COMBATING ANTIBIOTIC RESISTANCE THROUGH THE HEALTH IMPACT FUND

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Kevin Outterson
Boston University School of Law

Thomas Pogge
Yale MacMillan Center; Centre for Applied Philosophy and Public Ethics;
Centre for the Study of Mind in Nature

Aidan Hollis
University of Calgary - Economics

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Combating Antibiotic Resistance Through The Health Impact Fund

Kevin Outterson, Thomas Pogge & Aidan Hollis*

Abstract: The Health Impact Fund (Hollis & Pogge 2008) is an innovative financing mechanism for global drug discovery and dissemination, separating the recovery of sunk R&D costs from the market price of the drug, also known as de-linkage. Aaron Kesselheim and Kevin Outterson have recently proposed a mechanism to reimburse companies for antibiotics according to their social value, but conditioned on achieving conservation goals to limit resistance (Kesselheim & Outterson 2010, 2011). This paper will explore whether this antibiotic resistance pay-for-performance proposal can be adapted to the framework of the Health Impact Fund. If these proposals can be meshed, then antibiotics might be an interesting therapeutic class for a test of the Health Impact Fund.

I. Introduction

On April 7, 2011, the World Health Organization embarked on a yearlong campaign to combat antibiotic resistance. The project is driven by several concerns: resistance is rising, drug companies are producing fewer innovative antibiotics, and yet antibiotics continue to be used inappropriately. (WHO 2011; So, et al. 2011; IDSA 2011) These combination seem antithetical: if resistance is actually a major

* From Boston University (KO); Yale University (TP); and the University of Calgary (AH).
Correspondence to mko@bu.edu.
global public health problem in high income countries, then the market should respond with drugs to fill the multi-billion dollar market demand. Likewise, if the antibiotic pipeline is severely limited, then we ought to be carefully conserving the remaining drugs. But resistance distorts markets for innovative antibiotics in unusual and counterintuitive ways, giving major stakeholders economic incentives to waste these precious resources. (So, et al. 2011; Outterson 2010a; Kesselheim & Outterson 2010) A reimbursement system that rewards companies primarily for unit sales of antibiotics undermines public health goals such as the rational use of antibiotics. Conversely, rational use and infection control programs typically reduce antibiotic sales, undermining company R&D incentives. As a result, a prominent drug industry leader recently stated that antibiotic “incentives that separate the financial return from the use of a product are the only way to change this behavior.” (So, et al. 2011) Such mechanisms are called “de-linkage” in that they separate the markets for medicines from the markets for R&D.

One prominent de-linkage mechanism is the Health Impact Fund (HIF) which would reward companies for the health impact of their drugs. (Hollis & Pogge 2008) The HIF is a global mechanism, which is potentially valuable in the field of antibiotics. Effective antibiotics are a global public good, a potentially renewable resource that should be managed effectively on a global basis. (Laxminarayan & Malani 2007; WHO 2011; Nugent, Back & Beith 2010; Mossialos, et al. 2010)

This essay is organized as follows. In Section II, we describe the Health Impact Fund in greater detail, including some of the criticisms that have been

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1 See www.healthimpactfund.org for many publications and media discussions about the HIF as well as information about HIF supporters and their work.
lodged. The complex legal and biological complexities of resistance are explored in Section III, including the requirement that new antibiotic incentives be conditioned on meeting long-term public health goals. The confluence of antibiotic resistance and the HIF is the subject of Section IV, evaluating whether antibiotics might be an appropriate test of the HIF and whether the HIF might be an effective global coordination mechanism for antibiotics.

The stakes are huge for getting these policies right; the Infectious Diseases Society of America warns that the alternative may be a global ecological collapse in antibiotic effectiveness. (IDSA 2011, 2004)

II. The Health Impact Fund

A. Paying for Global Health Impact

Financed primarily by governments, the Health Impact Fund is a pay-for-performance mechanism that would offer innovators the option — completely voluntary — to register any new medicine.2 By registering a product, the innovator would undertake to make it available, during its first 10 years on the market, wherever it is needed at no more than the lowest feasible cost of production and distribution. The innovator would further commit to allowing, at no charge, generic production and distribution of the product after these ten years have ended (if the innovator still has unexpired patents on the product). In exchange, the registrant would receive, during that 10-year period, annual reward payments based on the product's health impact. The reward payments would be part of a large annual pay-

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2 Under certain conditions, the HIF might also permit a company to register a traditional medicine or a new use of an existing medicine.
out, with each registered product receiving a share equal to its share of the assessed health impact of all HIF-registered products in the relevant year. If the HIF were found to work well, its annual reward pools could be scaled up to attract an increasing share of new medicines. (Hollis & Pogge 2008)

The HIF would foster the development of new high-impact medicines — including against diseases concentrated among the poor that are now neglected because innovators cannot recover their R&D costs from sales to the poor. The option of an alternative reward based on health impact would transform heretofore-neglected diseases into some of the most lucrative pharmaceutical research-and-development (R&D) opportunities. For example, many have suggested that antibiotic research isn’t financially rewarding for large pharmaceutical companies. (So, et. al. 2011) The HIF would help to reverse that problem by offering an alternative revenue stream of several billion dollars.

The HIF would also promote access to new medicines by limiting the price of any registered product to the lowest feasible cost of production and distribution. In addition, the HIF would motivate registrants to ensure that their products are widely available, perhaps at even lower prices, and that they are competently prescribed and optimally used. Registrants would be rewarded not for selling their products, but for making them effective toward improving global health. For antibiotics, health impact will be maximized not necessarily through aggressive sales, but also through careful long-term stewardship. HIF incentives would need calibration to the unique characteristics of antibiotics.
If some pharmaceutical R&D were financed through tax-funded HIF rewards, most of the cost would be borne by affluent populations and people — just like today. But there are important differences. First, innovators would make no profit from the sale of their medicine as such — they would profit only insofar as this medicine is actually used to improve patient health. Thanks to this new incentive, patients are more likely to receive medicines that will actually improve their condition. Second, in order to profit from serving affluent patients, innovators would not need to exclude poor patients. On the contrary, they would profit equally from serving poor patients, too, at the same low price. Health gains achieved for any patients — rich or poor — would contribute equally toward the innovator’s bottom line.

The HIF will provide optimal incentives only if potential registrants are assured that the rewards will actually be there in the decade following market approval. Core funding of the HIF is therefore best guaranteed by a broad partnership of countries. If governments representing one third of global income agreed to contribute just 0.03 percent of their gross national incomes (3 of every 10,000 currency units), the HIF could get started with USD 6 billion annually. This is a reasonable minimum because the high cost of developing new medicines requires large rewards; at the same time, it is desirable to have many registered medicines so that the health impact assessment process can take advantage of economies of scale.

In the HIF, a fixed pool of funds is divided annually among registrants in proportion to the health impact of the registered drug. Thus, the HIF can be seen as an ongoing competition among innovators that ranges over all countries and all
diseases, with firms earning more money if their product has a larger impact on health. Health impact can be measured in terms of the number of quality-adjusted life years (QALYs) saved worldwide. The QALY metric is already extensively used by private and state insurers in determining prices for new drugs, so employing it in calculating HIF rewards is not a big leap.³ Taking as a benchmark the pharmaceutical arsenal before a registered medicine was introduced, the HIF would estimate to what extent this medicine has added to the length and quality of human lives. This estimate would be based on data from clinical trials, including pragmatic trials in real-life settings, combined with data on sales volumes and the demographic and clinical characteristics of patients using the product. Additional tools that could be used include tracking randomly selected medicines (identifiable by serial numbers) to their end users, and statistical analysis of sales data as correlated with data about the global burden of disease. These estimates would necessarily be imperfect. But so long as any errors are random, or at least not exploitable by registrants, HIF incentives would be only minimally disturbed.

The reward rate, in terms of dollars per QALY, would be calculated annually for each registered drug in the HIF. This rate would vary, depending on the total number of QALYs in the HIF for a given year. With the HIF so designed, innovators would choose to register products that can reduce the global burden of disease most

³ While QALYs are subject to many criticisms when they are used as the exclusive tool of measurement, these criticisms of the QALY possess less power in the case of the HIF since there would be an alternative way of being rewarded, outside the HIF. For example, a new drug formulation that increases patient convenience may be of considerable benefit to patients without generating many QALYs. If QALYs constitute the entire benefit measure in a strict cost/benefit calculation to determine the reimbursement price of a new drug, a drug that only increases patient convenience will not be reimbursed. Such a drug might not fit well in the HIF; the HIF is simply not designed for it, and the patentee would not register this product in the HIF.
cost-effectively. Products with the largest health impact would make the most money — creating exactly the right incentives for innovation. And because the HIF would be an optional system, the reward rate is self-adjusting. If rewards were too high, new registrants would enter and reduce the uniform reward rate (money per QALY). If profits were too low, the reward rate would naturally increase as firms would choose, for more of their new products, to forego HIF registration in favor of exploiting their patent-protected pricing powers. Competition would ensure that registered products are rewarded at a rate that is profitable for innovators and maximizes the effect of the HIF.

To be certain that the HIF is cost-effective relative to other public health expenditures, one can stipulate a maximum reward rate; if one year’s funds are not fully used, the remainder can be rolled over into future years. To reassure potential innovators, one can also add some protection against unreasonably low rewards. (Hollis and Pogge 2008)

**B. Advantages of the Health Impact Fund**

Let us sketch how the HIF would, without revision of the TRIPS Agreement, provide systemic relief for seven failings of the present system.

*High Prices* would not exist for HIF-registered medicines. In local markets where buyers were particularly price sensitive, innovators would have strong

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4 The TRIPS Agreement sets global minimum standards for intellectual property law.
incentives to reduce prices, possibly even below the cost of production, in order to increase health impact rewards through increased volume.

*Diseases Concentrated among the Poor*, insofar as they contribute substantially to the global disease burden, would no longer be neglected. In fact, the more destructive among them would come to afford some of the most lucrative research opportunities for biotechnology and pharmaceutical companies. The HIF counts health benefits to the poorest of patients equally with health benefits to the richest.

*Bias toward Maintenance Drugs* would be absent from HIF-encouraged research. The HIF assesses each registered medicine’s health impact in terms of how its use reduces mortality and morbidity worldwide—without regard to whether it achieves this reduction through cure, symptom relief, or prevention. This would guide firms to deliberate about potential research projects in a way that is also optimal for global public health, namely in terms of the expected global health impact of the new medicine relative to the cost of developing it. The profitability of research projects would be aligned with their value in terms of global public health.

*Wastefulness* would be dramatically lower for HIF-registered products. There would be no deadweight losses from large mark-ups. There would be little costly litigation as generic competitors would lack incentives to compete and innovators would have no incentive to suppress generic products (as these would enhance the innovator’s health impact reward). Innovators might therefore often not even bother to obtain, police, and defend patents in many national jurisdictions. To
register a medicine with the HIF, innovators need show only once that they have an effective and innovative product (Syed, 2009).

*Excessive Marketing* would also be much reduced for HIF-registered medicines. Because each innovator is rewarded for the health impact of its addition to the medical arsenal, incentives to develop me-too drugs to compete with an existing HIF-registered medicine would be weak. And innovators would have incentives to urge a HIF-registered drug upon doctors and patients only insofar as such marketing results in measurable therapeutic benefits for which the innovator would then be rewarded.

*Counterfeiting* of HIF-registered products would be less attractive. With the genuine item widely available near or even below the marginal cost of production, there is less to be gained from producing and selling counterfeits.

*The Last-Mile Problem* would be mitigated because each HIF-registered innovator would have strong incentives to ensure that patients are fully instructed and properly provisioned so that they make optimal use (dosage, compliance, etc.) of its medicines, which will then, through wide and effective deployment, have their optimal public health impact. Rather than ignore poor countries as unprofitable markets, pharmaceutical companies would, moreover, have incentives to work with one another and with national health ministries, international agencies and NGOs toward improving the health systems of these countries in order to enhance the impact of their HIF-registered medicines there.
C. Critiques of the Health Impact Fund

James Love of Knowledge Ecology International has criticized the HIF in a number of blog posts. (Love 2008a) Love has proposed several global mechanisms to pay for R&D outside of the market reimbursement system. (Love 2008b, Love & Hubbard 2007, 2009) His primary substantive criticism is that the HIF leaves patents in the hands of the patent owners, thereby delaying market-based generic competition from multiple producers. Others share this concern in the broader context of prize proposals that rely on contractual access provisions. (Wilson & Palriwala 2010; Light 2005, 2007, 2010) In response to these criticisms, the HIF proposal was adjusted to be open to licensing to generics; to tender systems; and to administratively determined prices. (Hollis 2009) The final form of the HIF has yet to be determined and it is likely that a variety of contract options may be most attractive. With respect to antibiotics, because of the interest in conservation, there is a strong rationale to prefer to limit the rights to produce and sell the drug, as we explore below.

Other practical concerns include measuring health impact in order to make the prize payments and obtaining sufficient support to fund the HIF. Measurement will be a complex task, with many real-world epidemiological problems to solve, including tracking and disentangling the various causal factors implicated in health impact. Substantial work is underway to articulate appropriate metrics, but will not be detailed here, as it was the subject of a two-day conference at Harvard in November 2009 and ongoing work thereafter. Measurement of the health benefits from antibiotics could be particularly difficult because of the issues of controlling for
the development of resistance in the population over time. In addition to current health impact, for antibiotics we face the issue of considering the future health impact of inappropriate antibiotic use today.

The funding question will be dependent upon the political will to initiate a realistic test of the HIF. This essay outlines a therapeutic category of drugs for a potential large-scale test, namely systemic antibacterials.

III. The Legal Ecology of Antibiotic Resistance and the Need for Global Coordination

Before turning to the potential case of antibiotics in the HIF, we must briefly explore some of the unique legal and biological aspects of antibiotics. Antibiotics may be the greatest single medical success of the twentieth century. But this achievement rests on an insecure foundation. As antibiotics are used, they create evolutionary pressure that threatens their undoing through resistance. If antibiotics were to lose their effectiveness, some of the advances in health over the previous seventy-five years would be threatened. The edifice of modern medicine rests upon the foundation of effective antibiotic therapies. (IDSA 2004, 2011; Mossialos, et al. 2010; Nugent, Back, & Beith 2010; Laxminarayan & Malani 2007)

Antibiotic effectiveness is a valuable common pool resource akin to productive fisheries. Common pools are prone to depletion and collapse through uncoordinated withdrawals, which is the history of the destruction of the vast herds of American bison in the Great Plains in the 19th Century. (Taylor 2011) In the case of antibiotics, withdrawals occur as antibiotic resistance grows through use and
misuse. The common pool is renewed through conservation and the addition of new antibiotic therapies. We face a tragedy of the antibiotic commons as uncoordinated use and misuse of precious antibiotics may prematurely destroy these important drugs. (Goeschl & Swanson 2003; Laxminarayan 2003; Outterson, 2005; Laxminarayan & Malani 2007) Incentives for new antibiotics must be conditioned on meeting long-term public health goals as well. (Kesselheim & Outterson 2010)

Resistance creates at least four important policy issues for antibiotic incentives. The first is the effect of conservation upon research and development of new antibiotics, as incentivized generally through patent law (Outterson 2010). At first blush, both conservation and R&D seem to be laudable, but in many ways conservation and R&D work at cross purposes, and difficult choices must be made between them. For example, insofar as antibiotic conservation is successful in curbing inappropriate use and maintaining the effectiveness of existing products, it will suppresses demand for new antibiotics. Viewed from the dynamic perspective of R&D into new drugs, conservation programs undercut market incentives by dampening future demand. This is known as the “conservation dampens R&D” hypothesis. But from the static perspective of public health, conservation is an unqualified success when infections are prevented or antibiotic resistance averted. In an optimally coordinated market, current antibiotics would conserved for as long as possible and new ones introduced on a “just in time” basis, perhaps with some antibiotics held in a “strategic antibiotic reserve” for emergencies.

The second problem is the financial incentives that the market gives to drug companies, hospitals, physicians, pharmacists and informal health care workers
around the globe. (So, et. al. 2011; Kesselheim & Outterson 2010, 2011) All of these parties are rewarded by moving product, especially through increased unit sales of antibiotics. In the U.S., most antibiotic sales (by volume) are for use in healthy animals, which raises questions for human health. A sale yields the same profit whether the use is actually appropriate or not. In ordinary drugs, this situation is wasteful if money is spent unnecessarily or if patients are needlessly exposed to pharmaceutical risks. With antibiotics, the damage of inappropriate use is multiplied because misuse promotes resistance, destroying the power of the drug for future patients as well.

The third quandary is the relationship between resistance and innovation. The conventional wisdom assumes that resistance is a problem in antibiotic innovation (Projan 2003; So, et al. 2011), but resistance may also stimulate innovation. (Outterson 2010) In other drug classes, new entrants must compete against generic drugs with proven records of safety and efficacy. Lipitor (atorvastatin) is an excellent statin, and when it transitions to fully generic status, atorvastatin will set a high bar against which new statin drugs must be measured. Importantly, the use of atorvastatin by one person does not undermine its value for any other person: the billionth dose is just as effective as the first. None of this is true for antibiotics. Penicillin was an outstanding antibiotic, perhaps better than almost anything we have seen in many decades. But resistance makes highly effective antibiotics obsolete over time, which clears the competitive field before a new drug enters the market. This trend of declining effectiveness favors entry of new antibiotic molecules. Paradoxically, speeding market entry of antibiotics may
actually accelerate resistance, by flooding the market with competing drugs that trigger another round of resistance. (Outterson, 2010)

The fourth issue concerns the policy levers employed in the battle against antibiotic resistance. Prior work has been perhaps too quick to turn to patent law as the preferred policy lever. For example, the Infectious Diseases Society of America (IDSA) catalogues the thin pipeline of new antibiotic therapies, but has called for significant changes in patent law to remedy the problem, including patent extensions and wildcard patent extensions for antibiotics. (IDSA 2004, 2011) In our view, patent law mechanisms are ill suited to address the resistance problem, in part because patent law is not flexible enough to account for the biological complexity of resistance. (Outterson 2005; Kesselheim & Outterson 2011) The traditional advantage of patent law is its reliance on market pricing, but many pharmaceutical prices are not really set by the market. (Outterson & Kesselheim 2009) To the extent that market-based pricing is an important element of the patent system, its absence in pharmaceuticals is quite troubling. If the primary market signals are muddled or broken, additional patent-based programs should not be rolled out before the reimbursement system is fixed. (Kesselheim & Outterson 2011) When prices are set above marginal cost, firms will have incentives to exploit their monopoly through over-producing (relative to the social optimum) during the exclusivity period. Nor is it clear that patients would be well served by pricing at marginal cost: unlike many drugs with deadweight losses due to lost sales, overuse of antibiotics could be welfare-reducing due to resistance.

An alternative pricing mechanism is pay-for-performance (P4P) or value-
based reimbursement, which could be implemented through insurance reimbursement. (Kesselheim & Outterson 2010, 2011) P4P is a powerful tool that is not yet well deployed to promote continued antibiotic effectiveness. Reimbursement has created both helpful and perverse financial incentives. Third-party reimbursement improves access to drugs but hinders conservation and (in some countries) allows physicians to receive additional payments for unnecessary prescriptions. Another example of a perverse financial incentive is reimbursement for hospital-associated infections. Historically, U.S. hospitals with poor infection control practices were able to bill Medicare for the incremental costs of hospital-associated infections. (Outterson 2011) Private incentives and social goals are seriously misaligned. But perhaps it is easier to fix the reimbursement system than to implement effective patent-based solutions. If so, focusing on reimbursement as a policy lever could add meaningfully to the debate.

Because of the threat of resistance, the antibiotic sector requires a global coordination mechanism that is not currently being provided by the market. Waves of expert reports have decried the looming shortage of new antibiotics in the pipeline (IDSA 2004, 2011; Nugent, Back & Beith 2010; Mossialos, et al. 2010; So, et al. 2011). The antibiotic innovation system is not functioning well. Compare antibiotic innovation with information technology: what if successive generations of laptops were larger and slower with diminished capabilities? Or suffered incremental safety problems with each new generation? No one would consider that situation acceptable for laptop innovation, and yet that is the landscape for antibiotics. Today’s antibiotics are in many ways inferior to the drugs available in
1950; most of the antibiotics approved in the “glory days” of the 1980s were subsequently withdrawn from the market, many with safety problems. (Seoane-Vasquez, et al. 2011) Antibiotics suffer from an innovation deficit.

But a significant increase in antibiotic drug approvals may not solve the problem. (Outterson, Powers, Gould & Kesselheim 2010) Companies are rewarded based on antibiotic unit sales, and often focus on the wrong types of innovation. In many antibiotic drugs, resistance can be transmitted within the antibiotic drug class (such as fluoroquinolones) to other drugs in the class, permitting market rivals to “pollute” on their competitors’ drugs. These resistance patterns can vary between different bacterial species. In this ecological context, bringing additional “me-too” drugs to market within an existing class can speed the destruction of all drugs in the class. Cross-class resistance complicates the problem even more, as the “pollution” affects more “distant” drugs. (Kesselheim & Outterson 2011; Outterson 2005) A patent race that results in too many molecules reaching the market at the same time is not success, but failure. Multiple simultaneous entries should be considered uncoordinated withdrawals by competitors from an exhaustible common pool. (Laxminarayan & Malani 2007) Such races may drive resistance instead of improving human health. By this account, the following chart may represent a hopeful sign rather than cause for alarm.
Antibiotic pollution externalities could potentially be managed by Coasian contractual mechanisms. The number of patent-owning firms involved is relatively small, but cooperation in this fashion would run afoul of the antitrust statutes in the US and competition laws around the world. As a result, limited antitrust waivers would be required for any coordinating mechanism. (Kesselheim & Outterson 2011)

A related but distinct issue involves truly innovative antibiotics, especially drugs with entirely new mechanisms of action. These antibiotics are the first entrant into a new “functional resistance group.” (Laxminarayan & Malani 2007) To the extent that competitors’ actions don’t damage the new drug, then the patent owner need not fear obsolescence through resistance pollution. But the patent clock ticks on, since the company owns a time-limited property right. The company has every incentive to bring this molecule to market quickly, even absent either clinical need or pollution risk. This market introduction begins the countdown to resistance
for a new functional resistance group of antibiotics. In short, the patent holder has strong financial incentives to waste the antibiotic, even if clinically appropriate alternatives exist. (Outterson 2005) For these first-in-class antibiotics, the common pool would be better served by keeping these drugs off the market until clinically necessary. One solution is the “Strategic Antibiotic Reserve,” which would pay patent owners handsomely to entirely forgo marketing the drug class until the day that resistance to other drugs necessitated a withdrawal from the Reserve. (Kesselheim & Outterson 2010, 2011) The analogy is to the strategic petroleum reserve, saving an exhaustible resource for a day of utmost need.

IV. Antibiotics in the HIF

In the following pages, we explore first the details of how the HIF would impact R&D incentives for antibiotic, before turning to the issue of conservation. In both cases, the HIF may be able to solve vexing problems in this sector.

A. An “Antibiotic Health Impact Fund” as a Global Coordination Mechanism

The HIF is very appealing as a global coordination mechanism for antibiotic R&D. For the first time, companies would be rewarded for producing antibiotics that were better than existing therapies, with the target being actual improvement in human health as opposed to unit sales. The HIF would not function as a bureaucratic expert panel picking “winning” research programs. Companies would continue to evaluate and prioritize their own research programs, but the HIF
reward will be based on the health impact rather than the ability to generate sales in high-income countries through aggressive marketing. And as discussed below, the HIF would offer little or no reward to a company for switching patients from an older but still effective antibiotic to its own, brand-new, HIF-registered product. This company does not appropriate the entire profit the other company derived from its sales, but it only gets rewarded if and insofar as the switch is beneficial to patients’ health. Similarly, this company makes little or no money on serving future patients who, in the absence of its drug, would have had access to older antibiotics. Yet, this company does, of course, have an incentive to bring its drug to patients who otherwise would have no antibiotic at all.

US sales of systemic antibacterials were US$11.2 billion in 2008 (IMS Health 2010); global sales were approximately US$42 billion in 2009. (Hamad 2010) The HIF has been initially scaled in the range of US$6 billion per year over 10 years. If the HIF were limited to systemic antibacterials and antibacterial vaccines, it would dramatically boost innovation incentives in this drug class, and serve an important coordinating function by steering the work towards antibiotics with the greatest potential global health impact. Investing US$6 billion per year in this fashion would likely be very efficient, since the social value of the unmet need for antibiotics is at least an order of magnitude higher (Kesselheim & Outterson 2010).

B. **HIF as a coordination mechanism for global conservation**

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5 Sales at ex-manufacturer prices (=manufacturer invoice). Includes rebates and certain discounts. Sales at consumer prices would include wholesaler cost and pharmacy fees.
The current global pharmaceutical market balances access and innovation primarily upon the fulcrum of generic entry. The global rollout of low-cost antiretroviral medicines was made possible by entry of generics. (Love 2008c) Access to many medicines accelerates after generic entry, due to the significant price reductions driven by generic competition. On a static level, deadweight loss is reduced through marginal cost production and generic distribution as soon as possible. A persistent criticism of the HIF raises the question of inadequate incentives for generic production. (Love 2008a) Whatever traction this criticism may or may not have in general, the calculus is different for antibiotics. For antibiotics, paradoxically, maximizing production and access may be globally counterproductive. Policymakers should avoid indiscriminately flooding the market with vast quantities of low-priced generic antibiotics. Generic access must be balanced with conservation goals if long-term human health is to be maximized.

If we focus solely on producing new antibiotics to the exclusion of long-term conservation, then all we have done is to accelerate the final ecological collapse of every functional resistance group of antibiotics. Consider the following two charts. The first is the oft-repeated chart on the decline in FDA approvals for antibiotics over the previous decades:
As we note above (p.16), this decline might actually be a hopeful sign, but the IDSA uses this chart to ask Congress for additional financial and patent incentives to spur production of new antibiotics together with conservation efforts (Spellberg 2010). Now consider the second chart, data on the near-extinction of the North American bison or buffalo in the 1870s (Taylor 2011):

Confronted with this buffalo hide export data, the rational response should not be increased financial incentives for hunting. The buffalo population was a classic common pool resource that suffered ecological collapse through
unsustainable withdrawals following a post-Civil War innovation in tanning techniques. Prices stayed high – and the profitability of exploiting the herd was maintained – because of the large export market for hides in Europe. (Taylor 2011) This led to the wholesale slaughter of the buffalo population in about a decade. Other economists focus on the late arrival of property rights as a factor in the near extermination of the herd. (Lueck 2002).

Any analogy between antibiotics and buffalo markets should be approached with great caution. However, the common pool problems are similar. If private benefits from the use of antibiotics are high, but private cost are kept very low, we can anticipate a rapid onset of resistance unless the common pool resource is managed for long-term sustainability. Put another way, we must understand global antibiotic policy as a primarily ecological management question. The battle against microbes cannot be “won.” Indeed, microbes are a significant percentage of our body weight and cellular census, with complex effects on health. The long-term goal is a sustainable balance between microbes and humanity.

In the HIF, long-term sustainability could be addressed by making the rewards contingent on long-term antibiotic conservation goals being met. Pay-for-performance is the second major feature of our proposal, after de-linkage. Pay-for-performance rewards are the mechanism for global antibiotic coordination through the HIF.

The HIF would require the assistance of public health experts to develop appropriate conservation goals. Outterson and Kesselheim have described one possible model, which would focus on surveillance data of resistance as the key
metric, leaving implementation to the companies themselves. (Kesselheim & Outterson 2010, 2011) The defining feature of this model is the reluctance to use government to specify detailed regulations, assuming that the companies have superior information about the contours of the antibiotic markets and the heterogeneous policy tools available to reduce inappropriate use. While other models are certainly possible, reliance on the companies while holding them accountable for actual resistance targets yields several interesting implications.

First, companies would have a significant financial incentive to manage their antibiotics for long-term public health, rather than short-term sales. Companies would benefit most from getting the right drug to the right person at the right price, and would deploy their remarkable marketing talents to discourage inappropriate use. For example, Bayer owned the patents on both ciprofloxacin and a related antibiotic used in agriculture. The battle to restrict non-therapeutic uses of antibiotics in animal feeds would be transformed if the company’s profits from exploitation of these two products were contingent on meeting conservation goals.

Second, as described above, the biology of resistance might require multiple companies to coordinate their actions in order to hit resistance targets, maximize health impact, and minimize pollution. Not only will limited antitrust waivers be required, but it might be necessary to make HIF registration an all-or-nothing offer to all antibiotic drugs in a functional resistance group. Unlike other therapeutic categories, antibiotics in the HIF face special challenges if some drugs are in the program but others – polluters with low health-impact – remain outside. It should be noted that any company with a HIF-registered antibiotic would have a clear
incentive to manage its entire portfolio in order to achieve the HIF resistance targets, even if it required changes to marketing plans for unregistered drugs. In this way, companies with one or more registered products would enjoy financial rewards for carefully managing even their antibiotics with minimal health impact.

It must be conceded that some companies might remain entirely outside the HIF and yet choose to market their drugs in a fashion that polluted other antibiotics, including registered products. Such extreme cases might call for other remedies, including denying (or revoking) market access for such polluting, low-value drugs.

Third, since resistance emerges gradually over time, the proper time frame for an antibiotic HIF might be much longer than ten years. If an antibiotic remained in the HIF for 20 years or more with significant continuing health impact, then the company should continue to receive the reward, so long as it meet the resistance targets. New antibiotics might be delayed, especially ones not quite as good as existing drugs, but that need not bother us. Indeed, social welfare over the coming decades would be enhanced by just such a delay. In addition to stretching the HIF reward period beyond the usual 10 years for antibiotics, one might also consider delaying this period. Here the aim would be to encourage the innovator to delay efforts to achieve wide use of its product to the future period in which such wide use can make the greatest contribution to global health.

Fourth, companies will be incentivized to solve many significant “last mile” problem in antibiotics. One such problem involves the availability of rapid point-of-care diagnostics to distinguish between viral and bacterial infections. In the absence of such a test, many clinicians resort to empiric therapy with antibiotics.
Treating a virus with antibiotics does not affect the virus, but may negatively affect the health of the patient while also facilitating resistance. From the financial perspective of a drug company that is selling antibiotics under the current system of incentives, these diagnostics can only decrease its sales and are therefore undesirable. In contrast, under the HIF, the company would have a significant financial incentive to promote appropriate use of diagnostics. Likewise, some vaccines dampen the demand for antibiotics by reducing the incidence of bacterial illness. Companies with antibiotics in the HIF could be financially rewarded for cooperating in the promotion of effective vaccines. Similar infrastructure issues include infection control measures and resistance surveillance; these tasks don’t have a billing code in most countries and are left to public health agencies with limited budgets. Companies with antibiotics in the HIF would have a financial incentive to support these efforts in many ways. In a similar fashion, the companies can deploy their impressive marketing operations in support of antibiotic conservation, rather than opposing these efforts through aggressive marketing.

Finally, most current efforts to conserve antibiotics are not global in scope. Global coordination is a significant collective action problem, akin to unregulated depletion of fisheries or pollution that falls on distant countries. Many of the benefits of antibiotic use are internalized, but many of the costs are externalized. The WHO’s program in 2011-2012, while laudable in aspirations, is not well funded and lacks enforcement and a norm-setting mechanism. The HIF could serve a significant global coordination role here, leveraging funding from the HIF sponsors into a true global strategy implemented by private actors. An antibiotic HIF would
give the global drug companies a direct stake in reducing the global health impact of communicable bacterial diseases, managing the common pool resource of antibiotics for the long-term health of the global population. The companies are well positioned to influence the utilization of their products in every region of the planet. Since the task is largely undertaken by the companies themselves, this mechanism can succeed without regard to the quality of local governance institutions.

**C. Patent-Related Issues for an Antibiotic HIF**

As described above, the patent policy of the HIF is not an essential design feature, but a functional and practical choice at this stage. We can think of several reasons why the companies may wish to keep the patent for a drug enrolled in the HIF, but in many cases the analysis is significantly different for an antibiotic HIF.

First, the patent holder may hesitate to transfer the patent in advance of the 10-year HIF reward payments. The HIF will gain credibility as a counterparty over time, so perhaps this issue will diminish in importance in future years.

Second, by transferring the patent, the company would lose the right to control certain follow-on innovations. For an antibiotic HIF, this issue may be less salient, as a successful HIF will delay the clinical need for many follow-on antibiotics. In antibiotics, we don’t necessarily want to promote additional drugs in class on an accelerated timetable. Society may be better off with spreading antibiotic approvals across a larger number of years, coupled with strong conservation incentives.
Third, retaining the patent gives the company additional control over operational issues such as how the drug is used in drug combinations and potential early exit rights under the HIF contract. Both of these issues are enmeshed with the antibiotic pollution externalities described above: in many cases, combination drugs offer much lower resistance profiles; and early exit may need to be discouraged in order to protect drugs remaining in the HIF.

One advantage of an immediate transfer (or open license) of the patent for a HIF-registered product is that it shifts competition from the molecule to finding more efficient manufacturing methods that might significantly reduce the marginal cost of production. While the company contractually promises production at marginal cost, the HIF does not necessarily create competitive conditions wherein companies strive to drive those costs down. In economic terms, the HIF will address the great majority of the deadweight loss associated with patent-based pricing, but may forego some opportunities for additional social welfare gains through reduced marginal costs. Insofar as manufacture is outsourced, the incentive to reduce the marginal cost of production for HIF-registered products is powerful, as competing manufacturers will want to be able to submit the lowest bid. Insofar as manufacture is not outsourced, the firm will want to lower its manufacturing cost. For even if the firm’s best option is to sell at cost, regardless of what this cost is, the firm will achieve more health impact if the product is sold at a lower price. The firm is better off producing and selling at $4 than at $5.

In the context of antibiotics, these issues are muted somewhat, since maximizing production volume and minimizing unit costs are not the primary
objectives. A key issue here is that while the HIF could stretch out and/or delay the reward period for antibiotics, such that the incentives for conservation were adequate, patents would inevitably expire, opening a path for uncontrolled generic production. Therefore a key component of antibiotics in the HIF would be an international agreement not to permit other firms to sell HIF-rewarded antibiotics, regardless of the patent status. Without the HIF, simply extending exclusivity rights is a non-starter, since it opens up opportunities for exploitation of consumers by innovators. With the HIF mechanism, extending exclusivity rights is consistent with maintaining roughly the same level of profits while improving clinical and conservation outcomes. The HIF can achieve conservation goals without rationing by means of high prices that effectively limit the use of the product to wealthy or well-insured individuals. To the extent that generic production incentives are a significant question raised for the HIF, in the antibiotic sector the issue loses some of its bite.

V. Conclusion

The antibiotic sector is an attractive but complex candidate for testing the Health Impact Fund. The ecological nature of resistance has led both industry and academic researchers to suggest de-linkage mechanisms as a means to simultaneously address problems with conservation and R&D. The looming crisis of antibiotic resistance is a high-value global problem, worth hundreds of billions of US dollars. Resistant diseases are significant health risks throughout the world. This problem threatens both high- and low-income populations, and it may prove impossible to solve this problem without an effective global coordination
mechanism. The HIF demonstration, while modestly sized compared to global pharmaceutical markets, is probably large enough to alter incentives in the antibiotic sector. Some of the questions raised about the HIF apply with less force in the antibiotic sector, making it an attractive candidate.

An antibiotic HIF is not without significant challenges. Financing must be robust and sustainable. Adequate and realistic resistance targets will have to be set globally, without political meddling. Achieving these targets will be fully delegated to the companies, but they will also be accountable to the HIF for failing to hit the mark. Drug companies will be encouraged to cooperate for global public health in unprecedented ways, with equally impressive financial rewards.

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