DRIVE-AB REPORT

Revitalizing the antibiotic pipeline

Stimulating innovation while driving sustainable use and global access

EXECUTIVE SUMMARY

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

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Executive summary

Introduction

Bacteria are becoming increasingly resistant to many antibiotics, and too few new antibiotics are being developed to combat them. Any use reduces the effectiveness of these drugs for other patients. Resistance developed to one antibiotic can limit the effectiveness of the associated class of such drugs.[i]

Antibiotic resistance is currently recognized as a critical problem at the highest political levels, as demonstrated, for example, in a United Nations declaration in 2016 and in recent G7 and G20 communiqués. Germany, as the leader of the G20 in 2017, launched the Global R&D Collaboration Hub on antimicrobial resistance (AMR) with a Berlin-based secretariat financed for an initial three-year period. The hub is intended to pinpoint important gaps in the development of tools to combat AMR, such as antibiotics, diagnostics and vaccines.

The research project DRIVE–AB (Driving reinvestment in research and development for antibiotics and advocating their responsible use) was a consortium of 16 public-sector partners and 7 pharmaceutical companies supported by the European Innovative Medicines Initiative (IMI). DRIVE-AB was tasked with defining standards and metrics for responsible use of antibiotics,[ii] identifying antibiotic-related public health priorities, calculating the societal value of having new antibiotics available for these priorities, and developing and costing new economic models to promote the desired antibiotic innovation and sustainable use of the resulting, novel antibiotics.[iii] The purpose of the project was to transform the way policymakers stimulate antibiotic innovation, and to ensure that these new antibiotics are used sustainably and are available equitably.[iv] To achieve this vision, DRIVE-AB used a research-based approach with significant stakeholder input to build policy recommendations to incentivize antibiotic research and development (R&D).

DRIVE-AB included stakeholders from commercial organizations, academic institutions, public health organizations and R&D funding organizations. This ensured balance in the outputs of the project. To ensure this balance was achieved in the final report, all stakeholder groups were represented on the report-writing team. Conflicts of interest were managed through full transparency of potential stakeholder biases.

This report is based on the research carried out by the different DRIVE-AB work packages as well as input from the wide range of stakeholders. The recommendations it presents were not unanimously agreed among DRIVE-AB members, but do broadly reflect the results of the research carried out. The areas of contention are few in number but relate to central concepts of our recommendations. Alternative views are noted in the report.

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i Within this report we generally refer to "antibiotics". This is to facilitate a general understanding among non-specialists. However, the findings of this report are applicable not only to small molecule drugs (i.e., antibiotics) but also other technologies that effectively treat a bacterial infection (e.g., bacteriophages), excluding tuberculosis.

ii Responsible use as defined by the World Health Organization is the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance.

iii Sustainable use 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.

iv Equitable availability means ensuring that innovative antibiotics are registered and priced affordably across countries with a public health need for them.

The problem

Without new antibiotics, it will be increasingly difficult to treat infections effectively, and procedures such as organ transplantation, cancer chemotherapy, or common surgical operations such as hip or knee replacements will carry an increased risk of untreatable infection. New antibiotics act as an insurance mechanism against the future impact of resistance. Governments and payers currently exclude this societal value from health technology assessments (HTAs). Ideally, entirely new types of treatments that do not cause bacterial resistance would eventually replace antibiotics, but such technologies may not be available for decades or more. Therefore, while it is necessary to invest in the discovery and development of alternative treatments, significantly increased investment in antibiotic innovation is essential.

The current pipeline for innovative antibiotics in various stages of R&D is insufficient, potentially delivering no more than one innovative antibiotic for a "critical" World Health Organization (WHO) priority pathogen within the next five years. At the same time, the number of infections caused by antibiotic-resistant bacteria is increasing, with the interval between introduction and the early establishment of resistance leading to the widespread need for new antibiotics becoming alarmingly brief in some countries.

The inadequacy of the pipeline has two main causes. First, there are significant scientific challenges around the discovery of new antibiotics, particularly those for Gram-negative bacterial infections. Secondly, the market for new antibiotics is in general not commercially attractive, as the potential revenues in a market where new antibiotics are reserved for last-resort use are not commensurate with the value for society.

While there is a clear need for increased antibiotic innovation, focusing only on innovation will not sustain our ability to address serious infections. Efforts must also be made to prolong the effectiveness of antibiotics. It takes over a decade to develop a new antibiotic and can cost more than US$1 billion (€850 million). This cost and time investment needs to be safeguarded by implementing sustainable use measures that will prolong the effectiveness of the antibiotic. This means using antibiotics responsibly in individual patients by ensuring they receive the right dose of the right antibiotic at the right time, and striving to eliminate unnecessary or inappropriate use or exposure, whether in people, agriculture or the environment.

At the same time, however, it is estimated that ten times as many people die from a lack of access to antibiotics as from resistance. Pneumonia and sepsis kill more than one million children every year but can often be treated by inexpensive generic antibiotics. While antibiotics should be used appropriately to restrict the development of resistance, ways must be found to ensure that controls on use do not hinder appropriate access. New incentives to stimulate antibiotic innovation must be coupled with provisions for sustainable use and equitable availability.

The solutions

The effective stimulation of antibiotic innovation requires a balanced combination of both "push" incentives (those designed to support R&D directly) and "pull" incentives (those designed to reward successful outcomes from R&D). Push incentives, such as grants, are important but not sufficient to fill the pipeline. Private-sector investment is based on anticipated future monetary returns. Push funding pays for R&D costs but does not improve the attractiveness of the overall market. Pull funding is required to attract private-sector funding; otherwise antibiotic-resistant infection risks becoming a "neglected" disease, solely dependent on the public and philanthropic financing of R&D. Data regarding financing of "neglected" diseases such as malaria and tuberculosis present a clear picture of consistent under-funding.

DRIVE-AB assessed more than 30 different incentives gathered from different industries. Each incentive possesses different qualities that may or may not be advantageous in the unique context of antibiotic innovation. We assessed how each incentive would affect

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innovation (in terms of R&D phases and actors), and what effect incentives would have on sustainable use and equitable availability. Four incentives were determined to be the most effective in stimulating the antibiotic pipeline and ensuring that critical antibiotics continue to be accessible and can be used sustainably:

• **Grants**: non-repayable funds for R&D given to academic institutions, companies and others;

• **Pipeline coordinators**: governmental or non-profit organizations that closely track the antibiotic pipeline (or subsets thereof), identify gaps, and actively support R&D projects both financially and technically to fill these gaps;

• **Market entry rewards**: a series of financial payments to an antibiotic developer for successfully achieving regulatory approval for an antibiotic that meets specific predefined criteria to address a defined public health need, with obligations for sustainable use, equitable availability and supply;

• **Long-term supply continuity model**: a delinked payment to create a predictable supply of important generic antibiotics.[v]

Each recommended incentive is intended to stimulate specific phases of the R&D process (see Figure 1). The models do not operate in isolation and are designed to be complementary: together they form an incentive "ecosystem" to maximize their effectiveness in stimulating innovation while ensuring sustainable use and access.

Figure 1. Incentives by R&D phase
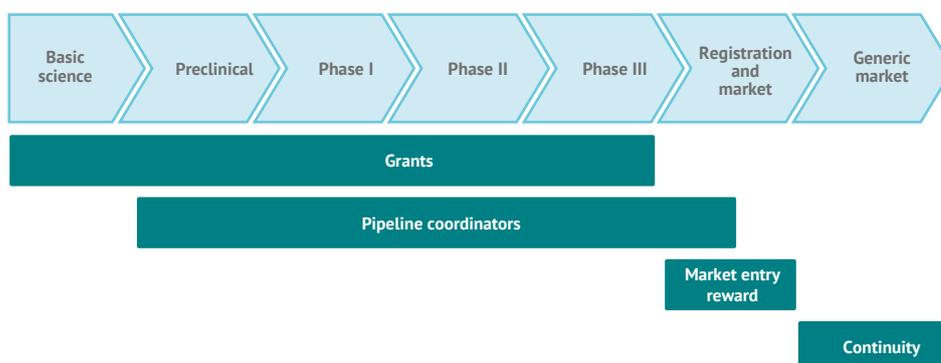
Grants and pipeline coordinators are intended to fill the early-phase pipeline with a large variety of projects – enough to survive the high scientific and early-stage development failure rate. This would push a robust pipeline into clinical trials, and on to market entry. There have been large increases in push incentives in the last five years, including from new initiatives such as CARB-X (The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) and GARDP (Global Antibiotic Research and Development Partnership). The OECD estimates that countries are investing approximately $550 million (€470 million) every year in grant funding for antibiotic R&D. While significant, this level of financing and commitment is still too low. Our analysis of the pipeline demonstrates that it is inadequate in both preclinical and clinical phases. We estimate that at this level of push funding, only

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v   Delinking means that revenues for the new antibiotic are either partially or fully delinked from the number of units sold, allowing for the revenues to be based upon the value to society.

about four new classes of antibiotics can be expected within the next 30 years, while antibiotic resistance in some pathogens may more than double in the same period.

The **market entry reward** aims to create an attractive market for investment in antibiotic R&D; it is designed to attract increased private-sector funding and support sustainable R&D investment. DRIVE-AB has determined that a market entry reward of $1 billion per antibiotic globally (in addition to unit sales revenues) could quadruple the number of new antibiotics coming to the market in the next 30 years. This recommended amount is similar to the values proposed by others including the United Kingdom's Review on Antimicrobial Resistance, which recommended between $800 million and $1.3 billion (in addition to unit sales), and the Boston Consulting Group's recommendation of $1 billion (again in addition to unit sales, but gradually paid back dependent on those sales).

DRIVE-AB's recommendation is a result of an extensive simulation based on a set of antibiotic-specific R&D and market parameters. This simulation calculated that $800 million–1.5 billion would deliver on average 16–20 truly innovative new antibiotics over 30 years. DRIVE-AB selected a global award of $1 billion as the most efficient choice because the value of increasing the amount of the market entry reward to ensure that all antibiotics reach the market significantly increases the overall expenditure. Arguably, the last, tail-end classes are the most scientifically ambitious, with the smallest patient populations or patient populations that are difficult to recruit for clinical trials, and thus require larger reward values to be commercially attractive.

The proposed amount of the market entry reward cannot be precisely stipulated. The exact amount needed to motivate different companies to invest will vary greatly. Some stakeholders argue for a higher market entry reward amount, and others that a billion dollars is excessive. We have set the parameters to ensure a reasonable return on investment for the developer, but one that is far lower than the profits achieved by the top-selling drugs in recent years.

We recommend a partially delinked market entry reward (or a reward that is given in addition to unit sales) for several reasons: it will minimize disruptive effects to existing national systems such as reimbursement; it functions in both public and private insurance contexts; it allows for variability of revenues based on the level of need; and it is relatively straightforward to pilot. Some members of DRIVE-AB argue that this model leaves in place a strong incentive for the manufacturer to oversell the antibiotic. This is a risk that must be closely monitored.

We also recommend a **long-term supply continuity model** designed to ensure continued supply of potentially low-volume but critical generic antibiotics through a series of annual fixed payments to the supplier.

The costs

We estimate that $800 million (€680 million) is needed annually for push funding (both for grants and for pipeline coordinators). Including the $550 million (€470 million) already invested in antibiotic R&D each year, this is an increase of about 50 per cent. This recommendation is imprecise because the data available on current investments are not comprehensive. DRIVE-AB was only able to access preclinical pipeline data from CARB-X based on an assessment of its applications. Better data are needed on the preclinical pipeline. We expect that the G20's Global R&D Collaboration Hub on AMR will help provide more insight into the current portfolio and R&D gaps. Under our proposal, push funding for clinical trials would be repaid by recipients of a market entry reward.

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On the basis of the antibiotics that are currently in development, we estimate that two innovative antibiotics could receive a market entry reward within the next five years. This may seem to contradict the earlier statement that we only expect about four truly innovative antibiotics to come to market in the next 30 years, but the current high-level political attention has produced a strong expectation that new antibiotic innovation incentives will be implemented. Without this expectation we anticipate that even scientifically promising candidates will not make it to the market. The first innovative antibiotic may receive regulatory approval as early as 2020 and the second in 2021. These represent significant advances in innovation and will address WHO priority pathogens.[vi]

If these antibiotics qualify for a market entry reward, we recommend that the market entry reward is paid out in equal payments of $200 million (€170 million) per antibiotic over five years after regulatory approval, but the obligations on sustainable use and access should remain for the lifetime of the antibiotic's related intellectual property protection. Therefore, our forecast for the near-term financing needs would start at $800 million (€680 million) per year in 2018, increasing to $1 billion (€850 million) per year in 2019 with the first market entry reward, and then to $1.2 billion (€1.02 billion) in 2021 with the award of the second market entry reward (Table 1). This does not include the implementation of the long-term supply continuity model. Individual countries or coalitions will need to determine if there is insufficient supply of essential, generic antibiotics to maintain a healthy market and implement accordingly.

Table 1. Estimated total global public-sector costs to incentivize antibiotic innovation, 2018–22 ($m)

	2018	2019	2020	2021	2022
Existing grant financing	550	550	550	550	550
Additional push financing	250	250	250	250	250
Market entry reward(s)	0	200	200	400	400
Total	800	1,000	1,000	1,200	1,200

Note: Clinical trial grant financing will be repaid on award of a market entry reward.

We expect that at least $1.2 billion (€1.02 billion) per year will be necessary every year after 2022 (since a market entry reward of this value should result in approximately 18 qualifying antibiotics reaching the market in the 30 years after implementation of market entry rewards). Until alternative therapies that do not develop resistance are available, antibiotic resistance will continue to be a challenge. To provide an adequate stream of antibiotics, these investments will need to continue. Yet they should not be made at the expense of investments in AMR surveillance, infection control, access initiatives, responsible use, or diagnostics R&D. It is essential to maintain support in all these areas in order to obtain optimal results.

vi World Health Organization. *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and the development of new antibiotics*. Geneva: World Health Organization, 2017; World Health Organization. *WHO Global Strategy for Containment of Antimicrobial Resistance*. Geneva: World Health Organization, 2001.

Recommendations

Governance

1. **The G20 Global R&D Collaboration Hub on AMR should be considered as one possible approach to achieving high-level coordination for both push and pull mechanisms.**
   This high-level coordination should act to align public funding towards important investment opportunities. The hub is not intended to be an extensive new organization, and will not create a new pooled fund or determine how member states' contributions will be allocated. While the mandate of the hub is still under discussion, this is certainly an excellent opportunity for it to act as a coordinating body for market entry rewards as well as push models. Since it will function at a political level, operational pipeline coordinators can inform the hub about existing gaps.

Incentives

2. **The G20 should work with member states and other like-minded countries to agree to implement and finance a market entry reward for a 20-year period including common sustainable use and equitable availability provisions.**
   To test the operational implementation, a pilot between two or three countries would be appropriate, to be initiated immediately and lasting for one to three years. When it is fully operational, we recommend a partially delinked market entry reward of $1 billion per antibiotic for innovative antibiotics meeting predefined target product profiles (TPPs).[vii] The reward should be paid out over at least five years, with contractual obligations for the lifetime of the intellectual property. If infection control and stewardship programmes are effective, there will always be a need for a market entry reward because the consumption of novel antibiotics should remain modest. We recommend this 20-year period not to indicate that the problem will be solved, but to learn from the implementation and fix any unintended consequences. This period is long enough to determine the impact of the market entry reward on innovation. Any shorter assessment would be biased by the existing antibiotic pipeline.

3. **The European Commission should work with member states to gauge interest in implementing a common European market entry reward.**
   Not all European countries will be interested in or able to contribute to a market entry reward, and those with the highest resistance levels would be better served by investing in improved national infection control and stewardship programmes. The European Union G20 countries are France, Germany, Italy and, until 2019, the United Kingdom. The Netherlands and the Scandinavian countries have also demonstrated strong public interest in AMR, including innovation. All European countries benefit from one overarching regulatory agency – the European Medicines Agency (EMA). They also benefit from the European Investment Bank (EIB), which is mandated to make a difference to the future of Europe and its partners by supporting sound investments that further European policy goals. DRIVE-AB sees potential in a group of like-minded European countries able to commit to pilot a European-based market entry reward paid out by the EIB for qualifying antibiotics approved by the EMA. It can be argued that Europe should be financially responsible for at least one-third of the cost of a global market entry reward.

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vii TPPs are specifications describing the criteria required for an antibiotic including, for example, indications, dosing, treatment duration, delivery mode and efficacy targets for antibiotic development. These must remain flexible enough to allow for innovative, non-traditional technologies.

The European Commission's Joint Action on AMR and Healthcare-Associated Infections could be utilized to assist in the implementation of this pilot.

4. **Countries should make long-term commitments to continue financing of antibacterial R&D and ideally increase push funding by about 50 per cent.**
   There may be capacity within existing multinational grant funding agencies – e.g. CARB-X, GARDP, JPIAMR (Joint Programming Initiative on Antimicrobial Resistance) – to absorb and effectively deploy more capital. Owing to the existing pipeline, much of this immediate funding should be placed in early- and mid-stage grants until the pipeline becomes more robust. Granting agencies should have specific calls for research targeting pathogens that pose the most urgent public health threats (e.g. WHO's priority pathogens list for the discovery phase and TPPs for the development phase).

5. **To ensure that progress is made on all identified priority pathogens, targeted portfolio-based approaches such as BARDA (Biomedical Advanced Research and Development Authority), CARB-X and GARDP – i.e. pipeline coordinators – should be supported and expanded.**
   A review of the current antibiotic pipeline demonstrates that not all pathogens are equally attractive for developers. Pipeline coordinators are needed to closely track the antibiotic pipeline (or subsets thereof), identify gaps and actively support R&D projects to fill these gaps. They work at an operational level and should not be confused with entities that work on political coordination, such as the G20's Global R&D Collaboration Hub on AMR.

6. **Sustainable use measures for developers should be contractually linked to both market entry rewards and long-term supply continuity awards.**
   A special working group (potentially under the guidance of the G20's Global R&D Collaboration Hub on AMR) should convene to develop standard sustainable use measures both for developers and for governments. DRIVE-AB has proposed measures that can be used as a starting point.

7. **Equitable availability measures for developers should be contractually linked to market entry rewards.**
   A special working group (potentially under the guidance of the Global Antibiotic Resistance Partnership, given its significant expertise) should convene to develop standard equitable availability measures. Again DRIVE-AB has proposed measures that can be used as a starting point. These measures will require testing and adaptation. This could be done with an approved patented antibiotic that is considered useful in low- and middle-income countries.

8. **Principal antibiotic R&D funders (e.g. BARDA, CARB-X, JPIAMR, IMI, the National Institutes of Health (NIH), the Wellcome Trust) and developers should agree to standard sustainable use and equitable availability principles that can be included in all pertinent push-funding agreements.**
   This will allow developers to begin to plan for making their antibiotics globally and sustainably available.

9. **To test the operational implementation of delinkage, interested countries and multilateral bodies (such as UNICEF, the United Nations Children's Fund) should initiate a delinked, joint procurement process for an antibiotic with a fragile supply chain which is included as an "access" antibiotic on WHO's Essential Medicines List (e.g. benzylpenicillin).**
   Testing a long-term supply continuity model can also test the implementation of a delinked model such as a market entry reward. This could be an immediate concrete action where countries can test the operational difficulties of coordination while waiting for a suitable antibiotic to receive regulatory approval.

10. **Grant funding should be allocated to undertake post-approval clinical trials in order to gather evidence concerning uncommon infections and special patient groups.**
Pipeline coordinators should map the public health gaps in this area and seek to gather empirical data to fill the gaps. Continued emphasis should be placed on improving clinical trial networks to facilitate the rapid identification of eligible patients.

11. **As a part of their ongoing health technology assessment (HTA) processes, countries should begin to integrate methods and frameworks that account for the enablement, option and diversity value for each new antibiotic submitted for regulatory approval.**
While market entry rewards are discussed and put in place, national authorities should address the economic challenges within their existing systems. This will ensure that incentives for antibiotic innovation can be improved in the near term to maintain current private investment into antibiotic R&D – for example, by developing HTA processes to better capture the societal value of antibiotics in coverage and reimbursement decision-making.

12. **To ensure that antibiotic innovation is targeting the highest-priority public health needs, WHO (or another suitable body) should develop target product profiles (TPPs) for its priority pathogens list.**
There should be broad consensus among public health experts and clinicians that these profiles represent unmet public health needs for antibiotic innovation. Developers should be consulted to ensure that TPPs are achievable. The development of TPPs should be an ongoing process as the priority pathogens list is updated over time. Once established, TPPs must remain stable for a decade to ensure predictability within lengthy R&D timelines.

The recommendations in the context of small and medium-sized enterprises (SMEs)

Globally, an estimated 400 SMEs are involved in antibiotic R&D. They are the engines for discovery and early development. However, for SMEs to deliver antibiotic candidates for late-stage development (phases II & III), additional direct funding in the form of push incentives need to be available and accessible in the short term, and the market needs to be fixed in terms of pull incentives to drive an attractive return on investment.

As highlighted at the DRIVE-AB conference in September 2017, although grant funding is available through initiatives such as InnovFin, the European Investment Bank's EU Finance for innovators programme, much of it cannot be accessed by SMEs as they lack the risk profile to qualify for it. Recent initiatives such as CARB-X have gone some way to addressing this lack of push grant funding. In its first year, CARB-X funded 18 innovative projects across North America and Asia and it has $455 million (€379 million) over five years to invest.

Pull incentives are also critical for a healthy SME sector in antibiotic R&D. The market for SMEs' medicines is commonly Big Pharma, which purchases SME molecules, or the companies in full later-stage development. However, this trend is changing and more SMEs are now launching, producing and distributing their own products. They will need assistance in building global distribution networks and can be helped by non-traditional actors such as GARDP, the Medicines Patent Pool or others. Outreach to venture capital firms is important to ensure that they understand both the short-term and long-term impact of market entry reward obligations on SMEs.

A full "ecosystem" of push and pull incentives financed publicly, privately and charitably is required to maintain and expand the number of SMEs investing in antibiotic R&D.

We believe that the above-mentioned recommendations should facilitate a robust SME presence.

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