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PERSPECTIVES

Buying Time: The AMR Action Fund and the State of Antibiotic Development in the United States 2020

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Antimicrobial resistance is a pressing global threat, but companies developing antibiotics are failing. Large pharmaceutical companies recently created the AMR Action Fund, which will invest $1 billion in small antibiotic development companies. To understand the state of antibiotic development in the United States, we conducted a case study of new agents against carbapenem-resistant Gram-negative bacteria. Factors contributing to market failures were slow clinical uptake of drugs despite their effectiveness and safety, relatively small numbers of target infections that are insufficient to support existing drugs economically, and an excess of recently approved and pipeline agents with redundant spectra of activity. The AMR Action Fund will provide an immediate lifeline to companies in danger of failing due to an inability to secure investment, but it will not address issues identified in the case study or fix the antibiotic development model or marketplace. The Fund buys time for reforms to salvage antibiotic development.

Keywords. AMR Action Fund; antibiotics; antimicrobial resistance; carbapenem resistance; marketplace.

Antimicrobial resistant (AMR) infections cause ~700 000 deaths annually worldwide, a toll projected to reach 10 million by 2050 [1]. Despite the burden of AMR, the antimicrobial pipeline is under duress. One third of companies behind antibiotics approved by the US Food and Drug Administration (FDA) over the past decade have failed [2]. Large pharmaceutical companies, having abandoned the field for more lucrative products, are currently responsible for only 3 antibiotics in clinical trials [3]. Therefore, it is notable that over 20 of the world's biggest pharmaceutical companies launched the AMR Action Fund in July 2020. The Fund will invest $1 billion in small antibiotic development companies with the goal of bringing 2–4 agents to clinic by 2030 [4, 5]. It will also provide expertise and technical support and develop public-private alliances that champion sustainable antibiotic development. Fixing the broken development model is crucial to solving the looming AMR crisis [4].

In this Perspective, we review the state of antibiotic development in the United States. In addition, we offer views on the AMR Action Fund and potential pipeline and marketplace reforms.

THE STATE OF ANTIBIOTIC DEVELOPMENT

The dire condition of the antibiotic pipeline drew widespread attention in the early aughts, leading to governmental and public-private financial "push" incentives for drug development [6, 7]. The number of investigational antibiotics in clinical trials increased from 13 in 2001 to the mid-30s by 2008–2009 [3]. The FDA has approved 15 new antibiotics since 2014. In 2019, however, US sales of all branded antimicrobials were only ~$750 million, a paltry sum compared with revenue in other spaces (Table 1) [8]. In making investment decisions, companies determine a product's net present value (NPV), defined as projected earnings minus expected production costs (both expressed in present-day dollars). The industry standard NPV to invest in a new drug is ~$200 million. The NPV of the average neurologic or musculoskeletal agent is $720 million–$1.15 billion, whereas that of the average antibiotic is minus $50 million [9]. After the flight of big pharmaceutical companies, antibiotic development is dominated by small companies. Twenty-five antibiotics were in trials in December 2019, the lowest total in 11 years [3].

CASE STUDY OF THE UNITED STATES ANTIBIOTIC MARKET

New antibiotics against carbapenem-resistant (CR) Gram-negative bacteria are a useful case study of the moribund market. Pathogens such as CR Enterobacteriaceae (CRE), CR *Pseudomonas*, and CR *Acinetobacter* have been designated as urgent drug development priorities for 2 decades [11, 12]. Carbapenem-resistant infections are associated with particularly poor outcomes, and polymyxins (colistin, polymyxin B), previous frontline treatments, are suboptimal and toxic. The FDA has approved 7 antibiotics with anti-CR Gram-negative activity since

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Table 1. Top 10 Branded Antimicrobials and Non-Antimicrobials, by 2018 United States Sales[a]

Antimicrobials			Non-Antimicrobials		
Drug (Brand Name)	Class	Sales (US$)	Drug (Brand Name)	Class	Sales (US$)
1. Ceftaroline (Teflaro)	5th-generation cephalosporin with activity vs MRSA	$138 M	1. Adalimumab (Humira)	TNF inhibitor approved for treatment of rheumatologic diseases	$13 680 M
2. Isavuconazole (Cresemba)	Azole class antifungal with activity against some Mucorales spp	$117 M	2. Lenalidomide (Revlimid)	Immunomodulator approved for treatment of multiple myeloma and myelodysplastic syndrome	$6470 M
3. Fidaxomicin (Dificid)	Macrolide with activity vs *Clostidioides difficile*	$115 M	3. Etanercept (Enbrel)	TNF inhibitor approved for treatment of rheumatologic diseases	$4800 M
4. Ceftazidime-avibactam (Avycaz)	β-lactam/β-lactamase inhibitor with activity vs CRE, CR *Pseudomonas*	$92 M	4. Rituximab (Rituxan)	CD20 monoclonal antibody used to treat hematologic malignancies and autoimmune diseases	$4240 M
5. Ceftolozane-tazobactam (Zerbaxa)	β-lactam/β-lactamase inhibitor with activity vs CR *Pseudomonas*	$46 M	5. Nivolumab (Opdivo)	Immune checkpoint inhibitor used to treat various malignancies	$4200 M
6. Dalbavancin (Dalvance)	Lipoglycopeptide with activity vs MRSA, approved for treatment of SSTIs	$39 M	6. Pembrolizumab (Keytruda)	PD-1 monoclonal antibody used to treat various malignancies	$4150 M
7. Tedizolid (Sivextro)	Oxazolidinone with activity vs MRSA, approved for treatment of SSTIs	$35 M	7. Ibrutinib (Imbruvica)	BTK monoclonal antibody used to treat hematologic malignancies and graph vs host disease	$4100 M
8. Telavancin (Vibactiv)	Lipoglycopeptide with activity vs MRSA, approved for treatment of SSTIs	$29 M	8. Aflibercept (Eylea)	VEGF inhibitor used to treat macular degeneration and metastatic colon cancer	$4100 M
9. Oritavacin (Orbactiv)	Lipoglycopeptide with activity vs MRSA, approved for treatment of SSTIs	$22 M	9. Pegfilgrastim (Neulasta)	Recombinant human granulocyte colony-stimulating factor	$3900 M
10. Minocylcine (Minocin)	Tetracycline with activity vs MRSA, also used in treatment of noninfections such as acne	$11 M	10. Apixaban (Eliquis)	Factor Xa inhibitor, anticoagulant	$3760 M

Abbreviations: BTK, Bruton's tyrosine kinase; CR, carbapenem resistant; CRE, carbapenem-resistant Enterobacteriaceae; M, million; MRSA, methicillin-resistant *Staphylococcs aureus*; PD-1, antiprogrammed cell death-1; SSTIs, skin and soft tissue infections; TNF, tissue necrosis factor; VEGF, vascular endothelial growth factor.

[a]United States prescription drug sales in calendar year 2018 were based on data from IQVIA (Durham, NC) [8, 10]. United States sales of each of the 20 top non-antimicrobials were ≥$2.3 billion ($2300 million). In contrast, combined sales of all branded antimicrobials were ~$750 million. Overall prescription drug sales in the United States are ~$375 billion annually. Therefore, antimicrobials account for ~0.2% of prescription drug sales in the United States each year. Global sales of adalimumab (Humira) in 2018 were $19.9 billion ($19 900 million).

2014; 8 other agents are in trials [3, 13].

Antibacterials carry significant built-in market disadvantages compared with other drugs, including stewardship mandates to limit inappropriate use, relatively short treatment courses, and effectiveness of cheap older agents against most infections. Three particular factors have also contributed to economic failure of new anti-CR Gram-negative agents. First, clinical uptake of drugs has been steady, but slow, despite their effectiveness and safety. Using US prescription data, we estimated that new antibiotic use against CRE infections did not exceed that of intravenous polymyxins until December 2018 [14]. Strich et al [15] subsequently used a US hospital billing database to estimate that prescriptions of ceftazidime-avibactam, the most widely used new anti-CRE agent, approached, but did not equal, those of colistin in the fourth quarter of 2017 (excluding cystic fibrosis patients). Factors constraining use may include cost, limited clinical trial data against CR infections, unavailability of commercialized susceptibility testing, holes in spectra of activity (eg, metallo-β-lactamases, pandrug-resistant *Acinetobacter*), and concerns about emergence of drug resistance [14, 15].

A second factor is that CR infections remain rare in the United States [16]. Carbapenem-resistant Enterobacteriaceae and CR *Acinetobacter* were estimated to cause ~13 000 and ~8500 infections, respectively, in US hospitals in 2017; ~32 500 multidrug-resistant (but not necessarily CR) *Pseudomonas* infections were identified [17]. Domestic sales of new anti-CRE

Table 2. Models for Antibiotic Marketplace and Development Reform in the United States[a]

Type of Model	Model	Features	Potential Strengths	Potential Weaknesses
Reimbursement reform	CMS reforms	Final Rule modifications: increase hospital payments for QIDP antimicrobials; waive "substantial clinical improvement" criterion for QIDP antibiotics to be eligible for add-on payments (NTAPs); ICD-10 codes modified to increase complexity of DRG codes relevant to AMR.	Reforms directly impact hospital reimbursement for use of new antibiotics active against AMR pathogens. CMS requires hospitals to implement stewardship programs. CMS reforms do not require Congressional legislation.	Add-on payments (NTAPs) last only 3 years and do not cover full cost of drugs. NTAP applications are burdensome, and, before CMS reforms, many hospitals did seek add-on payments. Reimbursement tied to per-unit use of antibiotic (no delinkage).
	DISARM Act	Bipartisan bill under consideration in US Congress would codify and extend CMS reforms by carving out QIDP antimicrobials from DRG, and reimbursing hospitals for use at or slightly above cost.	Reforms directly impact reimbursement for use of new antimicrobials active against AMR pathogens in all hospitalized patients. Bill requires hospitals to run stewardship programs and to report on antimicrobial usage. Potentially gives immediate boost to small companies, which may stave off imminent failures.	No delinkage of payments. Even with DISARM, US market for drugs against many AMR pathogens is too small to support more than a few new agents. For sustainability in mid- to long-term, this model likely would need to be coupled with another reform. Requires Congressional approval. DRG carve outs for antibiotics may create unwelcome precedent for other drugs. Removed from final version of CARES Act passed by Congress in March 2020.
Transfer of intellectual property rights (TIPR)	Market exclusivity voucher	Companies with FDA approval of specific novel antibiotics receive 12-month market exclusivity extension voucher, which could be used for existing brand name drug or sold.	Precedent for TIPR models over 3 decades in many types of drug development. Does not require spending line item by Congress.	Societal costs of delaying genericization of expensive drugs. Financial reward is not linked to societal benefit. Financially inefficient, compared with direct award to antibiotic developers. REVAMP Act proposing this model did not pass Congress in 2018.
Market entry reward (MER)	Fully delinked MER	Direct prize awarded to companies that introduce a priority antimicrobial, which can be given as series of payments and serve as main revenue stream.	Provides predictable revenue to companies. Units sold at contractually agreed-upon price with conditions on stewardship, access, transparency.	Necessary payments likely to be >$1B per drug. Financially unsustainable without accompanying method of revenue generation, such as tax on existing generics.
	Partially delinked MER	Direct prize with smaller awards than fully delinked model, designed to augment revenue especially as antimicrobial establishes market. PASTEUR Act under consideration by US Congress is a subscription model that has elements of a partially delinked MER.	Provides predictable revenue to companies. Can work within existing reimbursement models. Market disruptions are lower than fully delinked MER or exclusivity voucher models. Can still have conditions attached.	Companies will need to generate sustainable revenue stream based on unit sales.
Government procurement	Subscription ("Netflix")	Governments pay companies guaranteed revenue per year (subscription fee) to ensure access to certain quantity of an antibiotic within a defined time period. Antibiotic pilots initiated in the UK and Sweden; hepatitis C program in Louisiana. PASTEUR Act under consideration by US Congress.	Delinkage model. Provides predictable revenue to companies. Countries could pay for their "fair share" of antimicrobial development, as part of global or G20 initiative. Can be structured to help support sustainable R&D (as in UK), as well as assure access to drugs in event of need.	UK will implement roll-out with limited number of agents. Sweden's model includes any antibiotic meeting qualification standards, but it is not designed to stimulate R&D. Will need time to ramp up, and validation in pilot projects. Need decision making body and mechanisms for transparency.
	National stockpile	Government purchases stockpile of agent(s) that might be necessary if AMR pathogen becomes widely disseminated.	Delinkage model. Provides revenue to companies who have invested in producing antimicrobials against high-priority pathogens. BARDA has precedent with purchasing bioterrorism antibiotics.	Need criteria for assessing risks and prioritizing antibiotics. Need decision making body. BARDA and other government bodies also support drug development, creating potential conflicts of interest in selecting stockpile agents.
Up-front government investment in antibiotic development	Early-stage push funding	Government would de-emphasize focus on marketplace reforms and private sector profitability, and instead increase investment in potentially innovative early-stage products	Would place focus on developing novel products that add value by demonstrating superiority to existing antibiotics, rather than noninferiority. May attenuate pressure to maximize revenues postapproval.	Many innovative products are already in early-stage pipeline, including drugs and therapeutic approaches that differ from traditional antibiotics. No guarantee for returns on investment given costs, uncertainty, and time-intensive nature of drug development. Superiority trials for treating infections are complex, difficult to enroll, costly and often yield unpredictable and difficult to interpret outcomes [21].

Table 2. Continued

Noncommercial	Nonprofit research and development	Nonprofit entity(ies) would discover and develop agents against high-priority pathogens, modeled after programs for TB and malaria.	Removes pressure to maximize return to investors or profit. Can complement, rather than replace for-profit model.	No more likely than for-profits to successfully develop agents or pick winners. Concerns about numbers of new agents and innovation if for-profit companies are displaced. Antibiotic model must address multiple pathogens, unlike TB or malaria models. Even without profit imperative, entities still need to generate some revenue and face substantial fixed pre- and postapproval costs.

Abbreviations: AMR, antimicrobial resistance; BARDA, US Biomedical Advanced Research and Development Authority; CARES, Coronavirus Aid, Relief and Economic Security Act; CMS, US Centers for Medicare and Medicaid Services; DISARM, Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act; DRG, diagnosis-related group; FDA, US Food and Drug Administration; G20, Group of 20; ICD, International Statistical Classification of Diseases and Related Health Problems; NTAP, new technology add-on payment; PASTEUR, Pioneering Antimicrobial Subscriptions to End Upsurging Resistance; QIDP, qualified infectious diseases product; R&D, research and development; REVAMP, Re-Valuing Anti-Microbial Products Act; TB, tuberculosis; UK, United Kingdom; $1B, one billion dollars.

[a]Table has been adapted and updated from Theuretzbacher U, Outterson K, Engel A, Karlén A. The global preclinical antibacterial pipeline. Nat Rev Microbiol 2020;18:275–85.

drugs (each of which was also active against CR *Pseudomonas*) in 2018 were $101 million [16]. Based on positioning of agents at US hospitals, we calculated a potential market of $169 million–$439 million annually. Strich et al [18] used patient-level microbiology and pharmacy data from 134 US hospitals to estimate needs of 39–138.2 days of therapy (DOT) per 10 000 encounters for novel antibiotics against Gram-negative bacteria with difficult-to-treat resistance, including CRE, CR *Pseudomonas*, and CR *Acinetobacter*. Extrapolating from these data, treatment opportunities for such antibiotics are ~11 300–400 000 DOT/year. Taking 2018 ceftazidime-avibactam pricing (average wholesale: $1076/day) as a benchmark [16], the corresponding market size is $120 million–$430 million. At prices of $500/day, the expected annual US market shrinks to ~$56 million–$200 million. Antibiotic development costs often exceed $1 billion; postapproval costs of regulatory compliance, manufacturing, distribution, etc are at least $350 million over 10 years [2]. Therefore, the market cannot support all currently approved antibiotics against CR Gram-negative bacteria, let alone pipeline agents, even if polymyxins were fully displaced [2, 16].

Finally, antibiotic development suffers from lack of innovation. Most anti-CR Gram-negative agents in the clinic or pipeline are derivatives of well established classes that are directed predominantly against CRE, at least partially redundant in spectra with existing antibiotics, and vulnerable to cross-resistance [13]. Likewise, numerous investigational agents are directed against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides difficile*, targets for which newly approved agents have had difficulty establishing themselves (Table 1). Innovation is notable in the preclinical pipeline [19], but products are far from clinic, and they will face similar economic pressures without changes in epidemiology or the marketplace.

FIXING ANTIBIOTIC DEVELOPMENT

The AMR Action Fund will function as a push incentive for Phase 2–3 antibiotics, and it offers an immediate lifeline to companies in danger of failing due to an inability to raise money from investors [4]. The Fund embraces the "pay to play" concept that large pharmaceutical companies not developing antimicrobials should pay to support such efforts [1, 20]. Sponsoring companies are acknowledging the unique medical and societal value of antibiotics, and that many of their successful products depend upon preventing and treating infections. Other strengths are the number and experience of sponsors, potential for leveraging resources and expertise, outreach to public and private partners, and global focus. Challenges will be to identify and advance products against the most pressing clinical needs, limit pipeline redundancies, and foster innovation. A pipeline imbalanced toward derivative agents against pathogens such as non-metallo-β-lactamase-producing CRE or MRSA is inefficient and assures further product failures. The Fund's major weaknesses are that it does not directly address the 3 issues identified in our case study, nor will it fix the broken marketplace. Its most important charge will be to buy time to convince governments to enact reimbursement reforms ("pull" incentives) or implement new antibiotic development models. Descriptions, strengths, and weaknesses of proposals toward these ends appear in Table 2.

Most proposed pull incentives delink reimbursement from numbers of prescriptions. The United Kingdom and Sweden have enacted pilot subscription models, in which governments pay companies a fee for assured access to prioritized antibiotics. The US Congress has considered a linked model of enhanced reimbursement for use of new antibiotics against AMR pathogens at hospitals with stewardship programs (DISARM Act) and a delinked model that most closely resembles a subscription model (PASTEUR Act) (Table 2) [20]. The fate of legislation is uncertain. A recent article called for greater up-front government investment in early-stage discovery and development rather than focusing on private sector profitability, with the goal of producing more innovative products that demonstrate clear superiority to existing antibiotics [22]. Another proposal for a noncommercial model bypasses the private sector by funding nonprofit organizations to develop antibiotics [23].

CONCLUSIONS

The AMR Action Fund affords a window of opportunity to salvage antibiotic development. If these efforts fail, we risk returning to the dark days of 20 years ago. The task then will be more difficult and costly, even as AMR increases globally.

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