**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 cost constraints (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 are 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 antimicrobial resistance (AMR) R&D arena can be incentivized, including research teams at universities, hospitals, and research institutions, small- and medium-sized companies to research teams in large pharmaceutical companies.

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**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 (BARD, CARB-X, Wellcome Trust) to build a picture of existing activities, identify gaps and develop solutions to address those gaps.

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**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 compare 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 objectives, 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), GMP technology 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 resistance.

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**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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**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.

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**Figure 1.** Push funding incentives, research and development (R&D) phases, and major R&D bottlenecks. Top – antibotics 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 latter 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 frames 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 II clinical trial supported by a mid-stage grant. Otherwise, developer(s) can apply for clinical development grant independently of previous mid-stage grant and be subject to peer review process.