

Linking sustainable use policies to novel economic incentives to stimulate antibiotic research and development

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Abstract

There is now global recognition that antibiotic resistance is an emerging public health threat. Policy initiatives are underway to provide concrete suggestions for overcoming important obstacles in the fight against antibiotic resistance, like the alarming current paucity of antibacterial innovation. New economic models are needed as incentives for the discovery and development of novel antibacterial therapies especially for infections with too few patients today to justify private sector research and development (R&D) investments. These economic models should focus on rewarding the innovation, not the consumption of the antibiotic since sustainable use policies will reduce selection pressure and slow the emergence of resistance. To effectively stimulate greater innovation, the size of the reward must be commensurate with revenues from other therapeutic areas, estimated at about a billion dollar total pay-out. Otherwise R&D investment will continue to move away from antibiotics to areas where returns are more attractive. A potential sizeable public investment, if implemented, must be protected to ensure that the resulting antibiotics have a lengthy and positive impact on human health. Therefore, public investments in innovation should be bound to sustainable use policies, *i.e.*, policies targeted at a range of actors to ensure the preservation of the novel antibiotics. These policies would be targeted not only at the innovating pharmaceutical companies in exchange for the reward payments, but also at governments in countries which receive the novel antibiotics at reasonable prices due to the reward payment. This article provides some suggestions of sustainable use policies in order to initiate the discussions. These are built on planned policies in the US, EU, WHO and have been expanded to address *One Health* and environmental

aspects to form *One World* approaches. While further discussion and analyses are needed, it is likely that strong sustainable use policies will help to protect the sizeable public health investments.

Introduction

Resistance to antibiotics follows selection pressure and increases with their use. The current rate of resistance especially in Gram-negative bacteria to multiple, most, or all antibiotics has reached alarming levels in many parts of the world. Such multidrug, extensively drug and pan-resistant bacteria limit therapeutic options and complicate clinical care.¹ Since the late 1980s there has been a lack of true antibiotic innovation. No new classes of antibiotics meeting current unmet needs and being available for clinical use have been discovered for the last 30 years.^{2,3} This is due to a combination of factors. Firstly, new antibiotics have proven to be very hard to discover. Secondly, generating the data required for regulatory approval of a new antibiotic is difficult and expensive. Finally, antibiotics offer an unattractive return on investment to the private sector: revenues from antibiotics sales tend to be low, and higher revenues are offered in other disease areas.⁴ In 1980, there were more than 25 large, pharmaceutical companies with active antibacterial drug discovery programs; today only a few remain: GlaxoSmithKline, Novartis, Roche/Genentech, Merck, Sanofi, Medimmune.⁵ This creates an upstream knock-on effect, where small to medium enterprises (SMEs) and academics focused on antibacterial research may also struggle to secure financing as well as bring to market any promising products. The consequence of the innovation void is that doctors lack sufficient options for treating the most resistant infections in critically ill patients leading to significant morbidity and mortality. This also jeopardizes modern medicine's ability to safely perform other interventions such as routine surgeries and cancer treatment.^{6,7}

Fortunately, there is now global recognition that antibiotic resistance is an emerging threat to public health, and political action is materializing, including through the G7 and G20 groups of countries, the World Health Organization (WHO), the United Nations General Assembly, the Organization for Economic Co-operation and Development (OECD) and many others. Both the British government and the European Union (EU) have commissioned analyses regarding incentives to stimulate

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antibiotic innovation. The UK Review on Antimicrobial Resistance (AMR), chaired by Lord Jim O'Neill, delivered its final recommendations in May 2016 focusing not only on stimulating antibiotic innovation but also about increasing infection prevention and surveillance, examining alternative antibacterial technologies and improving rapid diagnostics.⁸ Other initiatives on AMR (this term is now often used as synonym for antibiotic resistance) are also underway to provide concrete recommendations for overcoming important obstacles in the field of antibacterial drug resistance. For instance, the international research project DRIVE-AB (*i.e.*, Driving reinvestment in research and development for antibiotics and advocating their responsible use, www.drive-ab.eu), is a consortium of 16 public sector partners and seven pharma-

ceutical companies supported by the European Innovative Medicines Initiative (IMI). DRIVE-AB is developing detailed recommendations regarding implementation, governance and financing of incentives to stimulate innovative antibacterial drug research and development (R&D). Its work is vetted by a broad range of stakeholders, and it is working closely with other ongoing initiatives related to antibiotic resistance.

Concrete actions to stimulate greater antibiotic innovation have also been initiated. The United States' Biomedical Advanced Research and Development Authority (BARDA), the Wellcome Trust and the UK based AMR Centre have recently launched an early phase research accelerator called *The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)*. It will fund antibacterial R&D from the first in-vivo proof-of-concept stage through Phase 1 clinical development with an initial total program funding of more than USD 250 million.^{9,10} The United Kingdom and China have recently launched *The Global Antimicrobial Resistance Innovation Fund* aiming to attract GBP one billion.¹¹ *The Global Antibiotic Research and Development (GARD) Partnership* is being incubated by the Drugs for Neglected Diseases initiative (DNDi) in collaboration with the World Health Organization (WHO) and in support of the Global Action Plan for Antimicrobial Resistance. GARD has secured seed funding commitments from several governments. This partnership will focus on new antibiotic treatments addressing resistance and to promote their responsible use for optimal conservation, while ensuring equitable access for all in need.¹² The IMI programme *New Drugs for Bad Bugs* (ND4BB) comprises currently seven projects and covers all aspects of antibiotic R&D. The EU continues to finance antibiotic resistance programmes across a range of areas via the Joint Programming Initiative on AMR (JPIAMR), the EU Framework Programme for Research and Innovation Horizon 2020. It will also launch a Joint Action focusing on AMR in 2017, likely including a call focused on R&D and innovation.

Novel economic models for greater antibacterial innovation

Antibiotics and other anti-infective agents are like no other class of medicine, since consumption increases the emergence of resistance and diminishes the utility of the medicine for treating the population

over time.¹³ Therefore, it is desirable to remove any incentives to unnecessarily consume these drugs. Yet the traditional reimbursement model for pharmaceuticals is based on sales volumes; manufacturers – both innovating and generic – earn revenues by maximizing unit-based sales, within legal standards. Many factors have contributed to the overconsumption of antibiotics, including, in the past, poorly regulated promotion and marketing practices.¹⁴ To avoid this undesirable incentive for antibiotic misuse, one option is to reward innovation by *delinking* revenues from volumes sold.

One delinked incentive recommended by O'Neill's AMR Review and others is called *market entry reward*.^{8,15} It also represents an incentive model that DRIVE-AB is further analyzing. A market entry reward is a series of lump sum payments awarded to an innovator for achieving regulatory approval of an antibacterial therapy that meets predefined requirements. To effectively stimulate antibacterial innovation, the total reward payment needs to be significant in order to provide a reasonable return on investment as well as shift industry focus from other investment opportunities.

Industry estimates that out-of-pocket costs of developing a new pharmaceutical in a global corporation are on average USD 1.4 billion, including failed programs and overhead costs.¹⁶ Whereas this figure is contentious and many argue that it is actually lower, no one contests that pharmaceutical innovation is very expensive.^{17,18} The R&D funds of large pharmaceutical firms are scarce, and shareholders expect that companies will allocate these funds effectively to deliver expected returns. Other therapeutic areas, like cancer or hepatitis C, can offer potential revenues of a billion or more USD per year. Therefore, a market entry reward designed to stimulate a multinational pharmaceutical company is estimated to require a total payout of between USD 0.8 to 1.3 billion paid out over a five-year period.⁸ This, of course, is a substantial amount for the public sector to pay out. So, the innovation delivered must meet carefully defined unmet public health needs. In other words, society's value for the specific antibacterial therapy must well exceed the billion dollar pay out.

Since selection pressure is exerted as soon as a new antibiotic begins to be used and resistance may emerge and spread, it is in society's best interests to conserve the effectiveness of these novel antibiotics as long as possible. This means that these products should be used solely for patients where the antibiotic is expected to achieve better outcomes than any another antibiotic.

This may translate into the novel antibiotic only being used rarely for confirmed targeted therapy, especially where current levels of multi-drug resistance are low and in countries with high standards of antibiotic stewardship and infection control. To ensure that society's significant investment is conserved, market entry rewards should be designed so that innovators will be incentivized and contractually bound to adhere to both sustainable use and access obligations, within their field of control. It is unethical to withhold life-saving antibiotics from patients anywhere in the world, and appropriate access, so long as the antibiotic is used appropriately, should expand the useful life time of a new antibiotic.

Sustainable use policies for new antibiotics

The drivers of antibiotic resistance are interlinked, and single, isolated interventions have little impact. Therefore, the concept of sustainable use for antibiotics developed under such a new economic framework goes beyond classical hospital or community stewardship programs. Sustainable use policies aim to ensure that a range of actors are incentivized to extend the life time of a specific antibiotic or group of antibiotics. This includes the pharmaceutical company as a part of its sustainable use contractual obligations, governments of countries which receive the antibiotic at a reasonable price potentially as a result of a market entry reward, and, of course, physicians who administer the antibiotic.

Examples of sustainable use obligations that pharmaceutical companies might need to agree to in order to receive delinked public payments could include:

- i. Restricting sales for human use only
- ii. Not promoting the antibiotic beyond assisting qualified professionals to appropriately place the antibiotic within national and local guidelines, preferably by providing all necessary information according to pre-specified rules
- iii. Not donating any excess stocks of the antibiotic but rather disposing of it in a manner that does not contribute to environmental exposure
- iv. Performing environmental monitoring of its factories' waste and those supplying active ingredients to ensure no leakage of the antibiotic into the environment
- v. Labeling the antibiotic for restricted use by facilities deemed appropriate for the particular antibiotic for the particular geographic region, like tertiary hospital

tals or specialist centers equipped with specialized consultation services

vi. Transparently reporting sales and implementing a warning system where a sudden significant increase in consumption by country is reported to the neutral governing body

Examples of sustainable use policies that would be implemented at national levels are listed below. One premise of these policies is that the innovation would be financed through a delinked reward, meaning that each, individual treatment would be affordably priced. These are focused on hospital antibiotics; orally available drugs for the community may need a different set of rules.

vii. Ensuring that mandatory hospital stewardship programs and responsible use policies are in place

viii. Implementing appropriate stewardship controls, for instance, allowing the antibiotic to only be given by specifically authorized and trained staff in the case of a microbiologically proven infection; any other empiric use would need to be justified and documented

ix. Monitoring consumption levels and addressing occurrences of inappropriate prescribing

x. Providing a centralized authorization procedure for outpatient antibiotic usage, in case of an orally available drug for multidrug-resistant microorganisms

xi. Return of any left-over drugs by patients (in case of novel antibiotics available in tablet formulation)

xii. Ensuring that there are no perverse incentives in place promoting the unnecessary consumption of the antibiotic

xiii. Incentivizing use of diagnostic tools as integral part of a stewardship programme and linking reimbursement to the use of diagnostics

xiv. When disposing new antibiotics classify them as potentially hazardous pharmaceutical waste

xv. Invest in research and implement policies for hospital waste water treatment that eliminates antibiotic residues¹⁹

Many of these sustainable use policies are also relevant for older, generic antibiotics. In this article we have linked the policies to novel antibiotics since they can be contractually stipulated as a part of a delinked payment like a market entry reward. This also provides an opportunity to study and evaluate the effectiveness of the policies on a handful of antibiotics. If found effective, the policies could then be implemented on an expanded subset of essential

antibiotics. The complex issue of market entry rewards will be discussed in 2017 during the G20 meeting. DRIVE-AB is working on such details that will be presented and published in mid-2017. DRIVE-AB has published a policy brief that covers ideas for governance and financing (<http://drive-ab.eu/wp-content/uploads/2016/08/PolicyBrief-GovernanceFinance.pdf>).

Examples of nationwide requirements for controlled use of antibiotics already exist. The Australian drug reimbursement agency through its Pharmaceutical Benefits Scheme (PBS) has classified specific antibiotics as *restricted benefit* or *authority required*. For example, physicians must obtain authority to prescribe quinolones from PBS and are only allowed to prescribe for specific PBS-listed infections. These restrictions have minimized resistance to these antibiotics in the outpatient setting compared to other countries.²⁰ The government of Australia also restricted the use of fluoroquinolones soon after they were registered for human use only in order to prevent their use in food-producing animals, resulting in successfully limiting resistance to this class in Australia.²¹

Implementing unified global controlled use provisions for especially critical antibiotics would likely strengthen the sustainability of these antibiotics. The United Nations Single Convention on Narcotic Drugs (1961) regulates narcotic drugs and certain psychotropic drugs globally to prevent the abuse of these substances and to protect society from the consequences of dependence while at the same time assuring access for appropriate medical use. However, the convention has been criticized since many low-income countries in particular have insufficient access to opioids resulting in the poor management of pain.²² Significant analyses are needed to determine the benefits of a controlled drug approach for the sustainability of critical antibiotics.

The idea of tying comprehensive antibiotic sustainable use requirements to financing sources or incentives is relatively new. There are no real-world experiences in the antibiotic field that can be drawn upon to demonstrate the potential impact. However, a few notable programs are being planned addressing important parts of sustainable use policies. The Centers for Medicare and Medicaid Services (CMS) have implemented a requirement combining antibiotic stewardship and infection prevention and control programs in all hospitals that receive federal funding (Conditions of Participation). Specifically, CMS seeks to require: i) implementation of a hospital-

wide antibiotic stewardship program (ASP), ii) enhancements to infection prevention and control programs and greater coordination of surveillance activities with the ASP, and iii) involvement of hospital leadership at all levels. An important component is defining accountability for prescribing practices.²³ Similarly, CMS has finalized its Conditions of Participation for long-term care facilities.²⁴ The European Centre for Disease Prevention and Control (ECDC) released draft EU guidelines on the prudent use of antimicrobials in human medicine. A comprehensive list of recommendations includes establishing a list of antimicrobials with restrictive measures for use (<http://ecdc.europa.eu/en/publications/Publications/draft-EU-guidelines-prudent-use-antimicrobials-human-medicine.pdf>). The US's CDC, the ECDC, and WHO are also discussing and planning overarching policies building in sustainable use to innovation incentives.

Conclusions

The discussions surrounding the restrictive, more sustainable use of antibiotics will stir much debate in the realm of clinical practice and decision-making, agricultural economics, and broader industrial policy. It will undoubtedly be seen as controversial. However, if large, public investments in antibacterial innovation are to continue, the results must be shown to add significant public health benefit for as long as possible. The public sector bodies financing new antibacterial incentives will need to reach consensus on how to use new antibiotics sustainably. Linking existing policies like stewardship policies, *One Health* approaches, and environmental aspects will be integral. Such integrated policies may be models for extension to all antibiotics in the future.

There is significant convergence in principles in the various initiatives calling for greater antibacterial innovation. These include: i) financing mechanisms that both support R&D and reward results in order to fill both early and late stage R&D; ii) implementing at least one delinked incentive rewarding innovators for bringing to market antibiotics effective against the most pressing public health threats related to multidrug-resistant bacteria; iii) building in provisions for both access and sustainable use into these innovation incentives; and iv) collaborating globally for both implementation and financing. There is no precedent for such sustainable use policies, yet through increased awareness and discussion, it is becoming rapidly apparent that

these policies are necessary to protect the current and future, sizeable public health investments in antibacterial drug innovation.

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