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Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy

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ABSTRACT A serious need to spur antibiotic innovation has arisen because of the lack of antibiotics to combat certain conditions and the overuse of other antibiotics leading to greater antibiotic resistance. In response to this need, proposals have been made to Congress to fund antibiotic research through a voucher program for new antibiotics, which would delay generic entry for any drug, even potential blockbuster lifesaving generics. We find this proposal to be inefficient, in part because of the mismatch between the private value of the voucher and the public value of the antibiotic innovation. However, vouchers have the political advantage in the United States of being able to raise sufficient amounts of money without annual appropriations from Congress. We propose that if antibiotic vouchers are to be considered, the design should include dollar and time caps to limit their volatility, sufficient advance notice to protect generic manufacturers, and market-based linkages between the value of the voucher and the value of the antibiotic innovation. We also explore a second option: The federal government could auction vouchers to the highest bidders and use the money to create an antibiotics innovation fund.

Bacteria constantly evolve, especially in response to antibiotics used in agriculture and medicine. Resistant bacteria already kill 23,000 people a year in the United States¹ and more than 700,000 people worldwide, including 214,000 neonatal deaths each year from sepsis.² Absent dramatic changes, ten million people could die annually by 2050 from resistant bacteria, viruses, retroviruses, and parasites.³ Much of this resistance is driven by wasteful overuse of antibiotics in inappropriate settings.⁴ In addition to this crisis of overuse, antibiotics are tragically underused in many parts of the world. Broader access to existing antibiotics could save 445,000 children younger than age five from death as a result of community-acquired pneumonia.^{2,4}

Many global stakeholders are mobilizing to respond to these threats, including the World Health Organization,⁵ the European Union,⁶ the United States,⁷ the Review on Antimicrobial Resistance,³ the Group of Seven (G7) member countries,⁸ and think tanks such as Chatham House in London.^{9,10} These stakeholders have made proposals that collectively call for a three-prong approach to resistant bacteria: access, to maximize the health impact of antibiotics, especially in low-income populations currently suffering from inadequate access; conservation, which decreases the need for antibiotics through infection control, vaccination, and antibiotic stewardship; and innovation, policies supporting the development of powerful new generations of antibiotics.¹¹ While these approaches are valuable and necessary, one com-

mon weakness they share is inadequate funding. For example, in keeping with the recommendations of the US National Strategy on Combating Antibiotic-Resistant Bacteria, President Barack Obama's 2016 budget called for an additional \$1.2 billion, but as of mid-April 2016, Congress had not yet acted.¹² Political realities in the United States and across the world could dampen a sufficient response.

In this environment, some US stakeholders have recently proposed "antibiotic vouchers" that could fund antibiotic innovation.¹³⁻¹⁵ These would work as follows: A company developing an innovative antibiotic could obtain from the Food and Drug Administration (FDA) a voucher that could be sold (transferred) to another pharmaceutical firm for the purpose of extending that firm's patent exclusivity on an existing drug. Most of the discussions about antibiotic vouchers have occurred in the US context, where this idea enjoys the powerful lure of not requiring annual appropriations from Congress. Through what some might call a budget gimmick, antibiotic vouchers can achieve a zero budget impact score from the Congressional Budget Office (CBO), so long as higher drug prices from the delayed entry of generic drugs do not occur during the ten-year CBO scoring window for assessing federal budget impact. The costs are shifted to government programs such as Medicare and Medicaid, private health plans, and other payers' health budgets in future decades.

In our view, these proposals are unwise for the efficiency and fairness reasons previously described in the literature¹⁶⁻¹⁸ and updated in this article. We also raise additional criticisms, but in an effort to be constructive, especially in light of urgent funding needs, we suggest key modifications that ameliorate some of the worst features of antibiotic vouchers, resulting in the "least bad" version of the proposal.

Antibiotic Vouchers

As the voucher scheme is currently envisioned, high-quality antibiotic innovation will be rewarded with a transferable voucher, similar in some respects to the existing Tropical Diseases Priority Review Voucher Program,¹⁹ but with a key difference. The priority review vouchers speed up FDA review times by allowing a standard drug to be given priority review status, saving about four months.²⁰ Antibiotic vouchers are transferable like the priority review vouchers; however, unlike the priority review vouchers, they extend the market exclusivity period for any other drug or biologic product by a year even if it is not an antibiotic. While priority review vouchers speed the market entry of a non-prior-

ity review drug, antibiotic vouchers delay generic entry of a competing drug against whichever drug the voucher holder desires to protect. For example, the holder of an antibiotic voucher could apply it to an oncology drug, delaying generic entry by an additional year. To allow manufacturers of generic drugs to plan, vouchers should not be used during the final four years of a drug's patent protection before generic entry. Companies that receive the voucher would also make binding commitments regarding antibiotic stewardship, which avoids wasteful misuse and unnecessary resistance. Some proposals for these vouchers also call for donations to public entities such as the National Institutes of Health or an antibiotic innovation fund.¹³

Earlier versions of this idea were called "wild-card" patents.¹⁵⁻¹⁸ At present, the mechanism is not patent law but a regulatory provision that delays generic entry of drugs. The concept is known as regulatory exclusivity. Current examples of nontransferable regulatory exclusivities include the seven years granted in the United States to orphan drugs, the twelve years for biologics, and the six months granted to a drug sponsor after conducting pediatric studies.^{21,22}

EFFICIENCY As a funding mechanism, antibiotic vouchers are not particularly efficient. In this context, "less efficient" means higher future drug prices, with less antibiotic innovation to show for it. This is the case for several reasons.

► **LENGTH OF EXCLUSIVITY PERIOD:** First, the efficiency of antibiotic vouchers depends greatly on the length of the exclusivity period (Exhibit 1). Methods for calculating efficiency are available in the online Appendix.²³ For example, if vouchers are granted only for very high-quality drugs,²⁴ then a reasonable target is no more than fifteen drugs per decade.³ From recent reviews of antibiotic research and development costs, each of these drugs will have required perhaps \$800 million in expenditures to bring it to market,^{3,15,24-26} with aggregate costs in the range of \$12 billion per decade for fifteen drugs. With these costs in mind, how long should the exclusivity period be for each voucher? If based solely on time (for example, twelve months), then a voucher—which delays generic entry—that is applied to a drug with US sales exceeding \$6 billion will protect those sales dollars from generic competition after the patent expires. Consumers and health plans (including Medicare, Medicaid, and private plans) will pay more, since the voucher will delay the significant reductions in price associated with generic entries, in the range of 80 percent or more.^{27,28} Therefore, the approximate nominal cost to the US health system of a single twelve-month voucher in this example exceeds \$4.8 billion (80 percent of \$6 billion), with

EXHIBIT 1

Cost estimates to US health system budgets for transferable antibiotic exclusivity vouchers

Exclusivity period	Research and development supported ^a	Direct costs to US health budgets	Efficiency	Imputed interest rate	
				5 years	7 years
TWELVE MONTHS					
Per antibiotic voucher	\$800 million	\$4.8 billion	16.7%	43.1%	29.2%
Per decade ^b	\$12 billion	\$72.0 billion			
THREE MONTHS					
Per antibiotic voucher	\$800 million	\$1.2 billion	66.7%	8.4%	5.9%
Per decade ^b	\$12 billion	\$72.0 billion			

SOURCE Authors' estimates. **NOTES** Efficiency is the nominal ratio of research and development supported over direct costs to health budgets. See the online Appendix for details on the calculation of imputed interest rates (see Note 23 in text). ^aSee Notes 3, 24–26 in text. ^bSee Note 3 in text.

aggregate costs of \$72 billion per decade for fifteen drugs. At a global level, a previous estimate using 2005 sales data found that a single one-year global voucher would cost health systems and consumers up to \$9.4 billion.¹⁶

This is an extraordinarily inefficient financing mechanism even if only limited to the United States, spending \$4.8 billion in higher future drug costs in exchange for each incremental \$800 million in antibiotic research and development. If this was structured as a loan from the company to the government, the implicit interest rate would range from 29 percent to 43 percent per year. Shortening the exclusivity period to three months would be much more efficient; priced as a loan, the implicit interest rate falls to 6.0–8.5 percent.

► **LINK BETWEEN VALUE AND REWARD:** Second, the value of the reward should be proportional to the effort undertaken, but the link between value and reward is particularly tenuous for antibiotic vouchers. Voucher values change over time, introducing risk for the companies and insurers. Value will vary based on the drugs sold by the company holding the voucher. It would be most valuable in the hands of the company with the biggest-selling drug nearing the end of its patent exclusivity and therefore nearing the time of generic entry. It would be less valuable for the company with the second-biggest-selling drug facing competition from generic entry. But values might also increase unexpectedly, perhaps in response to commercial opportunities or successful patent litigation against a branded drug that suddenly upset commercial expectations. So rewards will vary significantly over time, as we have seen with the value of priority review vouchers, which are awarded by the FDA but can be sold by the voucher holder to the highest bidder. Priority review vouchers have sold for increasing amounts. The first

voucher sold for \$67.5 million, but subsequent sales prices rose to \$125 million, \$245 million, and most recently \$350 million.¹⁹ These significant increases in value should not be viewed as evidence of success in incentivizing research and development, since the rewards are not proportional to the research and development costs or the value of the underlying innovation. Vouchers also entail significant transaction costs when sold, including paying the lawyers, brokers, and consultants who facilitate a voucher sale.

► **REWARDING HIGH-QUALITY INNOVATIONS:** Third, any system will have to be designed to limit rewards only to appropriate high-quality innovations. The first priority review voucher was granted in 2009 to Novartis for a combination drug containing artemether and lumefantrine for treatment of malaria, despite already being on the market in many countries outside of the United States.¹⁹ This development has continued. Knight Therapeutics gained a tropical disease priority review voucher in 2014 for miltefosine,¹⁹ despite the fact that it was already on the market and being used to treat leishmaniasis in many countries. By registering it in the United States, Knight Therapeutics became eligible for the voucher, which it then sold to Gilead Sciences for \$125 million, even though the voucher was not based on any new drug innovation.¹⁹ More disturbingly, vouchers are awarded even if the product is not actually registered for sale in low-income countries or is priced too high for global health needs. Any system needs to be robust enough to ensure that drug companies are given incentives to undertake more research and that their research leads to greater innovation that actually improves health, instead of receiving a windfall for something they would have done anyway. The recent history of the Generating Antibiotic Incentives Now (GAIN) Act of 2012, which extended by five years the exclusivity pe-

riod during which antibiotics that treat serious or life-threatening infections could be sold without generic competition, also raises similar concerns, as the standard for “qualifying infectious disease product” was set so low that almost every antibiotic qualifies.²⁹ Any new proposal for antibiotic vouchers or other significant incentives for innovation should set very high standards.²⁴

► **PRESERVING VOUCHERS FOR APPROPRIATE CASES:** Finally, while supporters may seek to use antibiotic vouchers as a special case, other groups and interests will rally to join the queue. In the short history of the Tropical Disease Priority Review Voucher Program, Congress has twice expanded access to the process, first for rare pediatric diseases in 2012³⁰ and then, two years later, for Ebola and related tropical diseases.³¹ A current bill proposes exclusivity vouchers for neonatal innovation.¹⁴ Given the immense market value of delaying generic entry by one year for a best-selling drug, other disease groups can be expected to lobby Congress to grant similar vouchers for innovation suiting their needs and interests. As more join, inefficiencies mount, and the reward value diminishes. For this system to work, proponents will need to successfully demonstrate that antibiotics are an exceptional—even unique—case that warrants particular treatment by government.

FAIRNESS While not technically a patent, antibiotic vouchers would delay generic entry for best-selling drugs after the patent has expired. Consumers and health insurance payers will pay higher prices in a system with antibiotic vouchers as a result of this delay; this is not a bug, but an unavoidable design feature of the program. Antibiotic innovation will be funded through higher drug prices on other drugs in the future. One can think of it as a tax on cancer or cardiovascular treatment to fund antibiotic innovation.¹⁶ If antibiotics are considered essential infrastructure for the health system, then perhaps this is appropriate, but it also raises important questions about fairness (and, in economic terms, deadweight loss), including ensuring appropriate access to all drugs both in the United States and abroad, where access to many therapies is already too limited.^{2,4,11,32} Delaying generic entry of a best-selling drug will have real implications for patients and health systems. If these rules are also imposed on other countries through trade agreements, then these risks of delayed access to needed therapies multiply in lower-income populations. Any solution to antibiotic innovation should be designed to minimize potential global challenges to accessing these drugs.³³

ADDITIONAL CONCERNS Antibiotic vouchers sever the most important linkage in innovation

policy. Throughout the history of US intellectual property law, exclusivity rewards have been tied to the innovative product itself. A copyright is awarded but only on the book authored. A patent prohibits infringing use by others for twenty years but only on the innovative product that was the subject of the patent. Never before in US intellectual property law has exclusivity protection been applied to an existing product because of an entirely unrelated innovation.

This historic step should give pause, for good reason. While empirical literature increasingly challenges the efficiency of the patent system outside of drugs and chemicals,³⁴ the iron-clad link between innovation and reward is a key part of the safety net protecting consumer welfare. Many promising inventions never pan out in practice, but if so, then the patent period was not a drag on the economy because few people bought the product. But antibiotic vouchers grant exclusivity to one product (such as a cancer drug) based on the registration of an entirely different innovative product (an antibiotic). Normally, the market for the innovation determines the value of the patent; here, an entirely different product determines the value. Vouchers replace the market function of patent valuation with a system designed by Congress.

Partly because of the above concerns, antibiotic vouchers may face constitutional challenges in the United States, since the Patent and Copyright Clause links the innovation and the reward. While the US Supreme Court has shown significant deference to congressional decisions to extend intellectual property protections,³⁵ in this case, the extension would be on an entirely different product. Alternatively, the voucher proposal might be grounded in the Commerce Clause,³⁶ but the US Supreme Court has not yet ruled whether a law prohibited under the Patent and Copyright Clause could be enacted under other provisions of the Constitution, especially given the recent moves by the Court to limit the congressional power in the Affordable Care Act litigation. Some Justices may find it difficult to support an innovation incentive that would have been anathema to the Founding Fathers. Generic drug companies might also pursue a claim that the government has taken property and must pay just compensation under the Fifth Amendment, arguing that their investment-based expectations were disrupted by the sudden application of transferable market exclusivity.³⁷ This issue may be partially addressed by requiring four years of prior notice before vouchers could be activated to enable companies developing generic drugs to plan adequately for generic entry. But advance notice of a taking generally does not resolve the claim, which might require compen-

sation to the companies developing generic drugs for their losses.

Redesigning Antibiotic Vouchers

Antibiotic vouchers are not a de novo policy idea; rather, they represent a second-generation modification to earlier wildcard patent extension proposals.^{13,15–18} Given the significant remaining limitations detailed above, we now describe what design elements third-generation proposals should feature.

Our primary goal was to make the mechanism more efficient. Two core insights drove the redesign effort: First, extending regulatory exclusivities was best understood as a financing mechanism for antibiotic innovation; second, most of the inefficiencies arose from the gaps between the efforts required to obtain a voucher and the value of the voucher in the hands of the transferee. To put this another way, the core inefficiencies resulted from the lack of a link between the value of the innovation and the value of the voucher. We offer two alternatives: first, an incremental tailoring of the voucher concept; and second, a more fundamental shift, with public auctions of vouchers to fund antibiotic prizes. Both recognize the financing aspect of vouchers front and center, while restoring proportionality between the value of the voucher and the underlying innovation. The results look somewhat more like a prize than a patent.

TAILORED VOUCHERS The first alternative is to tailor the vouchers to the social value of the antibiotic innovation. The two essential features are described below.

► **VARY VOUCHER REWARD BY SOCIAL VALUE OF ANTIBIOTIC INNOVATION:** Not all antibiotics are equally valuable. Another skin and skin-structure drug for Gram-positive bacteria is a lower priority and should not receive any voucher-based reward.²⁴ There has to be an agreed set of antibiotic priorities that cover the most crucial unmet human needs but that are not so broad that the system pays for products of limited incremental value. The Centers for Disease Control and Prevention has published a list of the most urgent bacterial threats to the US population.¹ New antibiotics targeting these urgent threats, then, should receive vouchers with significant market value. Researchers have outlined mechanisms for directing greater rewards to the most significant antibiotic innovations, based on target product profiles.^{3,10,24,29,38} A key question is how to make the market value of the vouchers more proportional to the value of the antibiotic innovation. This is addressed in the second essential feature described below.

► **DESIGN VOUCHER REWARD BASED ON REV-**

ENUES AS WELL AS TIME: A voucher period of twelve months, standing alone, is a blunt instrument. The tie between innovation and reward would be much tighter if the voucher capped the revenues that could be protected within the twelve-month time period. So, for example, the voucher would expire at the earlier of twelve months or \$1 billion in protected revenues, whichever occurred first. This provides a clear cap of the costs (protected revenues) of the voucher, giving policy makers a much more precise understanding of the costs associated with each voucher. Efficiency could be calculated by comparing this with the antibiotic research and development cost incurred to procure the voucher through public reporting of this data.

These two features should be combined, varying the dollar cap by the social value of the new antibiotic. These values would be set in advance for a specific target based on health needs. For example, a novel oral antibiotic for drug-resistant gonorrhea might be awarded a voucher good for up to \$1.5 billion in protected revenues, while an entirely novel class of drugs active against Gram-negative bacteria such as carbapenem-resistant *Enterobacteriaceae*—a family of germs difficult to treat because of high levels of resistance to antibiotics—might receive a voucher for as much as \$3 billion.²⁴

Capping revenues takes pressure off the decision about the length of voucher exclusivity and opens the market for purchasing vouchers to additional buyers, as the market is no longer limited to the best-selling drugs. Dozens of drugs have US annual sales exceeding \$1 billion.

The rules must articulate clear criteria for any particular voucher, and prospective changes to the voucher should occur only to give investors certainty. Since antibiotics are increasingly approved based on limited clinical data, vouchers should also not be awarded immediately upon FDA approval of the drug but at a later point when safety and effectiveness can be confidently and meaningfully assessed—in practical terms, no sooner than about two to three years after a drug reaches the market.^{3,24}

In all cases, companies developing generic drugs will need to have a clear idea of the latest point at which generic entry might occur. Additional protections might need to be explored to secure eventual generic entry. For example, if vouchers awarded because of the new antibiotics protect only \$1 billion in sales of a drug benefiting from the delayed entry of a competing generic, then these sales figures would need to be publicly reported in real time to allow timely generic entry. The question will also arise as to whether or not multiple vouchers could be activated on a single product.

AUCTIONED VOUCHERS The second alternative is a more fundamental reworking of the concept, with the vouchers no longer awarded for bringing a novel high-quality antibiotic to market. Instead, the government would directly auction several twelve-month \$1 billion vouchers each year, putting the proceeds into an antibiotic innovation fund. The fund would be used to support antibiotic access, conservation, and innovation, including significant cash payments for hitting research and development milestones,¹⁸ akin to the current practice at the US government's Biomedical Advanced Research and Development Authority but including significant payments after registration.²⁴ For example, if the government needed to raise \$1.8 billion in cash for the fund, it would sell perhaps \$2 billion in vouchers at public auction. The net proceeds would then be used to reward antibiotic innovation and support antibiotic stewardship. Auctions would be a highly efficient financing mechanism, with clear gains in accountability as well.

If the antibiotic innovation fund was large enough, full or partial antibiotic delinkage mechanisms could result.^{10,29} Rewarding companies for selling large volumes of antibiotics is inherently problematic because of drug resistance, leading the industry to recently call for prizes or value-based delinked reimbursement for antibiotics at the World Economic Forum in Davos, Switzerland.³⁹ Value-based delinkage is when companies are paid based on value or milestone not sales volume. Delinkage allows antibiotics to be held in reserve and used entirely on medical grounds, without commercial exigencies.³ Delinkage simultaneously addresses problems with access, conservation, and innovation—a major advance over current policies.^{10,24,29,38,39}

CHALLENGES For many governments with national social insurance systems, all voucher proposals discussed herein might look like nonsense: If all of the funds eventually come from the health budget, it would be more efficient to pay for antibiotic innovation directly. As a result, one challenge, or limitation, of a voucher system is the difficulty coordinating any US action with other countries that may choose a different path, including complexities relating to global agreements on intellectual property and trade.^{33,40}

But if antibiotic vouchers are understood primarily as a national financing mechanism, then it is possible for countries with significant private health care financing such as the United States to adopt tailored or auctioned vouchers to fund their share of antibiotic stewardship and innovation, while other countries might use general revenues or health budgets directly.^{33,40} Indeed, this could operate in the United States solely as a national system but with the programs linked to wider international action.

Finally, while these proposals do not make potential constitutional issues worse, those questions still remain unanswered.

Conclusion

Policy makers should be aware of the inequities and inefficiencies associated with antibiotic voucher proposals. If vouchers are to be used, they must be more carefully tailored by focusing only on the highest-quality innovation and capping protected revenues over specified time periods. Even more directly, vouchers could be auctioned to the highest bidders, and the funds then used to promote antibiotic access, conservation, and innovation. Either alternative is a significant improvement over current proposals. ■

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