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Repairing The Broken Market For Antibiotic Innovation

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ABSTRACT Multidrug-resistant bacterial diseases pose serious and growing threats to human health. While innovation is important to all areas of health research, it is uniquely important in antibiotics. Resistance destroys the fruit of prior research, making it necessary to constantly innovate to avoid falling back into a pre-antibiotic era. But investment is declining in antibiotics, driven by competition from older antibiotics, the cost and uncertainty of the development process, and limited reimbursement incentives. Good public health practices curb inappropriate antibiotic use, making return on investment challenging in payment systems based on sales volume. We assess the impact of recent initiatives to improve antibiotic innovation, reflecting experience with all sixty-seven new molecular entity antibiotics approved by the Food and Drug Administration since 1980. Our analysis incorporates data and insights derived from several multistakeholder initiatives under way involving governments and the private sector on both sides of the Atlantic. We propose three specific reforms that could revitalize innovations that protect public health, while promoting long-term sustainability: increased incentives for antibiotic research and development, surveillance, and stewardship; greater targeting of incentives to high-priority public health needs, including reimbursement that is delinked from volume of drug use; and enhanced global collaboration, including a global treaty.

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The public health threat from antibiotic-resistant diseases is growing, especially attributable to Gram-negative bacteria. The Centers for Disease Control and Prevention (CDC) recently issued a national threat assessment[1] documenting the looming crisis of antibiotic-resistant diseases, yet the pipeline of high-quality treatments remains thin.

Evidence supports the view that existing business models provide inadequate economic support for the creation and use of valuable antibiotic therapies.[2] Policy makers have taken notice, and several high-level initiatives are under way on both sides of the Atlantic to examine these economic issues and propose new business models. President Barack Obama recently issued Executive Order 13676 on combating antibiotic-resistant bacteria,[3] released together with a national strategy[4] and a report from the President's Council of Advisors on Science and Technology.[5] In England, Prime Minister David Cameron recently appointed the Review on Antimicrobial Resistance,[6] building on work by England's chief medical officer, Dame Sally Davies. The European Union (EU) has implemented the New Drugs for Bad Bugs (ND4BB) program in the Innovative Medicines Initiative, a public-private part-

nership currently funded at €686 million (approximately US$800 million).[7] One of those projects—DRIVE-AB—will develop and test better business models for antibiotics.[7] Major think tanks are also involved, including the Brookings Institution, the Pew Charitable Trusts, Chatham House, and the Wellcome Trust. And the World Health Organization is developing a global action plan on antimicrobial resistance.[8]

In this article we review the evidence and present new findings on weaknesses in the existing business model for antibiotic development in priority need areas. We then evaluate recent initiatives that attempt to remedy the situation. We conclude with three proposals to protect the most effective drug class in history.

Antibiotic Innovation Under The Historical Business Model

Pharmaceutical companies allocate research funds with the expectation of a return on investment. Company revenues are determined on a price/volume model: Higher volumes or higher prices (or both) yield higher revenues. Most profits are earned during the first years after introduction, especially with legal protection from generic entry. Particularly active areas currently include oncology and hepatitis C, with the introduction of new specialty drugs at very high prices. In contrast, the return on investment is relatively low for antibiotics as a result of low prices, limited market uptake, and modest government financial support.

LOW PRICES Antibiotics were the original wonder drugs, but they have never been very expensive. In community settings, some US pharmacies offer generic antibiotics free (or nearly so) to drive traffic to their stores. In US hospitals, antibiotics are generally included within a bundled payment, giving hospitals strong financial incentives to limit the introduction of more expensive drugs unless clinically necessary. In both settings, new antibiotics compete against an array of low-cost generics that remain effective enough to suppress pricing for the vast majority of clinical applications. As a result, antibiotics accounted for 6.4 percent of all US prescriptions in 2013 but only 2.6 percent by value.[9]

MARKET UPTAKE IS LIMITED Over the past few years US antibiotic prescriptions per capita have declined compared to all prescription drugs (see Exhibit 1). US antibiotic sales peaked in 2005 (see Exhibit 2). Most recent antibiotics have been approved on the basis of noninferiority trials[10] and so do not come to market with demonstrated superiority in efficacy or safety. While there is some portfolio value in antibiotic diversity, a true breakout antibiotic product will need evidence of superiority for important unmet medical needs.

A recent review of three decades of new molecular entity antibiotic approvals and withdrawals found that many antibiotics approved in the 1980s and 1990s had difficulty competing against already approved drugs.[11] Antibiotics suffered market withdrawals at three times the rate of other drugs. Causes for withdrawal varied, but little evidence supports resistance as a cause since drugs that remain on the market have similar resistance profiles. Interrelated causes included safety problems, lack of superior efficacy compared to existing treatments, and lack of market success.

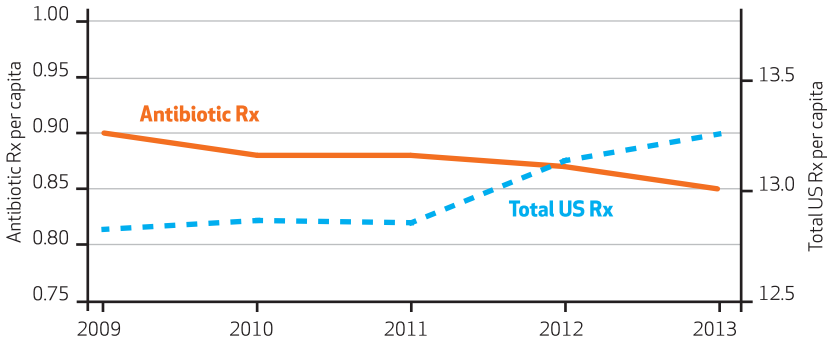
Furthermore, stewardship programs appropriately lead to limits on antibiotic market uptake.[12] Successful antibiotic education[13] and vaccination campaigns[14] have been partially responsible for the reduction in US antibiotic use and would also be expected to restrict the market for new antibiotics.

Finally, the value of new antibiotics for resistant diseases is not solely for the patients who actually use the antibiotics. Rather, it is also for everyone in the broader population who does not develop resistant infections because of the well-targeted use of new antibiotics. That public health value is not captured in the willingness to pay on the part of a specific patient or his or her health plan and thus in pricing models.

GOVERNMENT FINANCIAL SUPPORT IS NOT GROWING The principal US government financial support for antibiotic research and development is through the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA). While the NIH does not publicly categorize spending

EXHIBIT 1

Per Capita US Prescriptions, Antibiotic And Total, 2009–13



SOURCE Authors' calculations based on data from IMS Health (see Note 9 in text), and US Census Bureau (July 1 census estimates each year). **NOTES** Antibiotic prescriptions are denoted by the orange solid graph line and relate to the left-hand *y* axis. Total US prescriptions are denoted by the blue dotted graph line and relate to the right-hand *y* axis.

separately for bacterial resistance, overall spending on antimicrobial resistance is flat in real terms, reflecting secular trends in NIH funding (see Exhibit 3). BARDA funding has been important but faces similar challenges, even as the program has become more central to advancing antibiotic development. Funding in Europe has been modest in recent years.[15]

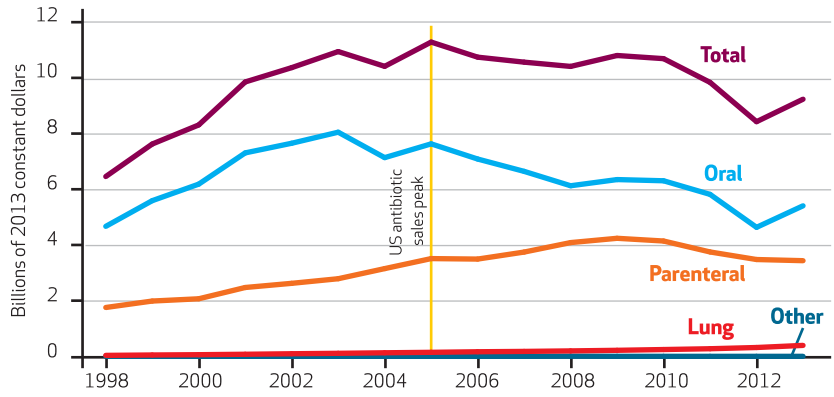
Additional government research funding is provided by the Orphan Drug Act of 1983, which supports many drug research and development programs, but it does not appear to be a good fit for antibiotics. While 464 drugs and biologics with orphan drug designations had reached the market as of October 2014, only ten treated bacterial disease, and none of those targeted disease attributable to resistant pathogens identified in the CDC threat assessment (see online Appendix Exhibit A).[16] Of the sixty-seven new molecular entity antibiotics approved by the Food and Drug Administration (FDA) since 1980, only one initially entered the market with orphan drug designation: bedaquiline for multidrug-resistant tuberculosis.

Antibiotics face special difficulties in meeting the criterion for orphan drugs—diseases or disorders affecting fewer than 200,000 US residents.[17] The number of US patients currently hospitalized with pathogens such as carbapenem-resistant *Enterobacteriaceae* falls below the numerical threshold for orphan drug designation. However, lack of diagnostics and empirical administration of study drugs means that most clinical studies cannot focus solely on patients with resistant diseases but rather enroll broader groups of patients. In clinical practice, the lack of rapid diagnostics for many infectious diseases results in empirical prescribing outside the target population, which does not occur in many other orphan diseases such as inborn metabolic diseases. Furthermore, even if antibiotics for resistant diseases could be targeted effectively with better diagnostics, that would likely exacerbate the revenue challenges by reducing the market potential for new antibiotics even more than at present.

COMPANIES DO NOT REGARD ANTIBIOTICS AS PROFITABLE For all of these reasons, companies find that the return on investment is relatively low for antibiotics.[18] In a recent analysis for the Department of Health and Human Services (HHS), the Eastern Research Group found expected net present values for several categories of antibiotic research to be remarkably low and in some cases negative. In no case did net present values exceed a target benchmark of $100 million, because of the factors mentioned above, including low prices and slow market uptake.[19] From a commercial standpoint, drug companies might not risk expending capital over the product development cycle if the expected returns from antibiotics are so low but instead may shift funds to other drug categories with higher earning potential. These low antibiotic valuations stand in sharp contrast to the social value of antibiotics and willingness-to-pay estimates, which are much higher.[19]

EXHIBIT 2

US Antibiotic Sales For Human Use, In 2013 Constant Dollars, By Mode Of Administration, 1998–2013



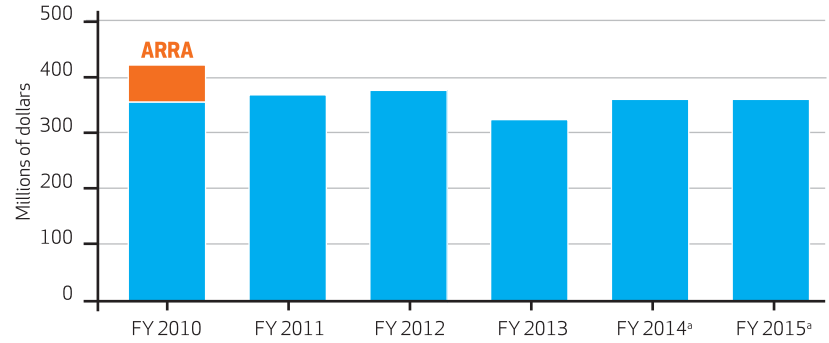
SOURCES IMS Health (US manufacturer US dollar sales at ex-manufacturer prices), and St. Louis Federal Gross Domestic Product deflator (2013 = 100).

Recent Initiatives To Improve Antibiotic Innovation

Many stakeholders are working on possible solutions to these economic problems with antibiotic business models. We review four potential

EXHIBIT 3

National Institutes Of Health Research Spending On Antimicrobial Resistance Research, United States, Fiscal Years 2010–15



SOURCE National Institutes of Health (National Institute of Allergy and Infectious Diseases) Research Portfolio Online Reporting Tool, Estimates of Funding for Various Research, Condition, and Disease Categories (August 20, 2014). **NOTES** Adjusted annually for US Consumer Price Index, fiscal year (FY) 2010 base. American Recovery And Reinvestment Act (ARRA) funding is for FY 2010 only. [a]Estimated.

interventions across the antibiotic life cycle and then assess their impact on innovation.

CLINICAL TRIAL SIMPLIFICATION After receiving direction from Congress, the FDA recently issued guidance simplifying antibiotic clinical trials, allowing approval with quantitatively less evidence of safety and efficacy.[20] The European Medicines Agency, the FDA's counterpart in Europe, has taken similar steps. Legislation is proposed in Congress to permit some antibiotics to reach the market with even less evidence, such as a single, very small clinical trial combined with other evidence.[21] The Antibiotic Development to Advance Patient Treatment (ADAPT) legislation, if passed, would permit early release with such limited studies, but with a label stating: "This drug is indicated for use in a limited and specific population of patients."

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Drugs

Of the 464 drugs and biologics with orphan drug designation that had reached the market by October 2014, only 10 treated bacterial disease.

The ADAPT Act and other forms of limited approval will get some antibiotics to market more quickly with less data than is currently the case. If the drugs are effective, this can improve outcomes for patients with otherwise untreatable infections. Since the patient numbers will be small, this reform will not improve innovation incentives unless the reimbursement per patient is dramatically higher or there is a clear pathway for much broader use. But if pricing or efforts to expand use are aggressive, then questions will be raised about resistance and whether the quality of the evidence on efficacy and safety adequately justifies increased costs. Higher prices also raise questions about access and companies' incentives for marketing beyond the limited population. Current reimbursement capabilities by payers also would be unable to support variable antibiotic pricing.

A better approach may be contractual, in which the company agreed to enforceable restrictions on marketing and use in exchange for temporary limited approval, pending required completion of the normal confirmatory trials (adequately powered human clinical trials with patient-centered outcomes). Postmarketing commitments have been difficult to enforce, so additional steps to limit utilization (for example, use of narrow coverage rules by payers) and other steps as described below may be needed.

These issues highlight why additional clinical trial simplification is unlikely to be a major innovation driver. The Eastern Research Group report calculated that reaching the $100 million net present value benchmark would require extraordinary increases in trial efficiency—for example, reductions in clinical trial time by up to 75 percent or more.[19] Such drastic reductions seem implausible, especially given reductions already achieved through recent initiatives. Moreover, reductions in clinical trial standards

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may lead to approvals with more limited safety and efficacy data, which might entail risks to the public[22] and make it more difficult for payers to support higher reimbursement.

PUBLIC-PRIVATE PARTNERSHIPS TO SUPPORT CLINICAL TRIALS Public-private partnerships have led to notable progress in drug development for infectious diseases. One example is the TB Alliance, which has accelerated the development of new treatments for drug-resistant tuberculosis.[23] The most prominent public-private partnerships in antibiotics are BARDA in the United States and ND4BB in the European Union. BARDA support has been an important source of nondilutive capital for some high-profile antibiotics in the pipeline (see Exhibit 4). For example, in a recent agreement with GlaxoSmithKline, BARDA committed up to $200 million for antibiotic research. The funding structure allows for switching among projects based on milestones. This approach is modeled on how private funding is allocated within companies: Further funding follows demonstrated progress. Another interesting example in the United States is the Antibacterial Resistance Leadership Group sponsored by the NIH, which is building more efficient clinical trial networks for antibiotics.

In the European Union, ND4BB has committed €686 million thus far.[7] One project under ND4BB—DRIVE-AB—is focused on improving business models for antibiotic access, use, and development, with an emphasis on delinkage of revenues from sales volume.[7]

While BARDA and ND4BB have had successes, they have been limited by their funding. BARDA has also been historically focused on a biodefense mission, although this recently changed with President Obama's Executive Order 13676.[3]

ADDITIONAL MARKET EXCLUSIVITY INCENTIVES In 2012, following the model used to encourage development of orphan drugs and pediatric drugs, the Generating Antibiotics Incentives Now (GAIN) Act granted five years of additional

market exclusivity for "qualifying infectious disease products." As of December 29, 2014, four antibiotics have reached the US market with this designation (dalbavancin, tedizolid, oritavancin, and ceftolozane/tazobactam), and at least sixty additional drugs in the pipeline have been so designated.

Qualifying infectious disease product designations should not be interpreted as evidence of accelerated antibiotic development. The four drugs mentioned above had been in development for many years before the 2012 law passed. None of them was approved based on studies designed to prospectively demonstrate superior efficacy compared to the older drugs to which they were compared. Thus, in these cases, this designation was something of a windfall for sponsors, mirroring questions raised about the extent to which another recent drug innovation initiative—Priority Review vouchers—has provided effective incentives for needed innovation.[24] (These vouchers allow companies to jump the queue at the FDA and obtain faster approval on a non-Priority Review drug. The triggering event to award a voucher is when the FDA approves a new treatment for a qualifying neglected disease. The voucher may then be sold for use on a different drug.)[25]

Even for new research programs, there is reason to doubt whether designation as a qualifying infectious disease product is an important innovation incentive. In the Eastern Research Group report, additional years of exclusivity did not significantly improve incentives because of the time value of money: When initial research projects are evaluated, the prospect of five additional years of exclusivity twenty years hence is deeply discounted. Indeed, even infinite extensions of exclusivity did not yield net present values achieving the $100 million benchmark.[19] The GAIN Act was scored as budget-neutral, another indication that its impact on economic incentives will be small in its first decade.

Furthermore, the qualified infectious disease product model might not be well targeted to high-priority antibiotic needs. First, although qualifying products are "intended to treat serious or life threatening infections," this language is much weaker than the standard applied to Priority Review drugs, which requires the sponsor to also demonstrate significant improvements in safety or effectiveness. Second, although the statute mentions "resistant pathogens," the final FDA list is very broad, covering both resistant and susceptible bacteria. Most striking is the absence of any prioritization within the list, contrasting with the CDC's approach in the threat assessment. Almost every major pathogenic microorganism is included.[26]

EXHIBIT 4

Biomedical Advanced Research And Development Authority's Broad Spectrum Antibiotic (BSA)–Supported Product Pipeline, 2014

	Sponsor	Compound	Development			
			Preclinical	Phase I	Phase II	Phase III
Antibiotics	Achaogen	Plazomicin (ACHN-490)	**Next-generation aminoglycoside: broad spectrum** Plague, tularemia, and carbapenem-resistant *Enterobacteriaceae* (CRE)			
	CUBRC/ Tetraphase	Eravacycline (TP-434)	**A novel fully synthetic tetracycline: broad spectrum** Plague, tularemia, complicated intra-abdominal infections and UTIs			
	Cempra	Solithromycin (CEM-101)	**Next-generation fluoroketolide: broad spectrum** Anthrax, tularemia, gonorrhea, community-acquired bacterial pneumonia			
	Basilea	BAL30072	**A novel sulfactam: broad spectrum** MDR Gram-negative infections, melioidosis, glanders			
	Rempex	Carbavance (meropenem/ RPX7009)	**Carbapenem/beta-lactamase inhibitor: broad spectrum** CRE, complicated UTI, hospital-acquired pneumonia/ventilator-assisted pneumonia, melioidosis, glanders			
	GSK	A portfolio approach	**Broad spectrum antibiotic portfolio:** A partnership to fund multiple compounds to combat antibiotic resistance at various stages of development			

SOURCE Biomedical Advanced Research and Development Authority (BARDA). **NOTES** The projects in this exhibit are supported by BARDA's Broad Spectrum Antibiotic (BSA) Program utilizing nondilutive funding via a contract and/or agreement. The stage of development is approximate as of July 2014 (please refer to the sponsors' websites for updated information). The exhibit represents the compounds' most advanced commercial indication being pursued by the developer. UTI is urinary tract infection. MDR is multidrug resistant.

It is difficult to identify any new molecular entity antibiotic approved by the FDA since 1980 that would not have been considered a qualified infectious disease product. As a result, we can expect almost every new antibiotic to receive this designation. Thus far, the FDA has granted qualified infectious disease product status to every antibiotic that has properly applied.

A better approach would be larger incentives than in the qualified infectious disease product designation, more closely targeted to priority therapeutic needs. Meaningful incentives will require something other than longer exclusivity and should be heavily weighted to the most urgent threats and therapies with the greatest added benefits.

REIMBURSEMENT REFORMS New approaches to antibiotic reimbursement are being explored in the United States in Medicare and in Europe through the work of Chatham House and DRIVE-AB. Traditionally, Medicare payments for inpatient antibiotics are based on Medicare severity diagnosis-related groups (MS-DRGs). The MS-DRG system is based on a set of fixed payment rates derived from the average treatment costs for a group of bundled services defined by specific diagnoses and other clinical characteristics.[27] While this creates incentives for hospitals to operate efficiently, MS-DRG rates based on historical average costs can create

disincentives for hospitals to use newer, more expensive technologies not yet accounted for in the MS-DRG calculations.

New technology add-on payments are viewed as a promising workaround. Introduced in 2001, such payments are a bridge to reimburse hospitals for the excess costs of new technologies not yet accounted for in the MS-DRGs during the first two to three years of product marketing.[28] Fidaxomicin for the treatment of *Clostridium difficile* diarrhea was granted new technology add-on payments beginning in 2012, providing an additional $868 per course, but only when the cost of the case exceeded the standard MS-DRG amount.[29] Fidaxomicin was superior to vancomycin, whose generic cost is about $120 per fourteen-day course of treatment, in sustained cure of *C. difficile* diarrhea, while noninferior on initial resolution.[30]

New technology add-on payments provide only short-term reimbursement adjustments for hospitals—that is, only long enough for the added cost to be reflected in the standard DRG amount. This process may have limited financial impact. In the first three months only thirty-eight new technology add-on payment claims were submitted by hospitals to CMS for fidaxomicin. Fidaxomicin recently failed to receive an extension of the add-on payment beyond the initial two years. Furthermore, these payments are awarded only for new technologies with demonstrated "substantial clinical improvement" over existing therapies—a challenging requirement for antibiotic development, since most antibiotic clinical trials for approval are designed to demonstrate noninferiority rather than superiority. In 2014 the Centers for Medicare and Medicaid Services (CMS) denied a new technology add-on payment for dalbavancin for failing to demonstrate "substantial clinical improvement" over existing therapy for acute bacterial skin and skin structure infections.[31] Dalbavancin was not superior in efficacy or safety to vancomycin but claimed improved convenience through once-weekly dosing.[32]

In March 2014 the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act of 2014 was introduced in Congress. DISARM, if passed, would create an additional add-on payment to the MS-DRG, similar to the new technology add-on payment, but as a permanent carve-out. This payment reform would apply only to antibiotics used in acute care hospitals that receive payments under Medicare fee-for-service (Part A) while participating in the Antimicrobial Use module of the CDC's National Healthcare Safety Network (or an alternative program determined by HHS). Because DISARM is budget-neutral, one challenge faced by hospitals is that the increased payments for qualifying antibiotics would come from a lower base rate for the MS-DRG.

Meaningful incentives should be heavily weighted to the most urgent threats and therapies with the greatest added benefits.

As originally introduced, DISARM applies to most qualified infectious disease products. The practical effect may be to exempt most new hospital antibiotics from the MS-DRG and, therefore, from the pressure to limit low-value treatments created by the DRG system. Once again, a more effective alternative would be to target incentives to the antibiotics that most improve outcomes for patients. This alternative version of DISARM is being explored in Congress because it results in a significantly lower budget impact and targets incentives more carefully.

In the outpatient setting, reimbursement rates for antibiotics are typically based on average selling price or some cost-to-charge ratio. Traditionally, low rates are a result of competition with low-cost generics and the absence of demonstrated superiority.[33]

Even if DISARM or similar reforms allow for higher prices, add-on payments as a percentage of drug price and conventional outpatient reimbursement still encourage higher sales volume instead of rewarding appropriate use. Comprehensive payment reforms for both settings are needed that move away from price/volume models toward rewarding better outcomes for patients and appropriate use, while ensuring appropriate access for patients.

Some more fundamental reforms to antibiotic reimbursement are being developed, particularly in Europe in the Chatham House process[2] and the recently launched DRIVE-AB project by the European Union.[7] One prominent model is "delinkage," which severs company revenues from sales volumes, reducing economic incentives for companies and other stakeholders to inappropriately market, sell, or use antibiotics. Under delinkage, companies will be rewarded for deliv-

Countries acting in isolation can have only a limited impact on antibiotic resistance.

ering new products to the market but with alternative payment streams such as registration prizes, patent licenses, service contracts, or payments akin to insurance premiums. Major pharmaceutical companies such as GlaxoSmithKline have expressed support for delinkage, while others are still evaluating the concept and have concerns about whether adequate payments will materialize. One goal of the DRIVE-AB project is to develop and test feasible delinkage models that work for all stakeholders.

Building Better Antibiotic Business Models

Three key features are needed to improve innovation and sustainably preserve antibiotics. These features are described below.

INCREASE INCENTIVES ACROSS PRODUCT LIFE CYCLES Building better business models will require incentives both before and after a new drug is approved, tailored to the unique requirements of each period.

First, government-funded basic research is the foundation for biomedical innovation. These programs are working well, but funding should be larger and more stable. NIH funding underwrites human capital in research and early-stage work that the private sector cannot adequately fund. The Eastern Research Group report suggests that such incentives could have a substantial impact.[19] A reasonable target was set in the US national strategy to combat antibiotic-resistant bacteria: doubling inflation-adjusted US government spending on bacterial resistance and related research, including surveillance, infection control, vaccines, diagnostics, and other nonantibiotic treatments. The national strategy also proposed sizable increases in BARDA funding relating to achieving important milestones toward antibiotic development. Properly targeted, these initiatives will stoke the pipeline with higher-quality projects.

An additional source of nondilutive capital could be refundable tax credits, perhaps modeled on legislation similar to the Orphan Drug Act. However, the same benefits could be achieved more directly through NIH and BARDA expansions, as the tax system has no easy mechanism to target credits to priority antibiotics.

These incentives affect company bottom lines immediately rather than decades in the future. To raise net present values, the amount of capital needed in clinical trial phases may range up to several hundred million dollars per molecule.[19]

Second, postapproval reimbursement reform must be comprehensive across all settings. Medicare can lead this effort in the United States with the involvement of private payers. Payments might be tied to availability of an antibiotic for the covered population rather than to volume, and eventually to outcomes such as reduced morbidity and mortality in the covered population from resistant infections.

The size of additional spending should be large but worthwhile, totaling perhaps $1 billion per successful high-priority antibiotic.[19] The United States spent $8.6 billion for human antibiotics in 2013.[9] At a societal level, an additional premium should be paid in order to sustainably preserve antibiotic effectiveness, akin to an insurance policy against returning to an era without effective antibiotics. Simply restoring the United States to 2005 spending levels in real terms would fully fund the national strategy.

TARGET INCENTIVES CAREFULLY The FDA approved a large number of relatively unimpressive antibiotics in the 1980s and 1990s, as reflected in their discontinuation from clinical use and withdrawal from the market.[11] These drugs were withdrawn for interrelated reasons including safety, lack of added benefits over available therapies, and poor commercial sales. That experience may be repeated unless incentives are carefully focused on the biggest threats and the greatest benefits. While this article focuses on antibiotics, it is necessary to look beyond just drugs and include incentives for vaccines, diagnostics that change clinical practices, and nonantibiotic innovations that reduce the burden of resistant bacterial infections.

The funnel must be widest at the basic research stage, allowing the NIH to fund a diverse range of fundamental research programs including a number of "long-shot" projects (see Appendix Exhibit B).[16] Standards will need to be tighter in the development phase, with larger payments for achieving developmental milestones for priority antibiotics supported by a larger but carefully targeted BARDA program. Enhanced reimbursement payments should have the narrowest focus of all: limited to products that target "serious" or "urgent" threats on the CDC threat assessment or for products that represent an

important improvement in efficacy or safety against the most serious multidrug-resistant diseases. Policy makers should not use the qualified infectious disease product list for this purpose, as every new antibiotic would qualify.

The public and politicians are appropriately supporting action on antibiotic research and development because of the threats posed by "superbugs." It would be a missed policy reform opportunity, and poor use of scarce resources, if most of the incentives went to less effective drugs treating less threatening conditions and if patients who have current effective options are put at risk from broad empirical usage of less well-tested drugs.

COORDINATE GLOBALLY Countries acting in isolation can have only a limited impact on antibiotic resistance. Pathogens and resistant genes do not respect borders. A key question is how these efforts will be coordinated globally.

One model could be a Framework Convention on Antibiotic Resistance.[34] The Framework Convention would set broad objectives for member countries that could be implemented locally. The key elements would be the ones we have described here—enhancing basic research and development support, reducing the cost of capital for clinical trials, and reforming reimbursement while supporting good stewardship—all targeted to priority antibiotic development areas.

First, government funding of basic research might be set at a target fraction of national antibiotic expenditures (20 percent would fully fund the US national strategy). Similar commitments could be set regarding surveillance of resistant pathogens and antimicrobial stewardship in all sectors including agriculture.

Second, countries would be encouraged to create targeted programs that reduce the cost and time of antibiotic clinical development and replace up to 50 percent of qualifying clinical research expenses with nondilutive capital. Examples include the NIH, ND4BB, BARDA, and an appropriately modified version of the Orphan Drug Act.

Finally, all countries would commit to reimbursement reforms to pay for value as opposed to volume, eliminate financial incentives for improper use of antibiotics, and ensure appropriate access based on clinical need.

Since the market for antibiotics is currently concentrated in high-income countries, the innovation work could proceed with just a relatively small number of countries leading the way. The United States, the European Union, and other wealthy countries are prime candidates. As antibiotic markets are growing in Brazil, Russia, India, China, and South Africa,[35] wider participation will be welcome. For stewardship, surveillance, and access commitments, truly global participation is needed, but that process can improve incrementally over time.

Given the substantial and growing global interest in antibiotic resistance, global progress need not wait for a comprehensive formal agreement. It is likely that some variations will emerge in the United States and Europe. Policy heterogeneity can work, so long as the reforms pull in the same direction. The framework we describe here can be a basis for reinforcing action globally.

Missing from the policy process for fighting antimicrobial resistance is strong global patient advocacy, which has proved to be effective with other diseases. Patient advocacy provides political thrust for policy reforms, investment funds, and clinical development data infrastructure. Examples include HIV/AIDS during the 1980s and 1990s and, more recently, cancer and cystic fibrosis. This is particularly challenging for antimicrobial resistance, since there are additional beneficiaries who do not develop resistant infections as a result of the success of these public health efforts. In addition, most patients with resistant infections identify more closely with another comorbidity such as cancer or surgery, instead of the resistant infectious disease.

Conclusion

The existing price/volume business model for antibiotics is not working and is a key barrier to achieving more rapid progress on resistance. The United States, the European Union, and other countries can build on recent promising steps by boosting funding for basic research and development, surveillance, and antibiotic stewardship; targeting these initiatives to priority unmet needs; and reforming reimbursement to support effective antibiotic access and use rather than volume. While the funding required is significant, it is a critical investment, protecting a key area of biomedical innovation from obsolescence and avoiding the hazards of a post-antibiotic era. ■

NOTES

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