DRUG DISCOVERY

Paying for innovation: Reimbursement incentives for antibiotics

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Reimbursement incentives could promote antibiotic research and development—in particular, for new drugs to treat complex infections commonly found in hospitals.

Antibiotics are arguably one of the great translational medicine success stories owing to their ability to reduce morbidity and mortality from infectious diseases. However, resistance to existing drugs has proliferated rapidly, while at the same time, few new antibiotics have achieved regulatory approval. One reason for the current innovation deficit is the lower perceived commercial potential of antibiotics in comparison with drugs in other classes, such as therapies for cancer and heart disease; this view drove several large pharmaceutical companies to abandon antibiotic research and investment in the early 2000s (*1*). In the United States, in September 2014, the President's Council of Advisors on Science and Technology called for stakeholders to accelerate the rate at which new antibiotics are discovered and developed (*2*).

The federal government can promote antibiotic development through greater investment in basic science research, which has supported the development of many transformative drugs (*3*). In parallel, innovations in the way antibiotics are reimbursed can alleviate economic barriers to private investment in antibiotic development. Thus far, the latter—so-called "pull" mechanisms—have been the focus of most legislative policy-making. Here, we examine one way in which payment policies could be adapted to promote the development of innovative antibiotics—in particular, drugs designed to treat hospitalized patients who demonstrate high rates of infection with multidrug-resistant organisms.

Is resistance futile?

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SOCIAL NEED AND INNOVATION ECONOMICS

Commercial expectations play a dominant role in how companies prioritize their drug portfolios (*4*). Economic factors, such as health-insurance reimbursement levels, act as a signal to current and future drug developers seeking to determine whether the likely market for a new product will be substantial enough to justify costly investments. Although several individual antibiotic products have been commercially successful (figs. S1 and S2), antibiotics have, in recent years, been less profitable than drugs in other disease classes (*5*).

Still, antibiotics have tremendous social value (Fig. 1). The difference between the mean net present value (NPV) of social benefits (for example, from reduced morbidity, prevention of mortality, and improved quality of life) and the NPV of private-sector returns from an effective new antibiotic that treats serious bacterial illnesses is estimated to exceed $500 million (*6*). As shown in Fig. 1, compared with uncomplicated infections such as acute bacterial otitis media, the social value of new antibiotics is particularly high in the case of infections that affect hospitalized patients, such as those with bacterial pneumonia. Such infections are more likely to be caused by drug-resistant pathogens, which are more expensive to treat than infections from drug-susceptible organisms and more likely to result in death.

PAYING FOR INPATIENT ANTIBIOTIC USE

Although there is a strong clinical and social imperative for new antibiotics designed to treat infections in hospitalized patients, antiinfective drug discovery faces commercial constraints in these settings. Given the need for stewardship of antibiotic resources, it would be inappropriate for developers to seek to improve a product's commercial performance through increased use alone. In contrast, revenues generated from inpatient-directed antibiotics might not offset lower sales volumes, as occurs for high-priced orphan drugs (*7*). A leading reason is that the payment policies of large payers such as the Centers for Medicare and Medicaid Services (CMS) incentivize inpatient providers to use inexpensive generics, placing downward pricing pressure on new entrants. Under the Inpatient Prospective Payment System (IPPS), CMS reimburses hospitals for each hospitalization according to diagnosis-related group-payment levels that are revised

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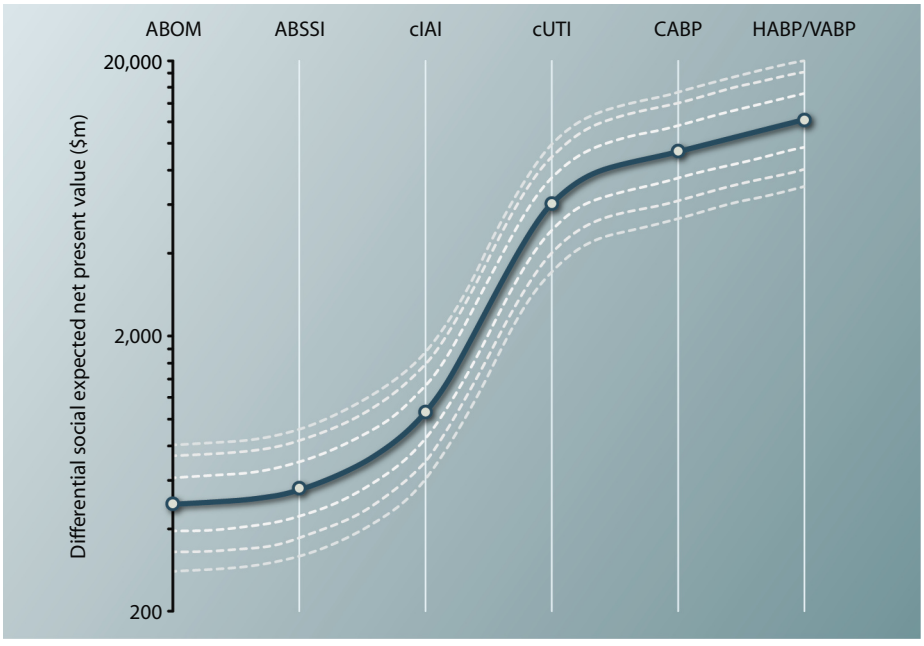

Fig. 1. Valuing new antibiotics. Depicted in graphic form are the estimates from (*6*) of the currently unrealized social benefits of antibiotics intended to treat common infections. The graphs, plotted on a logarithmic scale that spans the confidence intervals of these estimates, illustrate the difference between the estimated net present value (NPV) of a new antibacterial product to society (social expected NPV) and the NPV of the product to the developer (private expected NPV). The net present value represents the sum total of the benefits and costs of a particular product, after discounting future estimates to their present values. If positive, a difference between the social and private NPVs indicates that the social value of a product exceeds the private value of the returns expected to accrue to the developer. Data points are based on information in (*6*) for six categories of infections: (i) acute bacterial otitis media (ABOM), (ii) acute bacterial skin and soft-tissue infections (ABSSI), (iii) complicated intra-abdominal infections (cIAI), (iv) complicated urinary tract infections (cUTI), (v) community-acquired bacterial pneumonia (CABP), and (vi) hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP+VABP). Dashed lines represent 75% confidence intervals around the reported means.

every 2 years. The group-payment levels cover the cost of certain inpatient drugs, encouraging hospitals to minimize spending on covered drugs within the scope of these fixed payments. Whereas this system is appropriately designed to control overall costs to the Medicare program, new antibiotics that are more expensive than what is covered under the existing payment level—even if they benefit patients by, for example, reducing readmissions or the risk of infection transmission—would put hospitals in a difficult situation of either discouraging use of the drugs or treating patients and being reimbursed far below the actual incurred cost.

To ensure Medicare beneficiaries can access breakthrough technologies under its IPPS, CMS used its discretionary authority in 2001 to establish the New Technology Add-on Payment (NTAP) program (*8*). Under NTAP, the agency agreed to bridge up to 50% of the gap between a new technology's cost and the existing payment for the condition until the IPPS payment levels are recalibrated. In 2012, CMS granted a NTAP payment of $868 per case for fidaxomicin, a narrow-spectrum first-in-class macrocyclic antibiotic and the first new drug approved for the treatment of *Clostridium difficile*–associated diarrhea in several decades. The NTAP determination allowed the manufacturer of fidaxomicin to partly overcome the market challenge of having to compete with generic alternatives, such as vancomycin, on price alone.

NEW POLICIES AND PARADIGMS

In 2012, Congress enacted the Generating Antibiotics Incentives Now (GAIN) Act, which granted to qualifying antibiotics an additional 5 years of marketing exclusivity on top of the standard 5 years. However, because the median market-exclusivity period of most new antibiotics already exceeds 14 years (*9*), the value to companies of extensions in marketing exclusivity is heavily eroded by the time value of money because revenues expected far into the future are discounted to their present values.

In contrast to extensions in market-exclusivity periods, changes to a product's price have a more material impact on a research and development (R&D) investment's NPV and are, therefore, more likely to influence future investment decisions by affecting revenues for a drug in each year of its commercial life. As illustrated by the fidaxomicin case, expanding the scope of the NTAP program to first-in-class antibiotics of particular relevance to inpatient care—such as those used to treat multidrug-resistant bacteria—could have a profound impact on how companies and investors prioritize internal R&D efforts. By better aligning the expected returns from antibiotic drug development with the social value of these drugs, reimbursement-based incentive programs would offer the greatest chance of attracting further investments in antibiotic development.

Changes to payment policies that influence antibiotic prices would come amid important reforms to a country's medical reimbursement systems. Since the passage of the Affordable Care Act in the United States, new measures for so-called "pay for performance"—that is, tying reimbursement to quality improvement—have been rolled out nationally; a substantial number of these quality measures relate to infection control. For example, hospitals are evaluated according to the rates of catheter-associated urinary tract infections and central line–associated bloodstream infections. Starting in 2017, hospitals will implement two new pay-for-performance measures—the incidence of hospital-onset infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and *C. difficile*—that will further incentivize health care facilities to prevent hospital-acquired infections and infection-attributable readmissions.

An alternative approach to expanding the NTAP program was introduced in the U.S. Congress on 11 March 2014 by Representatives Danny Davis (D-IL) and Peter Roskam (R-IL): the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act (DISARM; H.R. 4187). DISARM would have established a new IPPS payment for antibiotics indicated to treat infections associated with high rates of mortality or morbidity. However, if a similar measure is reintroduced in the 2015 Congress, policymakers should clarify whether the new payment will pref-

erentially reward treatments with the highest potential to improve patient health outcomes, particularly given the additional costs that may be passed on to the public. For example, a key safeguard of the NTAP program is that qualifying products must show substantial clinical improvement over existing therapies (*8*). To ensure that taxpayers and patients receive value for their investments, an expanded NTAP program or a separate payment pathway for new antibiotics, as in the DISARM proposal, should be based on two key principles: robust clinical evidence and regulatory coordination.

Robust clinical evidence. First, qualifying NTAP products must demonstrate substantial clinical improvement over existing therapies, whether in clinical trials conducted to obtain approval by the U.S. Food and Drug Administration (FDA) or rigorous and post-approval studies before the NTAP adjustment. Through incentive payments, value-based reimbursement targets innovation for technologies with the greatest potential clinical benefits. Equally, without ensuring that qualifying products could improve patient health outcomes, additional CMS payments for new therapeutics may exacerbate market distortions—and contribute to Medicare's spending growth—by overpaying for products that would not otherwise be used by clinicians.

Traditionally, new antibiotics have been tested in noninferiority trials, which measure whether a treatment is not worse than another within a predetermined margin. However, this approach may hinder payers' uptake of new products. For example, in its decision on candidates for NTAP status, CMS stated that it preferred evidence of superiority of the applicant technology when compared with currently available treatments. To support value-based pricing and the development of safe and effective drugs, payers and regulators could encourage the use of innovative clinical-trial designs that measure clinically relevant and patient-centered outcomes.

In 2012, the Infectious Diseases Society of America developed a framework for the conduct of superiority clinical trials for new drugs targeting the treatment of infections caused by drug-resistant bacterial pathogens (*10*). One example of such an innovative design is plazomicin [ACHN-490 (Achaogen, San Francisco, CA)], a next-generation aminoglycoside currently being developed for the treatment of carbapenemase-producing *Enterobacteriaceae* bloodstream infections. This year, the sponsor initiated a randomized phase 3 clinical study using a superiority design comparing a plazomicin-based regimen with the standard-of-care colistin-based regimen.

Meaningful commercial opportunities arise from innovative and scientifically rigorous trial designs. For example, Achaogen received $60 million in funding from the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) to defray the costs of the phase 3 trial and may request a further $35 million to $40 million once the trial is under way. When ethically and practically feasible (*10*), superiority designs provide more useful clinical knowledge than do noninferiority studies—particularly for evaluating new treatments for hospitalized patients with multidrug-resistant organisms—as well as opportunities for product differentiation. To further encourage these trial designs, BARDA, in coordination with other agencies such as the U.S. National Institutes of Health, could provide similar cost-sharing agreements to sponsors of other types of risky clinical development programs, such as those for new therapeutic modalities or those intended to treat infections caused by Gram-negative organisms.

Regulatory coordination. Second, in lieu of a separate payment mechanism, as in the DISARM proposal, policy-makers could consider refining the NTAP model to further stimulate innovative pharmaceutical R&D efforts. For example, CMS and FDA could harmonize their review processes to minimize the delay between FDA approval and subsequent payment decisions. One precedent for such collaboration arose in 2011, when the two agencies launched a pilot program for the parallel review of medical devices for approval and coverage. In addition, any new incentives for antibiotic development should be coupled with renewed efforts to promote stewardship of our antimicrobial resources. For example, CMS could tie the incentive payment to guideline-concordant use—ensuring that innovators are adequately reimbursed without fueling inappropriate prescribing or antibiotic resistance—although such a program may be administratively difficult to implement. If a critical number of therapies receive NTAP or other incentive payments, it will be important to test how these incentive payments affect manufacturers' behavior and ultimately affect antibiotic resistance and health outcomes.

Innovative reimbursement programs could help promote the development of new antibiotics, which may have lower commercial potential than other drug classes and can be inadequately valued by existing payment systems. By preferentially reimbursing therapies that offer clinically relevant benefits, governments might encourage innovation with the greatest impact on patient health.

SUPPLEMENTARY MATERIALS

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Methods

Fig. S1. Median peak and present value of global sales of antibiotic, cancer, and cardiovascular drugs from 1990 to 2012.

Fig. S2. Cumulative global sales of selected branded antibiotics

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Funding: This study was supported by grants from the Interfaculty Initiative in Health Policy (Cordeiro Family Research Fellowship), the Center for American Political Studies, and Dunwalke Fund, all at Harvard University (T.J.H.); and by the Greenwall Foundation Faculty Scholarship and the Harvard Program in Therapeutic Science Ignition Award (A.S.K.).
Competing Interests: The authors declare that they have no competing interests. The authors' employers, grantors, and funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

10.1126/scitranslmed.aaa1429

Citation: T. J. Hwang, D. Carpenter, A. S. Kesselheim, Paying for innovation: Reimbursement incentives for antibiotics. *Sci. Transl. Med.* **7**, 276fs9 (2015).

Science Translational Medicine

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Sci Transl Med **7**, 276fs9276fs9.
DOI: 10.1126/scitranslmed.aaa1429