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DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

Push incentives to stimulate research and development of new antibiotics

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Introduction

While antibacterial resistance is increasing, the number of innovative products coming to the market is decreasing. Push incentives, by their support along the R&D value chain, are mitigating two major R&D bottlenecks: scientific (and methodological), and clinical development costs (Figure 1). R&D grants are an important push mechanism to stimulate basic and applied research in AMR. The OECD estimates that USD 547 million are invested annually in push mechanisms, which are overwhelmingly represented by grants.

The advantages of grant funding reside in the opportunity for targeted approaches to R&D, where the objectives of the research program can be broadly or narrowly tailored to tackle public health needs, and/or focus research efforts at questions that pose major scientific and technological bottlenecks. Additionally, different actors in the antibiotic R&D arena can be incentivized, including research teams at universities and research institutions, small- and medium-sized companies to research teams in large pharmaceutical companies.

Materials and methods

DRIVE-AB has assessed calls for grants application in the AMR field: retrospective grant funding from the European, Japanese, and US agencies and public-private partnerships. Feedback from representatives of small- and medium-sized enterprises (SMEs) was obtained during a stakeholder meeting on the overall structure and combination of push incentives across the antibiotic R&D pipeline, and how they address the challenges faced by SMEs. We have also simulated grant financing (Appendix). DRIVE-AB worked with national and international grant funding agencies (BARDA, CARB-X, Wellcome-Trust) to build a picture of existing activities, identify gaps and develop solutions to address those gaps.

Results

DRIVE-AB proposes a model of four related and partially overlapping grant incentives with the aim to stimulate R&D of new antibiotics (Figure 1). The intention here is not to replace the existing grant-giving mechanisms but recommend enhancements. Key characteristics of incentives are summarized in Table 1.

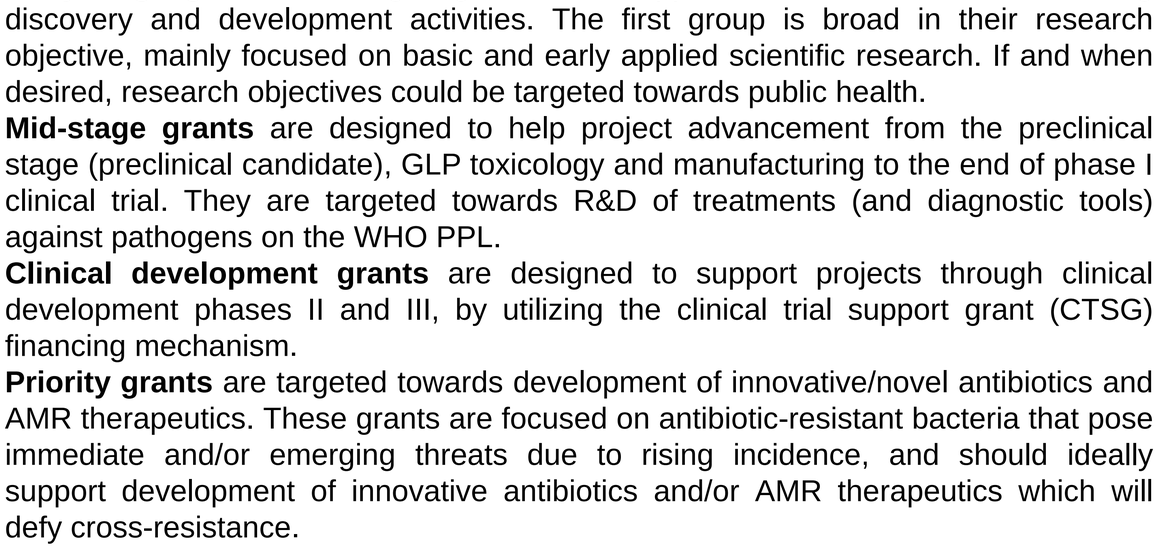
Early-stage grants are targeting basic and applied scientific research, and drug discovery and development activities. The first group is broad in their research objective, mainly focused on basic and early applied scientific research. If and when desired, research objectives could be targeted towards public health.

Mid-stage grants are designed to help project advancement from the preclinical stage (preclinical candidate), GLP toxicology and manufacturing to the end of phase I clinical trial. They are targeted towards R&D of treatments (and diagnostic tools) against pathogens on the WHO PPL.

Clinical development grants are designed to support projects through clinical development phases II and III, by utilizing the clinical trial support grant (CTSG) financing mechanism.

Priority grants are targeted towards development of innovative/novel antibiotics and AMR therapeutics. These grants are focused on antibiotic-resistant bacteria that pose immediate and/or emerging threats due to rising incidence, and should ideally support development of innovative antibiotics and/or AMR therapeutics which will defy cross-resistance.

Figure 1. Push funding incentives, research and development (R&D) phases, and major R&D bottlenecks.
Top – antibiotics R&D major bottlenecks: scientific and methodological, and clinical trials development and their associated costs (highlighted in red; these bottlenecks are major targets of push incentives). Other risks and bottlenecks along the value chain are presented by clear boxes.
Middle – R&D phases are represented from the basic science to post-marketing commitments, the later referring to safety surveillance, studies to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate, and maintaining manufacturing capability.
Bottom – push and pull funding, and their implementation time frame along the R&D phases. Specific push incentives are presented as green boxes. The link between the mid-stage and clinical development grants indicate that a developer can obtain direct support for clinical development conditional on successful phase I clinical trial supported by a mid-stage grant. Otherwise, developer(s) can apply for clinical development grant independently of previous mid-stage grant award and be subject to peer review process.



Summary points

- Significant **communication** between the grant-giving agencies is occurring (e.g. the Transatlantic Taskforce on Antimicrobial Resistance). But this has not yet resulted in **coordination**, where funders target common goals and work together to identify R&D gaps.
- **Additional annual push funding in the range of USD 200 – 500 million** will mostly benefit **early-stage research** (to increase the number of molecules entering the preclinical research), and help attract investors to support **clinical development** (by sharing financial risks of clinical trials with high attrition rates).
- **Without a 'pull' incentive increasing grant funding will have a negligible effect on bringing new antibiotics to the market**.

Grants	Early-stage	Mid-stage	Priority	Clinical Development
Objectives	• Research of basic phenomena in AMR/ABR • Research of virulence factors • R&D of new approaches to overcome existing and emerging resistance mechanisms • R&D new drug targets	R&D of treatments against pathogens on the WHO PPL	ABR/pathogens defined by gap analysis	• Clinical development of innovative AB candidates • New approaches to overcome existing antibiotic resistance
Scope	Broad in scope and objectives Mainly supports basic and early stage applied research	Targeted towards R&D of AM/AB strategies against pathogens on WHO PPL	Pathogens targeted for this grant support are defined by the expert panel under the WHO supervision	Clearly defined innovation criteria[1] Targeted against pathogens on the WHO PPL
Duration Support Costs cover (%)	Max 3 years € 100-500K 100%	Max 5 years € 500-2000K 50-100%	Expected max 10 years € 500-2000K + CTSG* 50-75%	Max 5 years € CTSG* 50%
Eligibility	International	International	International	International
Entities	Academia	SMEs Industry Public-private consortia	SMEs Industry Public-private consortia	SMEs Industry Public-private consortia
Cooperation and Collaboration	Required	• Required for academic research groups • Encouraged between academia and industry	• Voluntary, or • Strategic partnership as deemed necessary	• Voluntary, or • Strategic partnership as deemed necessary
Stipulations	• Data sharing after obtaining IP Results • Open access	• Data sharing after obtaining IP Results • Open access • Contractual obligations[4]	• Data sharing • % return upon ME[2] • MER reduction[3] • Contractual obligations[4]	• Data sharing • % return upon ME[2] • MER reduction[3] • Contractual obligations[4]

* CTSG – Clinical Trial Support Grant
1 Possibly in conjunction with MER preapproval
2 25-50% initial grant(s) investment return to funder during FY 2-6 post ME (those receiving support for phase II & III clinical trials)
3 If MER awarded after supporting phase II & III via grants, MER will be reduced by 50% of total award received via grants (inflation rate adjusted)
4 Contractual obligations are predefined, see chapter/page

Conclusions/Discussion

- Countries should make long-term commitments to continue financing of antibacterial R&D. Ideally funding should be increased by 50%, and existing multi-national grant funding agencies (e.g. CARB-X, GARDP, JPIAMR) should be the recipients.
- Most of this immediate funding should be placed in early- and mid-stage grants until the development pipeline becomes more robust.
- Granting agencies should have specific calls for research that target pathogens which pose most urgent public health threats (e.g. WHO's priority pathogen list).
- National and international R&D efforts should be better coordinated, including a focus on R&D gaps within the priority pathogen list. This can be performed through a virtual Global Collaboration Hub as proposed by the G20.

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