Clinical Infectious Diseases

VIEWPOINTS

Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations From the Transatlantic Task Force on Antimicrobial Resistance

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The Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR) in 2015 was tasked with exploring economic incentives for antibacterial drug development and providing recommendations for potential global implementation. Due to the continual decline of pharmaceutical companies investing in new antibiotic development and the rise in antimicrobial resistance, there is an urgent need to examine market mechanisms that are appropriate to encourage small, medium, and large companies to reinvest in this space. This review provides a summary of the various models that have been proposed and highlights positions posed by several policy documents, peer-reviewed publications, organization proposals, and government-sponsored reviews. The findings support a form of a de-linkage model and a combination of push and pull incentive mechanisms. This level of consensus could culminate in global coordination of incentives that strike a balance of rewarding innovation and ensuring appropriate antibiotic use.

Keywords. antibiotic resistance; economic incentives; antimicrobials; TATFAR.

Antimicrobial resistance (AMR) is an emerging and persistent public health threat. Over the last 3 decades, there has been a continual decrease in companies developing new antimicrobial drugs. The reasons for this are multifactorial but are generally related to limited commercial returns.

The pharmaceutical industry evaluates the overall risk/benefit and profitability of pursuing development utilizing a metric termed net present value (NPV). Net present value is the sum of all investment costs in development and expected present value of future revenues, considering discounted rate of the time value of money of a given development program. For antibacterial drugs, the NPV is estimated to be approximately −$42.61 million (converted from Euros to US dollars [current currency]) [1]. This contrasts to neurological or musculoskeletal drugs, where NPVs range between $720 million US dollars to in excess of $1.15 billion US dollars [1]. If the NPV remains low for new antibacterial drugs, few companies will invest in research and development. It has been suggested that a risk-adjusted NPV of approximately $200 million may ensure future pharmaceutical industry investment for new antibiotics [1].

Two primary means of economic incentives for antibacterial drug development are push and pull incentives. Push incentives subsidize the overall development cost and pull incentives reward successful development, providing guaranteed return on investment (ROI). Examples of push incentives include tax credits, direct funding of research, or public–private partnerships. Examples of pull incentives include milestone or prize payments, patent buyouts, advanced market commitments, and value-based or high reimbursement, as well as regulatory incentives encompassing tradable patent extensions, priority review vouchers, or extended market exclusivity. In addition, de-linkage models have been proposed, where companies are not paid on sales volumes, but by established revenues. Companies strive for high sale volumes to improve their ROI, which can increase overuse of antimicrobials and can contribute to resistance emergence. De-linkage models allow research and development investments for a successful product without requiring high product sales and could be adapted to simultaneously address conservation.

The need for economic incentives to spur antimicrobial product development innovation and conservation is not new, as these concepts have been increasingly discussed over the last 3–4 years. Several high-profile panels and working groups in both the European Union and United States have made recommendations to drive policy reform [2–7]. In January 2016, >80 companies from 16 countries as part of the World Economic Forum, in Davos, Switzerland, published a declaration on combating antimicrobial resistance [8]. The group acknowledged

Received 14 June 2016; accepted 10 August 2016; published online 30 August 2016.

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Clinical Infectious Diseases® 2016;63(11):1470–4

DOI: 10.1093/cid/ciw593

their commitment to the mission and in working with multiple governments. The declaration supports many of the initiatives described below including the O'Neill Review [6], the G7 declaration [4], and those from a number of government and international organizations.

Several coordinated groups have specifically been established to improve the global response to AMR. The Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR) was established in 2009 to improve cooperation between the United States and the European Union, and recently with Canada and Norway, in 3 key areas: (1) appropriate use of antimicrobial drugs in medical and veterinary communities; (2) prevention of healthcare and community-associated drug-resistant infections; and (3) strategies for improving the pipeline of new antimicrobial drugs. In October 2015, TATFAR agreed it would identify economic incentives for development and provide recommendations for further consideration.

This article summarizes the initial economic incentives that were identified through the analysis of several policy documents, peer-reviewed publications, organization proposals, and government-sponsored reviews. Ultimately, TATFAR will make an informed recommendation on a package of incentives that could be considered for implementation.

SUMMARY AND POLICY ANALYSIS

A total of 12 publications were analyzed and are listed in Table 1 [2–13]. All reports support the need for economic incentives to address AMR and nearly all reports agreed that a combination of globally coordinated push and pull incentives will be necessary. Of those reports that specifically analyzed various types of economic incentives, de-linkage models were recommended overwhelmingly. While variations on how de-linkage models would be administered exist, the general principle of using a substantial payment that rewards successful research and development as a pull incentive is conserved. Generally, these authors agree to 3 main areas of consensus. These include:

1. A global AMR threat assessment process to coordinate data on resistant pathogens, the public health threat, and effectiveness of existing antibiotics should be developed. This process should consider additional criteria to guide prioritization for which new antibacterial drugs receive a particular set of incentives.
2. A constellation of economic incentives comprised of both push and pull mechanisms that addresses all phases of antibacterial drug development is needed to effectively incentivize industry.
3. Models that fully or partially de-link profit from volume sold should be developed, implemented, and evaluated. Initially, these should be initiated by a core group of countries capable of obtaining funding. Over time, models that account for conservation and access should be developed and could be governed by a collective mechanism.

PUSH INCENTIVES

Push incentives were unanimously proposed to help fund the early development pipeline. Advantages include the ability to diversify the portfolio, manage risk, incentivize early participation by industry, direct funding to specific pathogens of interest, and target innovative approaches and defined target product profiles. As an example, push incentives have been implemented by the US National Institutes of Health, the Biomedical Advanced Research and Development Authority, the European Commission, the Innovative Medicines Initiative New Drugs for Bad Bugs program, and the Joint Programming Initiative on Antimicrobial Resistance, to name a few. Open funding for investigator-initiated AMR basic research will promote innovation that might not be considered through targeted initiatives. Several reports called for the establishment of global funds

Table 1. Summary of the Incentives and Actions Recommended to Improve Antimicrobial Drug Research and Development

Report	Push Incentives	Pull Incentives	De-linkage	Global Threat Assessment	Global Funder
BEAM Alliance [10]	Yes	Yes	Yes	NC	Yes
BCG report for G7 [4]	Yes	Yes	Yes	Yes	Yes
Carlet and LeCoz 2015 [11]	Yes	Yes	NC	NC	Yes
Chatham House Report [2]	Yes	Yes	Yes	Yes	Yes
DNDi GARD PDP [8]	Yes	Yes	Yes	Yes	Yes
EU Plan 2011–2015 [3]	Yes	Yes	NC	Yes	NC
IMI ND4BB: DRIVE AB [14]	Yes	Yes	Yes	Yes	Yes
Jackson CSIS 2016 [12]	Yes	Yes	Yes	NC	Maybe
OECD [5]	Yes	Yes	Yes	Yes	Yes
O'Neill Review [6]	Yes	Yes	Yes	Yes	Yes
PCAST Working Group [7]	Yes	Yes	Yes	Yes	NC
Renwick et al, 2015 [13]	Yes	Yes	Yes	NC	NC

The categorization of "NC" (not considered) does not imply that the report explicitly did not recommend the incentive or policy. In all instances, the report omitted recommending the incentive or policy.

Abbreviations: BCG, Boston Consulting Group; CSIS, Center for Strategic and International Studies; DNDi, Drugs for Neglected Diseases Initiative; EU, European Union; GARD, Global Antibiotic Research and Development Partnership; IMI, Innovative Medicines Initiative; OECD, Organization for Economic Co-operation and Development; PCAST, President's Council of Advisors on Science and Technology; PDP, product development partnership.

to support antibacterial research and development [2–6] or supported use of tax credits [2, 10, 11]. However, tax credits that could incentivize both early- and late-stage development could only be administered by the individual host nation and therefore is not a global responsibility.

PULL INCENTIVES

Pull incentives were also uniformly recommended to enable direct support for products and could be targeted to address unmet needs or priorities. Advantages include rewarding only successful antibiotic candidates or targeting specific research, and could be utilized to impact conservation. Although providing a known ROI, the funding provided may be too late for some developers and therefore will not incentivize early research. It is also difficult to ascertain optimal reward pricing, and all risk remains with the developer.

Tradeable vouchers could be received after bringing a new antibiotic to market and then used to extend the patent life of another unrelated drug or sold to a third party. While highly supported by industry due to profit potential by either selling the voucher or controlling market price on a highly valued drug for a longer period, the profit increase is smaller than the costs incurred by society for higher drug prices in other therapeutic areas [6]. A greater number of patients will pay higher prices for the drug for which the patent was extended vs the new antibiotic that will be held in reserve for the treatment of resistant infections, and therefore access may be limited. Another challenge with vouchers is that their implementation will need to be determined on a per-country basis. A less indirect use of such vouchers could be for a country to auction them, thereby creating a revenue-generating mechanism.

Alternatively, extensions of market exclusivity for an antibiotic developed (and not traded) may not incentivize early development, as the Chatham House Report states [2]. Resistance to the antibiotic could arise during this period of additional market exclusivity, and would lead to reduced sales, limiting the utility of this incentive. Furthermore, excessive promotion during this period could also lead to inappropriate use.

Higher reimbursement/pricing is attractive to industry, but there may be unknown secondary disruptive effects and it still may not be sufficient to generate an adequate ROI. Higher pricing could impact patient access to expensive antibacterial drugs, and cheaper, less effective drugs may be utilized instead. A targeted indication for a high-value antibacterial drug may also limit use and constrain the manufacturer from keeping a warm base for continued supply; if the antibiotic is needed, it may not be available. The US healthcare system currently subsidizes the global pharmaceutical market as a function of its healthcare system. Unless increased pricing were adopted globally, higher pricing will disproportionately affect the United States.

DE-LINKAGE MODELS

Pull incentives relying on de-linkage may have the lowest probability of secondary disruptive effects but require sustained funding to provide developers confidence in its reliability. De-linkage models combine 3 critical components: (1) provide developers with a known ROI; (2) remove the motivation for developers to market and oversell the antibiotic; and (3) allow access to patients who need antibiotics. The January 2016 Declaration by pharmaceutical and biotechnology companies supports measures that would reduce the current link of financial revenue gain with use of antibiotics [9]. Jackson highlighted a recommendation for the United States to examine the feasibility of a de-linkage model for combating AMR in the future [12]. In considering either national or global action, the characteristics of a particular de-linkage model will need clarification prior to implementation. Under a full de-linkage model, payment is provided at the point of regulatory approval, but could also be divided into smaller milestone rewards. The company continues to produce the drug, but agrees not to market or endorse the use of the product. Global governance will be needed to coordinate access and conservation of the antibiotic. Under a partial or hybrid de-linkage model, companies would continue to be allowed to sell their product. There would be a series of payments administered over several years (eg, 3–5 years) and could cap the total amount of product that could be sold annually. Overall, the payments should allow for restrictions on marketing and promotion.

Both full and partial/hybrid de-linkage models require significant amounts of funding to be impactful and sustainable.

With full de-linkage, the company would not promote, market, or sell its antibiotic, thus directly ensuring a level of conservation, preventing the potential for unnecessary use. In addition, due to the guaranteed revenue with a defined market, a warm base manufacturing level can be maintained even if the volume use is low. However, if payment is given at the time of approval, it may not be possible to determine the drug's effectiveness compared to the current standard of care as the drug would likely be approved based upon noninferiority data. With antibiotic drug development, there are substantial challenges in being able to conduct postmarketing comparative effectiveness studies due to the prevalence of resistant pathogens. To inform clinical use, descriptive efficacy studies against resistant pathogens should be conducted. However, under a partial de-linkage model, one could structure the payments over time and could attach them to milestones to receive the payment, such as studies that inform clinical use against resistant pathogens, complying with restriction on marketing or promotion, and agreeing to the total amount of drug that could be sold or produced annually. Partial de-linkage payments could be more politically and financially feasible to implement.

However, other incentives that reward all antibiotic developers may be needed as de-linkage would likely be a targeted

incentive that may limit focus on addressing public health priorities. For example, a refundable and transferrable tax credit that covers 50% of the phase 2/3 clinical development costs could be utilized. This tax credit, paid at regulatory approval, could serve as an effective pull incentive that would not require funding to implement. Overall, multiple incentives will be needed through all phases of antibacterial drug development.

CONSERVATION AND STEWARDSHIP

Many push and pull incentives will have direct or indirect impacts on antibiotic conservation and reducing the spread of resistance. The BEAM Alliance (Biopharmaceutical companies from Europe innovating in Anti-Microbial resistance research) wants regulators and stakeholders to consider strategies in novel therapeutic development and economic incentives that address the threat of antimicrobial resistance [10]. The January 2016 industry declaration supports enhancing conservation through appropriate stewardship programs, and removing financial incentives for prescribers to prevent misuse [9]. The full de-linkage model would control the amount of antibiotic entering the market, ensuring elements of conservation and stewardship as well as the hybrid de-linkage model where lump sum payments could link to stewardship [6]. Example milestone payments could include agreeing not to market the antibiotic, conducting an educational campaign for clinicians to inform appropriate use, or limiting the volume that is produced. Another example is taxation on human antimicrobial use, with a variable fee per antibiotic utilized, but a rate, equal to the societal cost of the antibiotic would need to be determined. The President's Council of Advisors on Science and Technology report [7] proposed a tax on antibiotic use to generate revenue to sustainably support incentive packages, but taxes could further increase healthcare costs and limit patient access. If structured appropriately, and targeted toward generic antibiotics used in the outpatient setting, taxes could limit inappropriate use and generate revenue to support these incentives.

GLOBAL COORDINATION

Many reports highlight the need for global coordination to administer the funding of various incentive packages. This is supported by the recent industry declarations for a global coordinated action [8]. Sustainment will be achievable through policy and leadership, defined priorities, financing, and working across international boundaries for effective coordination and cooperation [12]. The Chatham House Report recommends the establishment of a secretariat to administer a global de-linkage model and coordinate expenditures on behalf of the participating countries [2]. The O'Neill Review recommended a global innovation fund as well as a global purchaser [6]. Such a governance group would need to possess product development expertise, prioritize research and development initiatives, and manage development programs with strong decision points. The level of coordination among all countries to make a global fund function effectively may be challenging to achieve, and it is unclear what organization, whether existing or otherwise, could assume the role of a global purchaser. It may be more prudent to initiate de-linkage/funding models with a smaller subset of countries/markets initially to ensure that incentives are established in the near term.

In addition to funding coordination on a global scale, such international coordination could also promote and guide antibiotic development. The Chatham House Report strongly recommended the development of a global threat assessment to prioritize which antibiotics would qualify for potential pull incentives or de-linkage approaches [2]. They contend that the process needs to involve global stakeholders and needs to be transparent to the public to allow for coordinated investment and alignment of incentives that could generate maximal returns toward public health goals. The Organization for Economic Co-operation and Development report promotes a global collaborative platform to drive innovation [5]. The Boston Consulting Group supported global coordination through antibiotic clinical trials, alignment of regulatory approvals, and development of global target profiles [4]. Although global coordination could align pharmaceutical companies with a unified single strategy for global development and marketing, it may be challenging for such a group to accurately predict investment areas and priorities due to the changing landscape of antibiotic resistance. A diverse set of approaches and ideas may be the best approach to ensure a long-term vision of priority and coordination and to allow flexibility for antibiotic development. However, alignment of regulatory incentives among different regulatory authorities may be challenging.

Antimicrobial resistance requires a global response and a broad global organizational effort to propose and implement incentive plans. Although successfully demonstrated with funding alliances for other global infectious diseases (tuberculosis, malaria, HIV/AIDS, etc), there may be specific regulatory, political, or financial constraints within each country that may limit implementation of specific incentive approaches for antimicrobials. Global coordination will require further discussion and coordination before implementation.

CONCLUSIONS

Overall, there is consensus from the reports examined that a constellation of economic incentives is needed to support all phases of antibacterial drug development. Based on the strengths and weaknesses with push, pull, de-linkage, and conservation incentives, a mixture of various incentives may be necessary to broadly address antibiotic research and development. The incentive package should be applicable to academics and multiple companies, including small, medium, and large enterprises. Multiple push incentives addressing both early-

stage and advanced research and development are needed. It is thought that payments earlier in the product life cycle could have a stronger impact on the net present value, but risk of failure is higher. These could be administered through grants, contracts, product development partnerships, and/or tax credits. In addition, to balance the antibiotic development cycle, an internationally coordinated pull incentive, such as a form of a de-linkage model, may be needed where successful antibiotic development is prioritized to address unmet medical needs and subsequently rewarded to ensure an adequate ROI. A reliable ROI is critical. The recent pharmaceutical industry declaration exemplifies a growing consensus among these concepts. Refinement is needed to determine which incentive and associated characteristics will work best. How these incentives will be adapted, implemented, and funded will need further engagement by different governments (European Union, individual countries) to assess feasibility. Although there is general consensus on the need for future coordination at the global level on priorities and coordination of research and development activities, initial broad country alignment within these key incentive areas will improve the effectiveness and complementarity of funding, hopefully resulting in greater global impacts toward public health and conservation.

Notes

Acknowledgments. The authors recognize the support of all TATFAR members in preparing this manuscript for publication.

Disclaimer. The information and views presented in this article are those of the authors and do not necessarily reflect those of the European Commission or the governments of the United States of America, Canada, and Norway (ie, governments of TATFAR member countries).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Sharma P, Towes A. New drugs to tackle antimicrobial resistance: analysis of EU policy options, Office of Health Economics, **2011**. Available at: https://www.ohe.org/publications/new-drugs-tackle-antimicrobial-resistance-analysis-eu-policy-options. Accessed 2 May 2016.
2. Chatham House Report. Towards a new global business model for antibiotics delinking revenues from sales. Clift C, Gopinathan U, Morel C, Outterson K, Rottingen J-A, So A, eds, **2015**. Available at: https://www.chathamhouse.org/publication/towards-new-global-business-model-antibiotics-delinking-revenues-sales. Accessed 2 May 2016.
3. European Commission. Action plan against the rising threats from antimicrobial resistance, **2011**. Available at: http://ec.europa.eu/dgs/health_food-safety/docs/communication_amr_2011_748_en.pdf. Accessed 2 May 2016.
4. German Federal Ministry of Health. Breaking through the wall: enhancing research and development of antibiotics in science and industry, **2015**. Available at: https://www.bundesgesundheitsministerium.de/fileadmin/dateien/Downloads/G/G7-Ges.Minister_2015/Qualitaetswettbewerb_Gesundheitssystem_Whitepaper_2015-10-02.pdf. Accessed 2 May 2016.
5. Organization of Economic Co-operation and Development. Antimicrobial resistance in G7 countries and beyond: economic issues, policies, and options for action, **2015**. Available at: http://www.oecd.org/els/health-systems/antimicrobial-resistance.htm. Accessed 2 May 2016.
6. Review on Antimicrobial Resistance (chaired by Jim O'Neill). Available at: http://amr-review.org/Publications. Accessed 2 May 2016.
7. White House President's Council of Advisors on Science and Technology (PCAST). Report to the president on combating antibiotic resistance. Available at: https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf. Accessed 2 May 2016.
8. World Health Organization. Global action plan on antimicrobial resistance and Drugs for Neglected Diseases Initiatives (DNDi) investing in the development of new antibiotics and their conservation, **2015**. Available at: http://www.who.int/phi/implementation/GlobalAntibioticRD_Facility_13Nov2015_MeetingReport.pdf?ua=1. Accessed 2 May 2016.
9. Review on Antimicrobial Resistance. Declaration by the pharmaceutical, biotechnology and diagnostics industries on combating antimicrobial resistance, **2016**. Available at: http://amr-review.org/file/351. Accessed 2 May 2016.
10. BEAM Alliance. Position paper: key actions to reinvigorate investment and R&D in the antibacterial field now, **2015**. Available at: http://beam-alliance.eu/assets/2015-Position-Paper.pdf. Accessed 2 May 2016.
11. Carlet J, Le Coz P. Report from the Special Working Group for Keeping Antibiotics Effective. A report for the French Health Minister, **2015**. Available at: http://social-sante.gouv.fr/IMG/pdf/rapport_antibiotiques.pdf. Accessed 2 May 2016.
12. Jackson A. Combating antimicrobial resistance in 2015: back to the future and beyond. Washington, DC: Center for Strategic and International Studies, **2016**.
13. Renwick MJ, Brogan DM, Mossialos E. A systemic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. J Antibiot **2015**; 69:73–88.
14. Innovative Medicines Initiative. Available at: http://drive-ab.eu/. Accessed June 2016.