientists, and involves curricular innovations to increase student retention in STEM. This pedagogical approach is only part of an effective solution, to the global MDR crisis, however (18). Additional efforts must be realized, and incentives are needed by elected officials for long-term substantive changes to directly address the crisis in the short-term future.

In the summer of 2021, bipartisan legislation was introduced in the U.S. Senate and House of Representatives intended to jump-start the development of urgently needed new antibiotics, using a creative model that should efficiently incentivize interested pharmaceutical companies to begin antibiotic development once again, after a decades-long hiatus. This legislation is called the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act of 2021 (19). Introduced by co-sponsors Senators Michael Bennet (D-CO) and Todd Young (R-IN), this legislation is unique in a few ways. The PASTEUR Act is designed help to revive and restart new product development within the antibiotic pipeline by providing sizable, subscription-based financial incentives for broad public access to innovative, high-priority antibiotics. Traditionally, pharmaceutical profit margins are typically tied to how much of a drug is sold; however, PASTEUR contracts would instead pay for new antibiotics based on their exceptional value to public health. This approach solves the core problem facing antibiotic drug development: the pressing need for innovative drugs that don't have high sales potential in the private drug market. As a result, PASTEUR will not only encourage the development of new types of antibiotics, but also help ensure patients have access to these drugs once they come to market. Currently, S. 2076 awaits consideration by the Senate Committee on Health, Education, Labor, and Pensions.

Put simply, the PASTEUR Act outlines an innovative way for the government to enter into contracts with pharmaceutical companies which would direct existing personnel and resources for new product development. Under the PASTEUR Act, the federal government would create market incentives for the development of lifesaving antimicrobial drugs. Developers would be paid contractually agreed-upon amounts annually, for a duration ranging from five

years up to the antimicrobial's patent life. The subscription contract eligibility and value would be based on the clinical need and novelty of the drug. Thus, waste of funds is minimized because the subscription model allows for profit and funds accrued to be proportional to the need expressed by the company at the outset.

The bill also provides additional resources to support education and implementation of well-directed antibiotic stewardship efforts. For example, these actions would include educating health care providers and the lay community on how to avoid overuse or misuse of these life-saving medications in order to slow the emergence of antibiotic-resistant pathogens

To address this global crisis effectively, a cmprehensive multifaceted approach is needed. Many experts agree that no action will be taken by pharmaceutical companies unless incentivized by Federal intervention. Put simply, there is no national solution to an international problem. The co-sponsors of the PASTEUR Act feel that drug-resistant bacterial infections do not recognize borders, necessitating a coordinated, international approach to protect global health. Moreover, these bacterial infections will disproportionately affect underserved people who lack access to quality care – displaced refugees, families suffering from natural disasters, impoverished individuals, and the immunocompromised, among many others. All are affected directly or indirectly. Immediate federal action, through the PASTEUR Act, will address a fundamentally broken market for antibiotics so that patients will have access to novel antibiotics they need to treat increasingly resistant diseases.

What is the status of this legislation? At the time of this writing, senate and house approval is pending before it goes forward to the President for a signature and becomes law. Currently, S. 2076 awaits consideration by the Senate Committee on Health, Education, Labor, and Pensions. The process is moving slowly but with input from engaged stakeholders, lawmakers may be reminded of the urgency of this initiative. You are encouraged to contact the offices of the cosponsors of this legislation and encourage them to devote their efforts to seeing this legislation through to final approval. Then the real work must begin – augmenting this reinvigorated new antibiotic development with education for healthcare providers and the lay community on appropriate and effective antibiotic stewardship practices.

References

1. Martens, E., & Demain, A.I. 2017. The Antibiotic Resistance Crisis, with a Focus on the United States. *J. Antibiotics* 70:520-526.

2. Hutchings, M.I., Truman, A.W., & Wilkinson, B. 2019. Antibiotics: Past, Present, and Future. *Curr. Opin. Microbiol.* 51:72-80.

3. Khardori, N., Stevaux, C., & Ripley, K. 2020. Antibiotics: From the Beginning to the Future: Part I. *Ind. J. Ped.* 87:39-42.

4. Tan, S. Y., & Tatsumura, Y. 2015. Alexander Fleming (1881-1955): Discoverer of Penicillin. *Singapore Med. J.* 56:366-367.

5. Venter, H., Henningsen, M.S., & Begg, S.L. 2017. Antimicrobial Resistance in Healthcare, Agriculture, and the Environment: the Biochemistry behind the Headlines. *Essays Biochem.* 61:1-10.

6. Abadi, A.T.B., Rizvanov, A.A., Haertlé, T., & Blatt, N.L. 2019. World Health Organization Report: Current Crisis of Antibiotic Resistance. *BioNanoScience* 9:778-788.

7. Michael, C.A., Dominey-Howes, D., & Labbate, M. 2014. The antimicrobial resistance crisis: causes, consequences, and management. *Front. Public Health* 2:1-8.

8. Romo, A.L., & Quiros. 2019. Appropriate Use of Antibiotics: An Unmet Need. *Ther. Adv. Urol.* 11:9-17.

9. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf accessed 8.26.2022

10. https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_ for_combating_antibotic-resistant_bacteria.pdf accessed 8.26.2022

11. https://sites.nationalacademies.org/cs/groups/dbassesite/documents/webpage/dbasse_177288.pdf accessed 8.28.2022

12. https://kb.gcsu.edu/cgi/viewcontent.cgi?article=1002&context=urace Accessed 8.28.2022

13. Osborn, J.M., & Karukstis, K.K. (2009). The Benefits of Undergraduate Research, Scholarship, and Creative Activity. In (M.K. Boyd & J.L. Wesemann, Eds) *Broadening Participation in Undergraduate Research: Fostering Excellence and Enhancing the Impact.* Council on Undergraduate Research, Washington, D.C.

14. Linn, M.C., Palmer, E., Baranger, A., Gerard, E., & Stone, E. 2015. Undergraduate Research Experiences: Impacts and Opportunities. *Science* 347:1261757

15. https://www.pewresearch.org/fact-tank/2017/02/15/u-s-students-internationally-math-science/ accessed 8.2.2022.

16. United States Congress Joint Economic Committee. (2012). STEM education: Preparing for the jobs of the future. Washington, DC: Author. Retrieved from: http://www.jec.senate.gov/public//index.cfm?a=Files.Serve&File_id=6aaa7e1f-9586-47be-82e7-326f47658320 Accessed 9.2.2022.

17. http://www.smallworldinitiative.org/about Accessed 9.28.2022

18. Fluhler-Thornburg, G., & McKillip, J.L. 2023. Course-Based Undergraduate Research Experiences for Laboratory Learning in the Life Sciences. *J. College Science Teach.*, in press.

19. https://www.congress.gov/bill/117th-congress/house-bill/3932 accessed 9.30.2022