
The Global Innovation Model for Antibiotics Needs Reinvention

Manica Balasegaram, Charles Clift, and John-Arne Røttingen

Introduction

The dangers presented by antibiotic resistance (ABR) have now established themselves as a global health security issue. From an international policy perspective, three key pillars have been established: responsible access, conservation, and innovation. These pillars are intrinsically linked, meaning that any attempt to address one must take into account the implications for the other two.

An urgent need exists to address the innovation failure in ABR. In the field of anti-bacterials, the pipeline remains anemic in terms of therapeutics with novel mechanisms of action, new drug classes and strategies involving radically different, innovative approaches.¹ The key reasons for this failure have already been well established.² The slow development of new antibiotics is the result of a poor and uncertain commercial market and scientific challenges in research and development (R&D). If strong responsible use and conservation strategies are put into place, this further undermines the R&D incentive that derives from market value. The response from policymakers, states, and regions has been to introduce various economic and incentive strategies, such as the Innovative Medicines Initiative's (IMI) New Drugs for Bad Bugs program in the E.U. and the U.S. Generating Antibiotic Incentives Now Act (GAIN)³ and regulatory simplification to facilitate

new drug development.⁴ However, it is unclear if new regulatory pathways or extended periods of exclusivity will help overcome upstream scientific challenges, ensure the development of antibiotics serving global public health needs, and promote access together with conservation.

A multiplicity of publications, commissions, and reports has investigated this issue highlighting major problem areas and possible solutions. The concept of delinkage has been proposed to develop new business models to promote innovation into new antibiotics.² Delinkage would mean breaking the link between reward for R&D and innovation on the one hand and revenues (price and volume) of sales of an innovative product on the other. The concept is relevant in that it removes perverse incentives on the innovator (and others in the value chain) to increase utilization of a new antibiotic above levels defined by public health needs.

It is worth noting that the World Health Organization (WHO) Consultative Expert Working Group on Research and Development (CEWG)⁵ saw the concept of delinkage as a guiding principle for alternative and credible business models for biomedical innovation, and the concept has been supported in the WHO as well as by several business stakeholders. Furthermore, the CEWG also saw multiple combined strategies such as an open approach to R&D (including pre-competitive R&D platforms, open source and open access schemes), prizes (e.g., milestone prizes), equitable licensing, and patent pools as practical means to promote innovation through delinkage.

There is now a need to move beyond concepts, recognizing that current initiatives are as yet insufficient to address needs. This paper proposes to look at three key and interrelated steps that may help in moving

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There is now a need to move beyond concepts, recognizing that current initiatives are as yet insufficient to address needs. This paper proposes to look at three key and interrelated steps that may help in moving towards an alternative business model for antibiotic innovation that will promote needs-driven R&D while securing responsible access. The justification for a legal framework will be explored as a key enabler. Additionally, the need to go beyond a legal framework in order to implement an alternative business model will also be discussed.

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Key Principles towards a Successful Business Model for ABR

Drawing from the extensive work undertaken over the last several years, key principles can be derived that would underpin an improved and creative business model for ABR:

- First and foremost, there needs to be a clear reflection of an increased societal willingness to invest in the development of new antibiotics.
- Any alternative business model should be based on incentives that promote responsible use, as well as access and conservation. This also requires new, suitable, financial push-and-pull mechanisms to reward innovators. Delinkage using a variety of combined strategies may provide a platform for such an alternative model.
- Based on the needs, gaps and public health importance of the issue, adequate, sustainable and long-term financing must be mobilized.
- Such financing will largely need to come from the public sector and the antibiotics developed will need to be seen as global public goods.⁶
- As ABR is a truly global problem, innovation must transcend just local and regional perspectives; this begins with defining public health needs (e.g., through global threat assessments and then the creation of target product profiles or TPPs), but also continues into financial and regulatory incentives and mechanisms.
- Control and conservation mechanisms in the “antibiotic market” need to be defined at a global level, but adapted and adhered to nationally by governments, manufacturers, and distributors.

Linking incentives and rewards to conservation mechanisms may be useful.

- Monitoring, coordinating, and prioritizing R&D funding and activities will be important to ensure limited public resources can achieve maximal impact.
- While maintaining the need to harness the strength of the private sector, cooperation, knowledge sharing, and regulated use will be essential throughout the product development and marketing life cycle.

Looking at Alternative Models

A recent Big Innovation Centre/Chatham House publication and an upcoming Working Group report on business models for antibiotic innovation have already elucidated potential business models, including using examples specifically applied in other industries.⁷ These include insurance schemes, long-term service provision contracts, a corporate bond model, a value-based sales model, and a delinked payment regime to fund R&D allowing the final product to be made available at marginal cost.⁸

Recommendations have also been made for incentives that could be useful in the field of antibiotic innovation. In practice, some of these incentives proposed have already been piloted. These include traditional large-scale grants, milestone payments (notably by BARDA in the US), prizes (e.g., the recently introduced Longitude Prize) and advance marketing commitments (as used for the pneumococcal vaccine).⁹

The challenge in all of these policy proposals and models to date is how to move beyond a piecemeal series of national and international actions to a truly coordinated global response. Such a response should also seek to ensure that it would not compromise the conservation of, and responsible access to, future antibiotics, nor undermine access and innovation in other key public health areas – for instance by creating incentives (such as extended exclusivity) that actually require increased sales of antibiotics in order to generate revenue. Efforts should be focused on pro-

posals that come closest to delinkage of both R&D as well as the production/supply of antibiotics. For example, according to the Big Innovation Centre/Chatham House report, a viable business model could be a hybrid between a service provision contract – similar to what is currently being used in several industries – and an upfront revenue system as used, for instance, in academic publishing. In reality this may translate into contractual grants and milestone payments with clear clauses on timelines, transfer or sharing of IP rights, product supply, and marketing.

Another key issue to consider is who would be the paying customer. Rather than being a broad network of individuals within a health insurance system or a state, it would ideally be all countries or health systems that would potentially use the products developed. So, for example, a network of countries and funders could therefore come together to develop service-based contracts, prize payments and fixed, advance market commitments for a series of antibiotic R&D needs, possibly specified through TPPs developed.

Operationalizing a New Business Model

It should be feasible to consider an adapted business model using a combination of the proposals and incentives above in an international framework, capable of implementation through existing entities. There are three key elements in moving towards a new business model: (1) a global, potentially legal, framework; (2) an antibiotic R&D innovation fund; and (3) a global institutional mechanism for ABR.

A Global Framework

Both a global framework for R&D and an international framework have already been proposed. The CEWG report recommended a global framework for R&D, taking particular account of the health needs of developing countries. To date, a Global R&D Observatory with monitoring and coordination functions, as well as a voluntary pooled R&D fund for demonstration projects on neglected tropical diseases are being created.¹⁰ The WHO Executive Board also endorsed looking into longer-term needs.

In relation to resistance, there is also a proposal for a binding international legal framework via a WHO regulation or a UN general assembly treaty to encompass access, conservation and innovation.¹¹ Both legal mechanisms are viable and not mutually exclusive options. Considering the wider innovation needs,

it would nonetheless be useful to develop an R&D framework concerning key public health areas, notably infectious diseases, where market failure exists. Ideally, a framework would need to cover a few important aspects, including guaranteeing access through licensing or other means, securing conservation through stronger internationally agreed regulatory and trade instruments, and pooling and coordinating incentives for innovation that are conditional on the two first criteria. The ability to develop such a framework depends on how discussions between Member States advance at WHO during 2015. Following the events around the Ebola outbreak in 2014 and international recognition for the need to deal proactively with public health issues affecting health security, a clear opportunity exists to advance the agenda around antibiotic innovation and ABR in general.

It is important to see the legal framework as the glue that enables the subsequent measures to work. This cannot be underestimated because there are multiple objectives (access, conservation, innovation) that must be simultaneously addressed, and the efforts required need international collaboration with a long-term perspective. Short-term individual donor depen-

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dent initiatives will lack staying power and broader legitimacy.

An international regulatory platform where production, trade, sales, and utilization of antibiotics can be more tightly governed may be best achieved by utilizing international law, which can serve as a blueprint for national legislation and policies. However, more restrictive regulations can only work equitably if they are combined with mechanisms that both foster both access and ensure innovation.

Developing a legal framework combining these three objectives may result in a negotiation process

where benefits and disadvantages across the three areas may be properly balanced so that all constituencies may perceive sufficient net long-term advantages out of a bargaining process which would necessarily involve short-term losses for some participants. It will also be necessary to consider sufficient enforcement processes, which in the end may also need to be linked and balanced against economic interests as in trade agreements.

An Antibiotic R&D Innovation Fund

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The fund should be a vehicle for monitoring research flows, setting priorities, coordinating with other funding actors, and setting strategy. The global observatory being established in WHO could be further developed for such a purpose.¹²

Funding must largely come from the public purse with the aim of delivering global public goods in the context of a long-term global investment perspective for health security and public health. The size of such a pooled fund would need to be sufficient to ensure sufficient strength and ability to coordinate with different funding streams. A recent call by Jim O'Neill, Chair of the U.K. government's review on antimicrobial resistance, mentioned the need to create a US\$2 billion innovation fund.¹³ Such a figure would be consistent with both the CEWG report and Lancet Commission for Investing in Health.¹⁴ The U.S. government has called for an additional US\$800 million in BARDA funding to support clinical development of antibiotics.¹⁵

As noted above, the fund should support models in which the cost and reward for R&D is delinked from sales and supply by creating a separate competitive innovation market using the range of incentives already discussed. It would need to be decided which existing institution could best host such a fund, or whether a new, dedicated institution is required. Currently, a fund has been established in WHO's Special Programme for Research and Training in Tropical Diseases (TDR) to support demonstration R&D projects for diseases that particularly impact developing countries.

A Global Institutional Mechanism for ABR

A third key element of a global response would be a global institutional mechanism for ABR, to promote and accelerate the evolution of the antibiotic business model as well as to promote improved surveillance, infection control and responsible use. The entity will be directly related to and supported by the R&D fund, which in turn would be empowered by a framework. In other words, a treaty will facilitate or create a fund, which will then financially support a new, more operational entity.

Part of developing forward-looking responsible access and conservation strategies for new antibiotics will be to consider models to set up an "antibiotic drug facility" that could already focus on existing priority antibiotics. Close collaboration with global experts, WHO and relevant global health actors, such as the Global Fund to Fight AIDs, Tuberculosis and Malaria, will be key, including in areas such as quality standardization and assurance, procurement, pharmacovigilance, and implementing/monitoring rationale use schemes. In addition, responsible licensing standards between originator and generic companies could be applied to also promote responsible access. It has been suggested that the Medicines Patent Pool could play a role in this area.

The entity would play key roles including promoting R&D into antibiotics, developing and assisting states and regions in implementing conservation strategies for new antibiotics, and implement the disbursements of "delinked funds" for R&D employing an alternative business model armed with a range of different incentive mechanisms. For instance, this could include substantive grants, milestone and end stage prizes with clear access and conservation clauses, patent pooling and buyouts. While the initiative would not aim to be the sole source of antibiotic funding, it would be differentiated from other funders and especially other global health entities because it would fill key roles across access, conservation and R&D for innovation.

Key tasks for the entity might include:

- Financing R&D for products that are reserved for human use; possibly also financing alternative product lines that can then be reserved for veterinary/animal husbandry use.
- Developing global public health-orientated TPPs and a portfolio of projects (e.g., of products in development) by using a variety of new innovative financing instruments, including loans, grants, prizes, and collaborative research models to de-link the costs of R&D from the price of the product.

- Creating an international network of public and private entities from countries (e.g., companies, academic research institutes, not for profit product development partnerships) from all income levels engaged in research for new antibiotic agents.
- Taking measures to ensure any new products developed are used responsibly on a global level while also focusing on access programs for those most in need.
- Promotion of surveillance and laboratory capacities.

Conclusion

The reformation of the innovation business model is necessary in order to develop the next generation of antibiotics. The necessary reforms are feasible. However antibiotics need to be considered as global public goods and funding and conservation strategies largely need to come from public interventions. Reform of the innovation model can be enabled through three steps requiring national and international intervention: a legal framework (such as a WHO regulation), creation of an international, long-term pooled antibiotic innovation R&D fund, and establishment of an institution to carry this work forward. Such an idea has been proposed and endorsed by other reports.¹⁶ Each can be done concurrently; practically a well-set up initiative may even assist in the solid foundation of the other two aspects. Indeed, WHO and other entities have practically discussed these issues in recent months.¹⁷ It is essential now that countries seriously consider collectively supporting and funding such proposals in order to deal with the growing threat of ABR.

References

1. M. S. Butler, M. A. Blaskovich, and M. A. Cooper, "Antibiotics in the Clinical Pipeline in 2013," *Journal of Antibiotics* 66 (2013): 571-599.
2. K. Outterson, *New Business Models for Sustainable Antibiotics* (Chatham House, London: Royal Institute of International Affairs, 2014).
3. K. Outterson, J. H. Powers, G. W. Daniel, and M. B. McClellan, "Repairing the Broken Market for Antibiotic Innovation," *Health Affairs* 34, no. 2 (2015): 277-285.
4. Report on the event, "Best Use of Medicines Legislation to Bring New Antibiotics to Patients and Combat the Resistance Problem," European Medicines Agency, London, November 2013, available at <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/12/WC500158230.pdf> (last visited May 14, 2015).
5. World Health Organization, *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination*, Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (2012), available at <http://www.who.int/phi/CEWG_Report_5_April_2012.pdf?ua=1> (last visited May 14, 2015).
6. A. Hollis and P. Maybarduk, "Antibiotic Resistance Is a Tragedy of the Commons That Necessitates Global Cooperation," *Journal of Law, Medicine & Ethics* 43, no. 2 (2015): available via asmlme.org.
7. E. Jaczynska, K. Outterson, and J. Mestre-Farrandiz, *Business Model Options for Antibiotics: Learning from Other Industries* (Big Innovation Centre/Chatham House, London: Royal Institute of International Affairs, 2015); Chatham House Working Group, *New Antibiotic Business Model* (Chatham House, London: Royal Institute of International Affairs, 2015).
8. See Hollis, *supra* note 6.
9. Longitude Prize, available at <<https://longitudeprize.org/>> (last visited May 14, 2015); Gavi, "Pneumococcal AMC," available at <<http://www.gavi.org/funding/pneumococcal-amc/>> (last visited May 14, 2015).
10. Follow-up of the report on the Consultative Expert Working Group on Research and Development: Financing and Coordination, available at <http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_28Add1-en.pdf> (last visited May 14, 2015).
11. S. J. Hoffmann, K. Outterson, J. A. Rottingen, O. Cars, C. Clift, Z. Rizvi, F. Rotberg, G. Tomson, and A. Zorset, "An International Legal Framework to Address Antimicrobial Resistance," *Bulletin of the World Health Organization* (2015): 93/2/15-152710.
12. J. A. Rottingen, S. Regmi, M. Eide, A. J. Young, R. F. Viergever, C. Årdal, J. Guzman, D. Edwards, S. A. Matlin, and R. F. Terry, "Mapping Available Health R&D Data: What's There, What's Missing and What Role for a Global Observatory," *The Lancet* 382, no. 9900 (2013): 1286-1307.
13. K. Grogan, "AMR Review Head O'Neill Calls for \$2 Billion Innovation Fund," *Pharma Times*, available at <http://www.pharmatimes.com/Article/15-02-27/AMR_review_head_O'Neill_calls_for_2_billion_innovation_fund.aspx> (last visited May 14, 2015).
14. D. T. Jamison, L. H. Summers, and G. Alleyne et al., "Global Health 2035: A World Converging within a Generation," *The Lancet* 382, no. 9908 (2013): 1898-1955.
15. President's Council of Advisors on Science & Technology, Report to the President on Combating Antibiotic-Resistant Bacteria (September 2014) at 3, available at <https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf> (last visited May 14, 2015).
16. See WHO, *supra* note 5; Holli, *supra* note 6; Jaczynska et al., *supra* note 7.
17. World Health Organization, "Innovation for Antibiotics Development and Preservation," available at <http://www.who.int/phi/implementation/consultation_imnadrp/en/> (last visited May 14, 2015).