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Why More Incentives Are Needed To Tackle Antibiotic Resistance

ANKIT MAHADEVIA, M.D.

Antibiotic resistance is a real and immediate threat that is beginning to garner the global attention it needs and deserves. During a meeting of the United Nations in September 2016, the entire General Assembly — 193 nations — reaffirmed its commitment to developing national action plans on combatting antibiotic resistance. Speaking at the meeting, UN Secretary-General Ban Ki-moon said antibiotic resistance poses “a fundamental, long-term threat to human health, sustainable food production, and development.”

Currently, approximately 700,000 people around the world die every year from so-called “superbugs” or multidrug-resistant infections. This number is expected to rise with the emergence and spread of superbugs across the globe. A strain of *E. coli* resistant to colistin and carbapenem has now surfaced in Europe, China, and the United States. Without an urgent and coordinated global effort, we run the very real risk of falling into a post-antibiotic era in which surgeries and treatments that depress the immune system, such as chemotherapy, are too dangerous to perform, and minor injuries can kill again. According to the final report issued earlier this year by Britain’s Review on Antimicrobial Resistance, if we fail to find effective antibiotics, across the globe, 10 million people each year will die by 2050. This would make antibiotic resistance the world’s biggest killer, with a cost to the global GDP of \$100 trillion.

Until recently, there has been little incentive for drug developers to invest in antibacterials, which are designed to be used as infrequently as possible. Additionally, the American consumer has

come to expect antibiotics to be very inexpensive, which further discourages the development of new antibiotics. The high cost of development and the low rate of return leave little room for profit. In May 2016, The PEW Charitable Foundation found that there are only 37 new antibiotics in clinical development and only a fraction of those will make it to market. In 2001, Eli Lilly and Bristol-Myers Squibb left the market, while Roche spun-off its antimicrobials unit into a separate company. Only five traditional pharmaceutical companies (GlaxoSmithKline, Novartis, AstraZeneca, Merck, and Pfizer) are currently pursuing antibiotic R&D at a time when the world is in desperate need of new antibiotics. An area of particular need is new solutions for Gram-negative bacteria. The unique outer membrane of Gram-negative bacteria protects them against many of the currently available antibiotics and makes them generally less susceptible to antibiotics than their Gram-positive counterparts. There hasn’t been a new antibiotic class approved to treat Gram-negative infections in more than five decades.

GOVERNMENTS ARE TAKING NOTICE

Today, governments around the world are taking steps to encourage responsible use of antibiotics to control the spread of drug-resistant infections. In the United States, the CDC has found that not only are people misusing antibiotics, but that at least 30 percent of antibiotics prescribed in the United States are unnecessary. The CDC, the U.S. FDA, United States Agency for International Development (USAID), and Systems for Improved Access to Pharmaceuticals and Services (SIAPS) have all implemented

educational campaigns encouraging doctors not to overprescribe antibiotics and to inform patients about the dangers of antibiotic overuse and misuse. Local public initiatives on hand washing and the importance of compliance with antibiotic prescriptions have been enacted to help stop the spread of infections and reduce the emergence of antibiotic resistance. Updated antibiotic stewardship guidelines have been recommended by numerous professional organizations including the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).

Public education campaigns and antibiotic stewardship programs play an important role in reducing further damage, but they do little to address the current limited number of effective antibiotics for the toughest-to-fight infections.

Governments are also beginning to fill in these gaps with additional funding and support for antibacterial development. In July, the U.K. established a new Antimicrobial Resistance Center to provide research and funding for startups working in the field. The center has a £180 million (U.S. \$236 million) plan with the ambition of getting 20 products into preclinical development by 2020 and advancing 10 of those to clinical trials by 2022.

As another step in realizing the goals set forth in the White House-led National Action Plan on Combating Antibiotic-Resistant Bacteria (CARB), CARB-X was launched in August 2016. CARB-X is a biopharmaceutical accelerator to help move projects from the lab to clinical trials. In the first year, CARB-X will commit \$50 million to research with the goal of getting at least two new drugs into clinical trials in the next five years.

In addition to providing direct funding for R&D, governments have also begun to take a serious look at the regulatory hurdles faced by antibiotic developers. Passed in 2012, the Generating Antibiotic Incentives Now (GAIN) Act provides an accelerated approval pathway and a five-year regulatory extension of exclusivity for novel antibiotics that address serious or life-threatening infections. Companies such as Allergan and The Medicines Company have begun using the benefits of the GAIN Act. Without the GAIN Act, biopharmaceutical startups would not have been able to raise the capital needed to begin development as a company. More recently, the 21st Century Cures Act was passed in December 2016 and establishes a new FDA-limited population-approval pathway for antibiotics that treat serious or life-threatening infections with unmet medical needs. The Cures Act provides a streamlined regulatory process for medicines treating rare illnesses for which there are few or no available alternative treatments.

THE POTENTIAL OF PUSH AND PULL INCENTIVES

Accelerators, additional funding, and public-private partnerships are critical “push” incentives that reduce a company’s R&D expenses, but more can be done to transform the entire economic model. In addition to incentives that “push” new drugs to market, we also need incentives that will “pull” larger companies into the space to ensure there is a sustainable ecosystem that will continue to deliver new antibacterial solutions well into the future.

Pull incentives reward successful development of a drug by increasing or ensuring future revenue. Pull mechanisms include outcome-based rewards such as monetary prizes and advanced market commitments or policies that accelerate the market approval process, extend market exclusivity rights, and increase reimbursement prices. Some specific pull incentives that have been discussed and should be considered to help drive and sustain antibiotic development include:

- ▶ **Market-Exclusivity Vouchers** — Upon approval, the company that developed the new antibiotic could be granted a voucher that would extend market exclusivity for the newly approved antibiotic. The company could retain and use the voucher or could sell it to another company for use on another drug. In order to be eligible for the voucher, the new antibacterial would need to meet stringent criteria for innovation and its ability to address an unmet medical need.
- ▶ **De-Linkage** — The concept of “de-linkage” refers to separating a company’s return on investment from the number of product units it sells (vials, pills, etc.). Instead, companies would receive one or more lump-sum payments upon product approval and/or other developmental milestones in exchange for agreeing to marketing constraints and stewardship provisions.
- ▶ **Value-Based Reimbursement** — Value-based pricing would price products according to their value for patients based on a health-technology assessment. Society would pay for what it benefits from and values, which would better reflect the life-saving and societal value of these medicines. An opportunity for reevaluation of reimbursement rates to reflect changes in antibiotic effectiveness would be worked into the proposal, and the higher prices may also minimize inappropriate use of antibiotics.

WE NEED A COOPERATIVE ECOSYSTEM

Innovative medicines that truly address unmet needs do not need policy solutions to get to market and be successful, whether in antibacterials or otherwise. However, a healthy ecosystem where biotechs, academic labs, regulators, policymakers, and pharma work together to advance new drugs treating infection is crucial. Any exits from the ecosystem make biopharmaceutical companies’ jobs harder.

We support incentives that solidify the momentum we have in the field by continuing to increase parity between therapeutic areas. With dozens of public policy proposals, now is the time to move forward with a set of solutions. **L**



➔ ANKIT MAHADEVIA, M.D., is president, CEO, and a member of the board of directors of Spero Therapeutics, which he founded in April 2013.