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# Antibiotic Resistance Is a Tragedy of the Commons That Necessitates Global Cooperation

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## Introduction

Antibiotic resistance presents a classic example of the “tragedy of the commons.” In this eponymous tragedy, the commons — shared, public access lands — are overgrazed because farmers can send their livestock onto the land at a zero price. The “tragedy” occurs because overgrazing destroys the land and reduces its ability to provide fodder. The application to antibiotics is obvious: the use of antibiotics creates selection pressure leading to increased proportions of resistant bacteria in the patient and the environment. The increase in frequency of resistant organisms diminishes the effectiveness of antibiotics in treating future infections; thus, the long-term value of the antimicrobial resource is reduced. This problem is aggravated when individuals or companies misuse antibiotics — for example, by not using them to treat a bacterial infection, or by taking only a partial course, or by feeding them at low doses to livestock — resulting in increased resistance with little or no compensating benefit.<sup>1</sup> In the language of economics, there is a “negative externality” from antimicrobial use. At a national level, governments pay attention mostly to domestic issues, without considering the externalities imposed on other countries. Thus, most countries have policies that are too lax, since the benefits from antimicrobial consumption are local, but the costs of resistance are local and global. The overall goals of effective policy must address problems of access to antibiotics, as well as effective conservation and innovation.

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Despite increased levels of resistance, investment in antibiotic innovation has been inadequate.<sup>2</sup> New antibiotics are typically reserved for resistant bacteria, which may lead to slow uptake for some innovative products. As a result, the volume of sales during the period of exclusivity (the first 10 to 15 years) may be expected to be relatively small.<sup>3</sup> A further related problem is that resistance is often shared across drugs within the same class, so that increased volume of sales of one molecule may undermine the effectiveness of a different, but related, molecule.

The combination of these “commons” problems suggests that some kind of global coordinated response is desirable, through an international agreement that combines tools to reduce inappropriate use and to increase investment into developing new antibiotics. At the same time, there is a pressing need to increase access to antibiotics in some settings, since lack of access to effective antibiotics is deeply problematic for human health and may accelerate the development of resistance.<sup>4</sup> In this short article, we discuss the insights of economics into possible solutions.

## Conservation Mechanisms

Economists have extensively studied issues relating to the tragedy of the commons. One solution is privatizing the commons. This is essentially an application of the “Coase Theorem,” according to which negotiations over an asset will lead to an efficient outcome, provided the rights to the asset are well defined.<sup>5</sup> This approach has also been proposed for antibiotics: extending the period of exclusivity, possibly indefinitely, would give the patentee the ability to charge high prices and thus indirectly restrain overuse by some users.<sup>6</sup> In effect,

the patentee would have an incentive to maximize the present discounted value of its invention's profitability. Extending the period of exclusivity would also, of course, modestly increase incentives to invest in new antibiotics. Extending exclusivity, however, is only effective if it deters use by consumers who are willing or able to pay little. A solution in which poor people are prevented from accessing drugs that could save their lives is not a desirable solution, nor is it likely

designed to reduce low-value uses of antibiotics, while also supporting innovation and enabling appropriate access where needed.<sup>8</sup>

An important observation is that such policies would differ across countries according to the particular administrative capabilities, culture, clinical practice, and bacterial flora of each country. For example, in many countries the number of health workers is relatively low, there is inadequate diagnostic capacity,

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one to which low-income countries would agree. This Coasean solution would also not address the problem of cross-drug resistance, and it would not address the more general problem of misuse of existing unpatented antibiotics.

A Pigouvian tax on antibiotics is another possible solution. Such a tax could increase the price for use by all consumers, but again would harm access by the poor without doing much to deter inappropriate use by insured or affluent patients. This suggests that it would be much more appropriately applied for industrial and agricultural uses where there is a more equal sensitivity to costs.<sup>7</sup> A particular advantage of this approach is that distinguishing between growth promotion and other subtherapeutic uses (e.g., metaphylaxis, prophylaxis) is difficult and may be non-verifiable. A user fee of this sort would also generate revenues that could support conservation or innovation activities. An international agreement to charge Pigouvian taxes on antibiotics for non-human use could create a centralized, pooled fund, or could fund local activities in each country. If a tax were applied to human-use antibiotics, we suggest that would only be appropriate in high-income countries.

A third possible solution is to impose regulations on usage or new policies to support conservation activities. Such an approach gives everyone the same limited access and may therefore be perceived as fair. An international antibiotic agreement could require countries to establish regulations and policies

and it is almost impossible for people in rural areas to obtain antibiotics prescribed by a physician based on a laboratory-diagnosed infection.<sup>9</sup> Thus, a standard that might be appropriate for high-income countries would effectively bar many people from accessing antibiotics at all.

Similarly, in other countries, despite a larger number of health care workers, antibiotics are used extensively without prescription, based on self-diagnosis. Preventing this culturally customary behavior would be difficult, and would involve real costs of regulating the sale of pharmaceuticals, particularly antibiotics. For many drug retailers, antibiotics sold without a prescription are an important source of revenue. For example, a recent study showed that in northern Vietnam, antibiotics sold without a prescription made up 21% (16%) of revenues in urban (rural) pharmacies.<sup>10</sup> Eliminating such sales is challenging given the financial consequences to pharmacy owners, and likely would take many years.

### **Innovation and Delinkage**

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support the development of new antibiotics, a goal that faces significant obstacles.<sup>11</sup>

Increased profitability of antibiotics, however, generally seems to imply that consumers or governments are going to be paying more. The only way to obtain higher revenues from consumers is through extending exclusivity or adding taxes on antibiotics, which, as we described above, is not an attractive or sufficient option for therapies for people and is likely infeasible in the context of an international agreement. Governments would have to contribute more, perhaps through increased subsidies to the development process. Thus, one aspect of the agreement would be focused on increasing and coordinating public funding to support innovation in antibiotics. This would naturally be matched by a public interest in ensuring increased access to antibiotics when needed. The challenge is to maintain private sector interest in investing in antimicrobial research, along with prices that enable widespread access when needed.

To achieve these seemingly conflicting goals, a model with “delinkage” could be used. Delinkage, in which the profit stream of the innovator is delinked from prices and volumes, offers more flexibility in how innovation is rewarded; for example, the innovator could obtain prizes or other payments connected to the extent to which important pathogens continue to be susceptible to the drug after 5 or 10 years. Such payments would be funded directly by governments. Delinkage, which has come to be a central part of international discourse on pharmaceutical pricing, was recommended by the 2012 report of the WHO Consultative Expert Working Group on Research and Development, and is of particular relevance for antibiotics.<sup>12</sup>

### Economics of Coalitions

There are two important strands of literature on solving “commons” problems through an agreement: the theory of cooperative games, which focuses on the conditions for establishing a stable coalition; and Elinor Ostrom’s work on how local communities have organized themselves to extract the most from commonly held resources.

A key insight from games theory is that a coalition requires that each of the players individually, and any group of the players collectively, should not be able to do better by leaving the coalition. In the context of an international agreement on antibiotics, demonstrating that at least a large number of countries are better off in the coalition is challenging because benefits and costs of participation differ substantially across countries with varying incomes, capacities, and objectives.

Many low-income countries have limited administrative capacity to establish and enforce conservation policies and at the same time are dealing with many other pressing priorities. (Low-income countries are also likely to be the ones the most seriously affected by resistant organisms, since they have the least resources to control infections in other ways.) For such countries, it is essential to include a mechanism to support investments in surveillance, conservation, and innovation. The *Montreal Protocol on Substances that Deplete the Ozone Layer* provides a positive example of such a support mechanism. During the last 25 years, its Multilateral Fund, financed by high-income countries, has committed over \$3 billion for implementation of projects including industrial conversion, technical assistance, training and capacity building in qualifying countries.<sup>13</sup>

Delinkage, if implemented appropriately, could also provide an incentive for lower-income countries to commit to an antibiotics agreement, since it would mean that price would not be a barrier to use of new antibiotics where needed. However, to make delinkage effective in sustaining commitment, it would be necessary that low prices be available only if the country was in compliance with the agreement. This would be practically and ethically challenging. From a practical perspective, there would have to be a process to decide whether countries were non-compliant, and then a mechanism established to prevent such countries from purchasing patented antibiotics at the low prices available elsewhere. From an ethical perspective, this would require “punishing” sick people because of policy failure on the part of their government. Using a tool such as the Multilateral Fund designed explicitly to support compliance would be more productive. First, in countries with severe resource constraints, such a fund could provide direct financial support for desired conservation activities. Second, a fund would enable a more nuanced approach to non-compliance. For example, countries that failed to direct resources appropriately to effective conservation policies might receive less funding or none at all.

Delinkage could be of particular importance for middle-income countries, which typically have better public health care facilities than low-income countries, but face limited financial capacity to purchase expensive new antibiotics. While delinkage would improve access and also increase the overall attractiveness of an international agreement on antibiotics, it is difficult to see how it could be easily tied to compliance with obligations under the agreement. One possible tool to discourage non-compliance would be reduced funding to support surveillance and conservation; of course, this could be self-defeating.

High-income countries could find the economics of an antibiotics agreement compelling, even with substantial financial support for conservation activities in low-income countries. If resistant organisms develop and spread in other countries, they will also pose a significant health threat in rich countries, regardless of local conservation policies and practices.

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High-income countries have even more (but still limited) resources and capability to support conservation policies appropriate to their situation. In principle, a country that does not participate in, or comply with the agreement may have lower costs from conservation, while benefiting from less resistance caused by use of antibiotics in other countries. However, in practice, resistance against specific antibiotics has a strong local component, and countries, such as Sweden, that have aggressively pursued antimicrobial stewardship programs have seen meaningful changes in resistance levels nationally. Thus, there are good local reasons for investing in conservation activities, which are buttressed by the important externalities in other countries.

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What mechanisms could be used to discipline high-income countries that fail to live up to their commitments under the agreement? Depending on the type of non-compliance, some combination of moral suasion and trade restrictions may be possible. For example, trade restrictions might be possible on agricultural products, if the non-compliance related to agricultural use of antibiotics.

The second strand of literature on solving “commons” problems relates to the research of Ostrom on “design principles” of stable local common pool resource management.<sup>14</sup> While her research focused on *local* cooperation, several of Ostrom’s insights are relevant for agreements between governments as well. First, she noted that rules regarding the appropriation and provision of common resources should be adapted to local conditions. The implication in the context of antimicrobial innovation and conservation is that an agreement must respect the significant differences in needs and capacities of different governments while also providing a common foundation for achieving its goals. Second, she noted that there must be effective monitoring with accountability of the monitors. This is particularly difficult for antibiotic conservation since the key metrics relate not only to the volume of use but also how products are used.

Along with monitoring, Ostrom’s principles include graduated sanctions for rule violations. In international treaties such as Kyoto, the difficulty of applying sanctions has always been a serious obstacle. The Montreal Protocol, which uses positive financial support to induce participation, rather than punitive sanctions, provides a positive model of implementing graduated sanctions. There are a variety of collaborative research activities that could be limited for different degrees of non-compliance. (Delinkage, while it offers other important benefits, does not easily offer a mechanism to enable graduated sanctions for non-compliance.)

One of the key principles Ostrom outlines is the importance of having “resource appropriators” (i.e., countries that use antibiotics) participate in the decision-making process.<sup>15</sup> Inclusiveness in setting up the terms of an international agreement creates the legitimacy that is essential for sustainability. This is particularly important in the case of an antibiotic agreement because of the differences in conservation goals and targets across countries. Assuming that an agreement evolved over time with conditions and its goals, it would be essential to have the widest ongoing participation in the governance of the agreement.

### Summary

Antibiotics are of enormous importance to global health, yet face multiple challenges: owing to over-use and misuse, their value is being undermined by resistance, even while millions of people lack effective access to these life-saving products. Individual countries lack the motivation, the commitment, and the

resources to address important issues of conservation and innovation. If designed appropriately, an international agreement could substantially mitigate these problems, and provide an important improvement in global health in the decades to come.

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