INTRODUCTION
Stimulating Research and Development of New Antibiotics While Ensuring Sustainable Use and Access: Further Insights from the DRIVE-AB Project and Others

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Background

Antimicrobial resistance (AMR) is a recognized global public health threat.[1] In recent years, global awareness has increased considerably to elevate AMR onto the international political agenda and call for action.[2] One of the tools to fight AMR is safe and effective antibiotics to treat infections caused by resistant bacteria. However, antibiotics research and development (R&D) has been insufficient in the last 20 years, due to significant scientific, regulatory, and economic hurdles.[3]

The research project DRIVE-AB was funded by the Innovative Medicine Initiative (IMI), the largest European public-private partnership in healthcare.[4] DRIVE-AB's aims were to develop and cost new economic models that would promote innovation as well as sustainable use of antibiotics. The project's vision was to "transform the way policymakers stimulate innovation, sustainable use and equitable availability of novel antibiotics to meet public health needs."[5] Sixteen public and seven private partners worked three years to reach this goal. One of DRIVE-AB's research work streams aimed to create and test new economic models. As presented in the DRIVE-AB final report, four complementary approaches, each able to stimulate specific phases of the R&D process, were selected as strategies to stimulate innovation while ensuring sustainable use and access of innovative antibiotics. Those were grants, pipeline coordinators, market entry rewards (MER) and a long-term supply continuity model.[6]

In this Symposium issue, funded by DRIVE-AB, we present several supporting studies conducted fully or partly within the DRIVE-AB project, which are either directly related to one of the selected DRIVE-AB incentives, or are part of a broader analysis. These articles are part of the research that was performed within the economic incentive work stream of DRIVE-AB. Several other articles are or will be published elsewhere. We welcome as well in this Symposium a contribution from colleagues at the Duke-Margolis Center for Health Policy, who are also actively working on this topic.

Further Insight into the DRIVE-AB Recommended Push Incentives

"Push" incentives directly support R&D, while "pull" incentives are intended to reward successful R&D outcomes. The first two articles in this Symposium feature the detailed research that supports the two DRIVE-AB recommended push incentives. First, Savic and Årdal[7] assess ongoing global grant funding mechanisms. Based on the gaps of these current initiatives, the authors propose a detailed framework of grants aiming to cover and stimulate the entire process — from basic research on AMR to clinical development of new antibiotic drugs — while also addressing specific antibiotic R&D bottlenecks. Next, Baraldi et al.[8] define the concept and role of antibiotic "pipeline coordinators" which are governmental/non-profit organization(s) that closely track the antibacterial pipeline and actively support R&D for indications and pathogens that are less attractive to the private sector.

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Such organizations could play a key role in ensuring a comprehensive and diverse pipeline. The authors analyze which organizations are currently assuming this role and describe which financial funding tools they could employ.

Pull Incentives: How Would Successful Antibiotic Innovation Be Rewarded

A market entry reward (MER) is the main pull incentive recommended by DRIVE-AB. Details on the different design features (MER type, amount, etc.) that this incentive would include are in the final report.[9] One of the key characteristics of a MER is whether it should be fully delinked (the reward fully replaces unit sales of the drug) or partially delinked (the reward is provided in addition to unit sales, and can be sales-adjusted to a maximum amount or not). Looking at both fully and partially delinked MER, Okhravi et al.[10] present in detail the agent-based model developed within DRIVE-AB to assess the impact that different reward amounts would have on the likelihood of innovative antibiotics reaching the market. In other words, what MER amount could bring public funders and patients the best value for money (or the most new antibiotics meeting unmet public health needs at the lowest investment cost). This model takes into account all key parameters of the antibiotic R&D ecosystem (for example, financial parameters used by private sector actors for investments, R&D failure rates, etc.). It confirms that an MER would stimulate antibiotic R&D and shows how different reward amounts (up to $3 billion USD) may affect productivity of the pipeline.

An MER to date is a theoretical concept in the field of antibiotic R&D, untested by any country. Therefore, any efforts to implement the model would add valuable operational knowledge. Årdal et al.[11] share the experience of a cross-section of Norwegian health agencies designing a delinked antibiotic incentive suitable for national context, including the Norwegian legal framework, market size, health system, and AMR situation. Their conclusion is that in Norway a partially delinked model fulfills the aims with the least disruptive impact.

Daniel et al. have performed a similar exercise, but looked at the much larger US market.[12] Building on a type of MER they have designed, called the Priority Antimicrobial Value and Entry (PAVE) Award,[13] they comment on the potential implementation within the US healthcare system, including financing mechanisms.

Next, Bhatti et al.[14] present a viewpoint on pull incentives in which they discuss a need for multiple pull incentives, which would stimulate development of different types of antibiotics. This would also create flexibility to take into account the different implementation challenges created by the global diversity in health systems. In this view and as an example, Lum et al.[15] present another pull incentive called the diagnosis confirmation model (DCM), which incorporates value-based pricing and could be implemented for new antibiotics addressing hospital-acquired resistant infections in markets of high-income countries.

There is no simple solution to the challenge of stimulating antibiotic innovation and any implemented measure will likely not fully demonstrate results for 10-20 years — the duration of bringing an antibiotic through the R&D process from discovery to approval. Yet, now is the time for all stakeholders to come to a consensus or at least to act together in a coordinated fashion and start piloting and testing different solutions. Only through these pilots can significant new knowledge be gained about the effectiveness of different models.

Sustainable Use Conditions for DRIVE-AB Recommended Incentives

Sustainable use of antibiotics refers to "the implementation of measures targeting a range of actors to ensure the long-term effectiveness of a specific, novel antibiotic or an antibiotic class."[16] Sustainable use obligations must accompany any publicly-funded incentive in order to maximize the benefits of these investments for patients and society. A set of such measures is proposed in the report.[17] In this supplement, Morel and Edwards[18] comment on how the different incentives selected by DRIVE-AB impact the sustainable use of new antibiotics and present a range of sustainable use obligations that could be placed on both countries and drug developers.

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Learnings from Other Governance Models

Finally, as part of the broader assessment looking at potential governance models, Storehagen et al.[19] conducted an analysis of the United Nations Single Convention on Narcotic Drugs from 1961. Several experts have indicated that antibiotics may require a similar convention,[20] since it aims to control the consumption of products that impact public health. Balance between drug access and control is a key challenge in such conventions. The authors show that although some of its elements could be useful in the antibiotic context, the benefits of developing a convention would be limited in view of the current integration of antibiotic stewardship measures into national action plans against AMR — as required in the 2015-adopted WHO global action plan on AMR.[21]

Concluding Remarks

It is our intent that the articles in this special Symposium issue bring to the table interesting and new insights and evidence into the different economic incentives that are needed to stimulate antibiotic R&D. There is no simple solution to the challenge of stimulating antibiotic innovation and any implemented measure will likely not fully demonstrate results for 10-20 years — the duration of bringing an antibiotic through the R&D process from discovery to approval. Yet, now is the time for all stakeholders to come to a consensus or at least to act together in a coordinated fashion and start piloting and testing different solutions. Only through these pilots can significant new knowledge be gained about the effectiveness of different models.

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