DRIVE-AB REPORT

Revitalizing the antibiotic pipeline

Stimulating innovation while driving sustainable use and global access

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

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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 lead of the G20 in 2017, launched the Global R&D Collaboration Hub on 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 seven 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

[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.

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.

The problem

Without new antibiotics, it will be increasingly difficult to effectively treat infections, 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

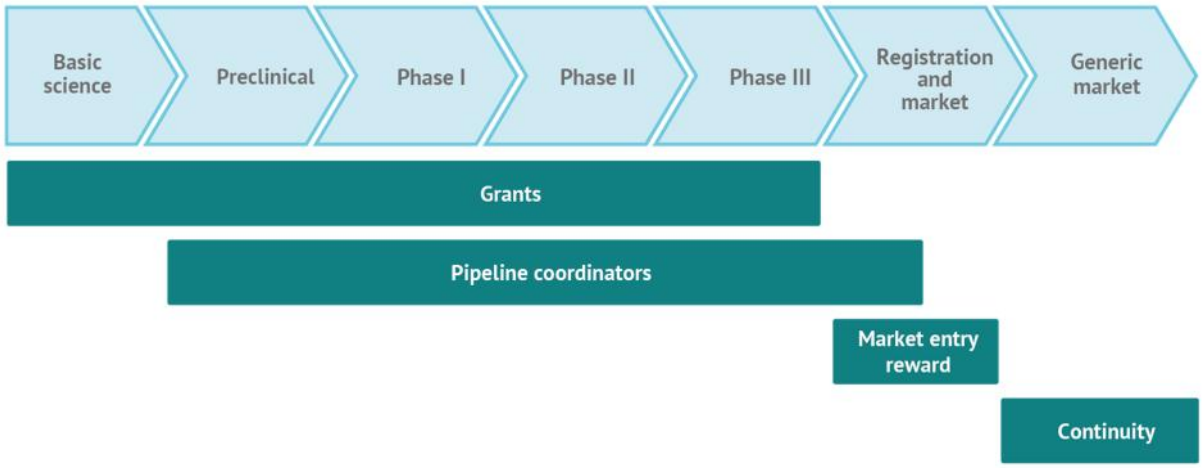
fill the pipeline. Private-sector investment is based on anticipated future monetary returns. Push funding pays for R&D costs but does not improve the attractiveness of the overall market. Pull funding is required to attract private-sector funding; otherwise antibiotics risk becoming a "neglected" disease, 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 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 pre-defined 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



[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.

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 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 requiring 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.

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 other in 2021. These represent significant advances in innovation and will address WHO priority pathogens.[vi] [1]

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

[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.

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.

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

[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.

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. 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 of 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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Acronyms

$	US dollars
3GC	Third-generation cephalosporin
AMED	Agency for Medical Research and Development
AMR	Antimicrobial resistance
ANR	French National Agency for Research
API	Active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
ASTRID	Accompagnement Spécifique des Travaux de Recherches et d'Innovation Défense
ATC-DDD	Anatomical Therapeutic Chemical – Defined Daily Dose
BARDA	Biomedical Advanced Research and Development Authority
BSAC	British Society for Antimicrobial Chemotherapy
CARB-X	The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	The United States' Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics, & Policy
CEFAIA	Centre for Anti-Infective Agents
CEPI	Coalition for Epidemic Preparedness Innovations
CERN	European Organization for Nuclear Research
COMBACTE-NET	Combating Bacterial Resistance in Europe
DDD	Defined Daily Dose
DNDi	Drugs for Neglected Diseases initiative
DRIVE-AB	Driving reinvestment in R&D for antibiotics and responsible antibiotic use
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EFPIA	European Federation of Pharmaceutical Industries and Associations
EIB	European Investment Bank
EMA	European Medicines Agency
ENABLE	European Gram Negative AntiBacterial Engine
eNPV	Expected net present value
ESCMID	European Society of Clinical Microbiology and Infectious Diseases

FD	Fully delinked
FDA	Food and Drug Administration
GAIN	The United States' Generating Antibiotic Incentives Now
GARDP	Global Antibiotic Research and Development Partnership
GARP	Global Antibiotic Resistance Partnership
Gavi	The Vaccine Alliance
GLP	Good laboratory practices
HICs	High-income countries
HTA	Health technology assessment
ICU	Intensive care unit
IMI	Innovative Medicines Initiative
InnovFin	The European Investment Bank's EU Finance for innovators programme
IP	Intellectual property
IV	Intravenous
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMICs	Low- and middle-income countries
LPAD	Limited population antibacterial drug
MDR	Multi-drug-resistant
MDRO	Multi-drug-resistant organism
MRC	Medical Research Council
ND4BB	New Drugs 4 Bad Bugs
NDA	New drug application
NIH	National Institutes of Health
NPV	Net present value
ODA	Official development assistance
OPAT	Outpatient Parenteral Antimicrobial Therapy
PD	Partially delinked
PDP	Product development partnership
PDR	Pan-drug resistant
PPL	Priority pathogens list
QALY	Quality-adjusted life year

R&D	Research and development
RCT	Randomized controlled trial
RfP	Request for proposal
SBIR	Small Business Innovation Research
SMEs	Small and medium-sized enterprises
STTR	Small Technology Transfer Research
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TPP	Target product profile
UHC	Universal Health Coverage
UNFCCC	United Nations Framework Convention on Climate Change
UNGA	United Nations General Assembly
UNICEF	United Nations Children's Fund
VC	Venture capital(ist)
WHO	World Health Organization

Definitions

Antibiotics: 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 (this was not included in the scope of DRIVE-AB owing to the other initiatives focused solely on the disease).

Delinkage: delinking the revenues for the new antibiotic either partially or fully from unit sales; that is, the revenues are based upon the value to society of a new antibiotic being developed and not on the number of units sold.[viii]

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

Responsible use: the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance.[2]

Sustainable use: the implementation of measures targeting a range of actors to ensure the long-term effectiveness of a specific, novel antibiotic or an antibiotic class

Target product profiles: 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.

[viii] Delinkage has another definition in the context of health technology innovation specifically for the diseases disproportionately affecting developing countries. The World Health Organization's Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property defined "delinkage" as disconnecting the unit price of a medicine/product from the R&D costs. This is an important principle as it can lower the prices of new medicines, which are often a barrier to patients in low- and middle-income countries. The two definitions of "delinkage" have very different aims. The Global Strategy's delinkage is an attempt to reduce the price of new medicines. Our definition seeks to make antibiotic innovation more attractive to the developer while at the same time encouraging anbiotic stewardship. It is, of course, also important that new antibiotics are affordable in low- and middle-income countries, but they should be more expensive than existing first-line antibiotic therapies to avoid the perverse incentive of switching to the newest antibiotics because they are the cheapest.

Introduction

DRIVE-AB's vision: **Transforming the way policymakers stimulate innovation, sustainable use and equitable availability of novel antibiotics to meet public health needs**

To achieve this vision, DRIVE-AB used a research-based approach with significant stakeholder input to build policy recommendations. The strength of DRIVE-AB was its ability to bring together a wide diversity of expertise across the academic and industry partners with a common objective. The academic partners included infectious disease clinicians, microbiologists, health economists, modellers and experts in public health, innovation management, business, the law and health policy. Industry partners included commercial and clinical experts covering drug discovery and clinical development, regulatory approval, market access and pricing, commercial strategy, policy and analytics. DRIVE-AB's recommendations have received feedback from a broad range of stakeholders including policymakers, healthcare insurers (both national and private), medicines regulatory authorities, small and medium-sized pharmaceutical companies, national research funding agencies, academic research institutions, civil society, philanthropic foundations. Although principally European in focus, DRIVE-AB engaged globally (including with high-, middle-, and low-income countries) to ensure that its recommendations worked within the broader context of ensuring access to effective antibiotics and combating resistance.

Bacteria are becoming increasingly resistant to many antibiotics, and too few new antibiotics are being developed to combat them.

The availability of effective antibiotics is central to the practice of modern medicine. Antibiotics not only treat and prevent infectious diseases, but they also underpin the safety of many medical procedures, including surgery, chemotherapy and neonatal care.

The problem is that resistance to antibiotics increases with their use – an unavoidable natural process whereby bacteria evolve so that the antibiotic is no longer effective. The development of resistance is accelerated by the inappropriate use of antibiotics in healthcare and food production, and through pollution of the environment through the release of antibiotic manufacturing waste.[3] When bacteria become resistant to one antibiotic, another will be needed to treat the infection. Antibiotic resistance becomes a serious problem when bacteria become resistant to many antibiotics so that there are few or even no effective antibiotics to treat an infection. For example, the treatment of gonorrhoea has become problematic for this reason. Action is needed today to slow the development of resistance and accelerate the development of new tools against resistant bacteria.

Box 1

Barriers to antibiotic investment

A company's return on investment for developing a novel antibiotic is significantly lower than in other competing therapeutic areas because:

- Many older and inexpensive antibiotics are still highly effective for most patients since resistant infections are still relatively rare. Therefore, hospitals and primary care providers rationally prescribe proven, inexpensive antibiotics.
- The desire to preserve the use of novel antibiotics, limited data on resistance, limited availability and use of diagnostics, and reimbursement structures all contribute to slow initial uptake.
- Although the overall antibiotic market is large in volume terms, it is fragmented into multiple markets by hospital speciality and resistance patterns. Thus the markets for each of the different antibiotics can be relatively small.

Since the late 1980s there has been insufficient antibiotic innovation. Only three new classes of antibiotics have reached the market in the last 20 years.[4-6] This is due to a combination of factors.[7] First, there are scientific challenges which have made effective and safe antibiotics very hard to discover.[8] Secondly, generating the data required for regulatory approval of a new antibiotic is difficult and expensive. Both of these barriers could be surmountable, but not when combined with the third barrier – most antibiotics offer the private sector an unattractive return on investment. Revenues from sales of most antibiotics tend to be low, and higher revenues are often possible in other disease areas (see Box 1). In 1980, there were more than 25 large pharmaceutical companies with active antibiotic drug discovery programmes; today only six remain (AstraZeneca/MedImmune, GlaxoSmithKline, Merck, Novartis, Roche and Sanofi).[9] In order to reverse the trend of disinvestment in antibiotic research and development (R&D), new incentives are needed to stimulate new investment to overcome antimicrobial resistance (AMR).

New technologies that aim to replace antibiotics will not be available for decades.

Non-antibiotic therapies or alternative technologies for treating infections that could potentially reduce reliance on antibiotics have been suggested. Some are under development. These include therapeutic antibodies, bacteriophages, antimicrobial nanoparticles and antimicrobial peptides, among others. While these technologies may have promise, they are considered decades away from providing viable alternative treatments, and even then may never fully replace the need for effective antibiotics.[10,11]

Stimulating antibiotic innovation alone will not address antibiotic resistance over the long term. Ensuring infection control, sustainable use and greater access are also key.

Antibiotic resistance is a global problem, but far more people die today from a lack of access to antibiotics than from resistant infections. More than one million children die every year from pneumonia and sepsis, often treatable with inexpensive, older antibiotics.[12] Increasing access to effective antibiotics is therefore a global priority. At the same time, with growing incomes and weak

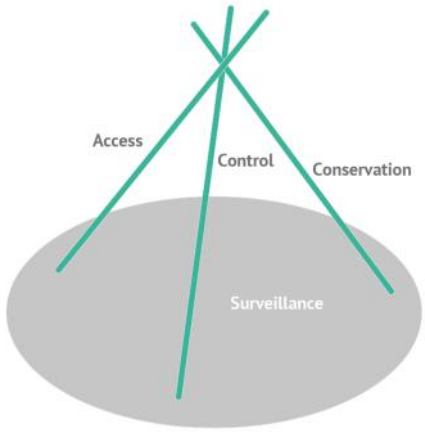
regulatory frameworks to control use, many countries also face the challenge that antibiotics are used inappropriately – for example, to treat virus infections. If antibiotics are used inappropriately, drug resistance will accelerate, increasing the need for innovation. The key challenge is to ensure access to new and old antibiotics without generating excess use due to the lack of health infrastructure and effective sustainable use mechanisms such as surveillance and antibiotic stewardship.

Pharmaceutical innovation is time-consuming (at least 10–15 years from discovery to market), risky (approximately 95 per cent of candidates fail) and expensive – from $250 million (€206 million) to more than $1 billion (€850 million).[13-16] Developing completely new antibiotics is scientifically complex, and there is no guarantee of success. It is critical to maintain the effectiveness of the world's existing antibiotics to reduce the need to develop new ones to replace them. Innovation will always be necessary, but the pressure to find entirely new antibiotics can be reduced by prolonging the efficacy of existing antibiotics. This includes the continued evolution of existing classes through incremental innovation.[17]

"Prevention is better than cure" remains true in AMR as in other areas of infectious disease. The objective is to maximize the availability and utility of antibiotics as the last defence against AMR, while minimizing the need to use that intervention. Infection control is critical, through investments in water quality and sanitation, increased vaccine use, good hygiene and other infection prevention practices.

To be successful, all incentives should link to four *additional* pillars central to treating patients, protecting society and tackling antibiotic resistance in the broader context: (1) improving equitable and responsible **access** to antibiotic therapies; (2) ensuring that antibiotic therapies are used in a **sustainable** manner (3) increasing **infection control** measures to prevent infections; and (4) implementing and maintaining effective **surveillance** systems to monitor all of the components (see Figure 2).[18] These pillars take a broad One Health perspective, including human, animal and other uses of antibiotic therapies. If investments across these five areas (access, infection control, innovation, sustainable use, and surveillance) are not made, resistance will increase.[18]

Figure 2: Pillars to support innovation[19]



Source: adapted from Hoffman SJ, Outterson K. JLME 2015

Significant efforts are under way to improve antibiotic innovation, including ensuring sustainable use and equitable access.

AMR has been recognized as a global challenge in the top echelons of governments. In September 2016 the United Nations General Assembly agreed a political declaration to tackle AMR, only the fourth time a health-related issue has been on its agenda.[20] Both the G7 and the G20 groups of countries have also included AMR in their agendas.[21-23] In 2017 Germany used its G20 presidency to push for concerted action on AMR, resulting in the establishment of a Global R&D Collaboration Hub on AMR. The World Health Organization (WHO) launched the Global Action Plan on Antimicrobial Resistance in 2015, and this resulted in the development of national action plans to tackle the threat of AMR at a local level.[24]

While DRIVE-AB has been active, new collaborations have been initiated to boost investment in innovation to combat AMR, including the Global Antibiotic Research and Development Partnership (GARDP),[25] the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X),[26] the European Investment Bank's (EIB) InnovFin,[27] and the UK/China Global Innovation Fund.[28] GARDP partners with the public and private sectors to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists, initially prioritizing neonatal sepsis and sexually transmitted infections. CARB-X targets priority gaps in antibiotic R&D, focusing on the preclinical pipeline. InnovFin offers a range of bespoke financial products which will make available more than €24 billion in support of R&D projects undertaken by companies. The non-profit, independent Antimicrobial Resistance Benchmark was launched in 2017 to assess company performance regarding actions to hinder the development of antibiotic resistance.[29] An older initiative, the Global Antibiotic Resistance Partnership, started in 2009 to assist low- and middle-income countries with developing and implementing policies to hinder antibiotic resistance.[30]

In the same period, other initiatives have made proposals on new incentives to stimulate antibiotic R&D. This has enabled DRIVE-AB to share early findings with these initiatives, and to learn from their outputs. The UK AMR Review, chaired by Lord Jim O'Neill, delivered a series of reports recommending a set of high-level actions needed not only to stimulate antibiotic innovation but also to increase infection prevention and surveillance, examine alternative antibiotic technologies and improve rapid diagnostics. It delivered its final report in May 2016.[31,32] The German government commissioned the Boston Consulting Group to assess antibiotics R&D; its results were published in February 2017 in the report *Breaking Through the Wall*.[33] The Duke Margolis Center for Health Policy has proposed innovation incentives aimed at the US market in 2017.[34] The US Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) published a report in September 2017 with recommendations for incentivizing the development of vaccines, diagnostics and therapeutics to combat AMR.[35] DRIVE-AB differs from these initiatives in the depth of its analysis and its strong focus on sustainable use and equitable availability.

The antibiotic pipeline

Methods: DRIVE-AB assessed both the preclinical pipeline (through published data from collaboration with CARB-X[36]) and the clinical pipeline (utilizing data from the Pew Charitable Trust[37] and WHO[38]). For the purposes of identifying gaps in the clinical pipeline, innovation is defined narrowly: namely, antibiotic drug candidates ideally free of cross-resistance to existing classes, including drugs with a novel chemical scaffold, novel molecular target/binding sites and associated novel mode of action. Innovation at this level will be infrequent, but the strong definition is used to identify only truly innovative products.

The current pipeline for innovative antibiotics is insufficient, potentially delivering only one truly innovative antibiotic for at least one critical-priority pathogen within the next five years.

In February 2017 WHO published a priority list of antibiotic-resistant pathogens to guide research, discovery and development of new antibiotics based on global need.[1] The list represents three priority levels: critical, high and medium priority, and was updated in September 2017 to include tuberculosis. The US Centers for Disease Control and Prevention (CDC) published Antibiotic Resistance Threats in the United States in 2013, also with three priority levels (urgent, serious and concerning).[39] The two lists overlap considerably, but assign different priorities to specific organisms, partly because the CDC list was intended to indicate the most pressing public health concerns, rather than guide R&D decisions. DRIVE-AB has utilized the WHO list as a starting point for global priorities for antibiotic R&D.

DRIVE-AB has mapped the identifiable antibiotic pipeline onto WHO's priority pathogens list (Table 2).[40-42] This mapping demonstrates that there are some priority pathogens where there is no evidence of any innovative products in clinical development, according to our definition of innovation (see methods box above). This is not meant to imply that the products in development will not benefit patients; only that few have the potential to meet the high bar for innovation used for this analysis. Ideally, the pipeline would be well-stocked with a variety of entirely new classes of product that are not affected by known resistance mechanisms. The preclinical pipeline appears to be more robust, but it is also important to remember that a very large proportion of these products will fail.[13]Owing to these high attrition rates, a large number of candidates are needed in the early-phase pipeline if a few novel antibiotics are to emerge. This is especially important for the most resistant pathogens where few or no treatment options exist. There is also little information available to assess the attributes of the preclinical candidates, and what is available may be preliminary. In drug discovery and the early stages of drug preclinical development there are not enough publicly disclosed data to estimate the activity of compounds against different species. When these products progress to clinical development, more details will be known including targeted pathogens.

Table 2: Innovative antibiotic candidates in preclinical and clinical development targeting WHO's priority pathogens list, priority level critical and high

Bacteria (WHO category)	WHO (2017)	# in preclinical dev	# in clinical dev
Acinetobacter baumannii, carbapenem-R	Critical	52 + 14 biologics	0
Pseudomonas aeruginosa, carbapenem-R	Critical		1 + 2 biologics
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical		0
Enterococcus faecium, vancomycin-R	High	6	0**
Staphylococcus aureus, methicillin-R, vancomycin-I/R	High	23 + 8 biologics	5 + 7 biologics
Helicobacter pylori, clarithromycin-R	High	0	0*
Campylobacter spp., fluoroquinolone-R	High	0	0*
Salmonellae spp., fluoroquinolone-R	High	1	0
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High	1	2

Notes: The numbers of antibiotic candidates are gathered from sources that are almost certainly incomplete, but are the best currently available. One candidate has activity against both *N. gonorrhoeae* and *S. aureus* and therefore is identified in both rows under clinical development. The preclinical numbers are taken from a sample size of 261 preclinical projects that were submitted to CARB-X in 2016. Only small molecules and biologics (antibodies, endolysins) were considered and other approaches excluded (e.g. combinations, modified old drugs, potentiators including ß-lactamase inhibitor combinations). The clinical numbers were taken from the WHO pipeline analysis and Pew Charitable Trust.[37,38] There are also candidates in the pipeline that offer incremental improvements to existing classes and likely benefit to some patients. For example, as of March 2017 Pew Charitable Trusts had mapped 41 antibiotic candidates in clinical development.[37]
* Indicates that public health measures exist to stop infection.
** Indicates that several antibiotics in clinical development have *in vitro* activity.

Our assessment identifies only one innovative new antibiotic class in clinical development against at least one of the WHO critical-priority pathogens and six against high-priority pathogens (five against *S. aureus* and two against *N. gonorrhoeae*, but note that one candidate has activity for both *S. aureus* and *N. gonorrhoeae*). Projects in the early stages have a high attrition rate and low chance of actually reaching the market within five to ten years, whereas the seven innovative antibiotics against WHO's critical-and high-priority pathogens in clinical development have a higher chance (25–67 per cent depending on clinical trial phase) of reaching the market in the next three to five years.[11,13]

Although the global clinical pipeline for innovative, traditional antibiotics is very thin, additional pathogen-specific biologics (e.g. antibodies, vaccines) are in clinical and preclinical development, but with unknown potential to treat infections. In general, the clinical pipeline reflects the attempts to address class-specific resistance mechanisms by modifying existing antibiotic classes. These drugs are reducing the resistance rates of individual pathogens with specific antibiotic resistance mechanisms. Although our assessment of the preclinical pipeline provides only a high-level view of candidates

based on a sample of projects, there is evidence of an encouraging trend and increasing number of innovative approaches.

Our assessment is also based on developer-provided data indicating which pathogen(s) the antibiotic candidate is targeting. This assessment was not geared towards a defined target product profile (TPP), which could include specifications regarding indications, dosing, treatment duration, delivery mode and efficacy targets. TPPs can define desirable product attributes beyond priority pathogens. Neither WHO's priority pathogens list nor the CDC list has yet been translated into TPPs. To give developers clear expectations of the type of product profile that is desirable, it is important that these TPPs are developed with broad international consensus. This should be an ongoing process as the priority pathogens list must be updated regularly to reflect evolving priorities. However, to give antibiotic developers some predictability, if any pathogen is removed from the list, this should be done with a ten-year grandfather period.

Recommendation: 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.

Predicting the spread of antibiotic resistance

Methods: DRIVE-AB developed methods to use country-level data about resistance levels and population size to estimate the current number of infections caused by two organisms (*E. coli* and *K. pneumoniae)* characterized as "critical" public health priorities by WHO owing to limited treatment options and high rates of mortality. We also used data from four large antibiotic resistance surveillance systems to predict the future spread of antibiotic resistance in individual countries. For each country and selected organism/antibiotic pair, we estimated the number of infections in 2014 and the number of deaths, and we predicted the percentage of resistance and number of infections in five, ten and fifteen years.[43]

The number of infections caused by antibiotic-resistant bacteria varies regionally. In Europe it is moderate but expected to rise. Countries with insufficient infection control measures should expect to see large increases.

Rising global resistance and the emergence of new resistance mechanisms, coupled with a lack of effective antibiotics, are taxing healthcare systems worldwide. Variations and limitations in the available data make it difficult to estimate the current number of resistant infections or predict future trends. For example, the European Centre for Disease Prevention and Control (ECDC) estimated in 2009 that at least 25,000 people die in the European Union each year from bloodstream infections caused by antibiotic-resistant bacteria. The CDC estimated in 2013 that at least 23,000 people in the United States die annually of infections caused by resistant pathogens.[32,39,44] The 2014 AMR Review Report estimated that currently 700,000 deaths worldwide are attributable to infections caused by six AMR species, but this figure includes deaths from resistant HIV, tuberculosis and malaria.[31] Accurate and reliable estimates of the number of infections and their clinical consequences are required to estimate the current and future impact of resistance on healthcare systems and determine future public health needs.

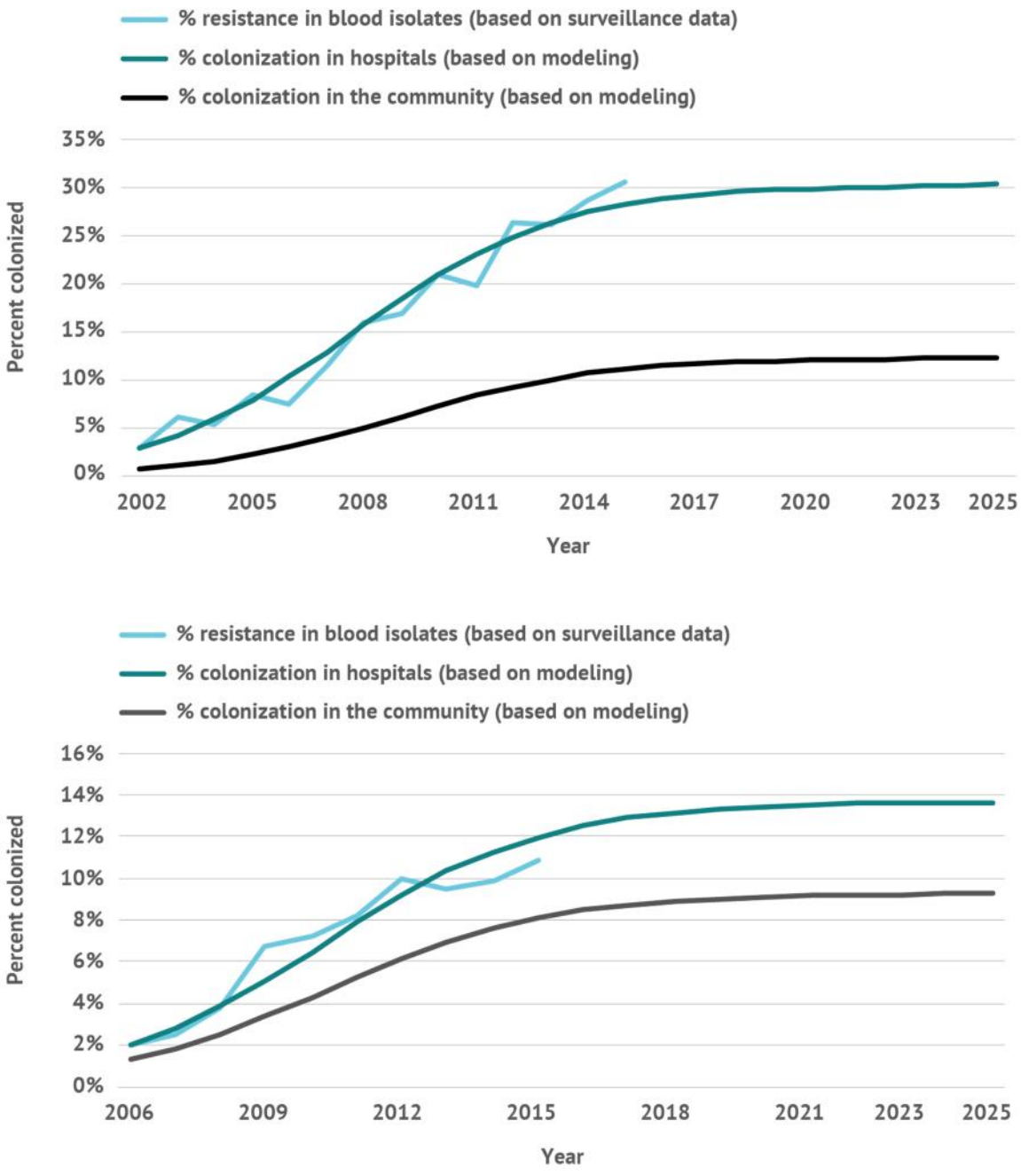
DRIVE-AB has developed methods to estimate the number of infections caused by two "critical" WHO priority pathogens for which treatments are highly limited or non-existent: third-generation cephalosporin (3GC)-resistant *E. coli* and *K. pneumoniae* and carbapenem-resistant *E. coli* and *K. pneumoniae*. We estimate that in the EU in 2014, 3GC-resistant *E. coli* and *K. pneumoniae* caused 91,000 bloodstream infections, 656,000 serious infections, and 2.2 million outpatient infections. Carbapenem-resistant strains caused 11,000 bloodstream infections and 68,000 serious infections.

Given our estimates of the current rate and patterns of spread, we predict that in the EU in 2050 3GC-resistant *E. coli* and *K. pneumoniae* will cause 93,000 (52,000–134,000) bloodstream infections, 672,000 (372,000–971,000) serious infections, and 2.23 million (1.23–3.23 million) outpatient infections – an increase of about 3 per cent across all types of infections. We predict that in the EU in 2050, carbapenem-resistant *K. pneumoniae* will cause 22,000 (12,000–32,000) bloodstream infections and 130,000 (72,000–188,000) serious infections if the current trends continue – an increase of about 107 per cent across all types of infections. We could not predict the future levels of carbapenem resistance in *E. coli*, as it is still in the very early stages of spreading. If this resistance becomes established and spreads in a pattern similar to 3GC-resistant *E. coli*, we can expect at least double the number of carbapenem-resistant *E. coli* infections as predicted for carbapenem-resistant *K. pneumoniae*.

In some EU countries 3GC resistance has already spread widely and has plateaued (or is expected to by 2025), whereas in other countries 3GC resistance will continue to rise through to 2050. We predict that carbapenem resistance will also continue to rise through to 2050. Each country reaches a plateau at a different resistance level. For example, Finland had 5.3 per cent 3GC resistance among *E. coli* in 2014. Our model predicts that this will rise to 6.4 per cent in 2025 and stabilize thereafter. For carbapenem-resistant *K. pneumoniae*, Germany had 1.1 per cent resistance in 2014. Our model predicts that this will rise to 3.8 per cent in 2025 and to 20 per cent in 2050. Resistance to 3GC is at an advanced stage of spread and, although it is responsible for a high number of infections, our model predicts this number will not rise dramatically in the coming years. By contrast, carbapenem resistance in *K. pneumoniae* is still in an early stage of spread in many countries and will continue to rise steadily through to 2050 unless stringent infection-control and antibiotic stewardship measures are adopted.

We found high variability between countries regarding the current and predicted future rates of resistant infections. For example, Figure 3 compares the current and predicted rate of *E. coli* resistance to third-generation cephalosporins in hospitals and the community in Italy and France. France appears to have fairly stable colonization rates in both, whereas Italy's hospital colonization is significantly higher than in the community, expected to reach over 30 per cent of hospital patients.

Figure 3: Percentage of hospitalized patients and people in the community colonized by third generation-cephalosporin-resistant *E. coli*

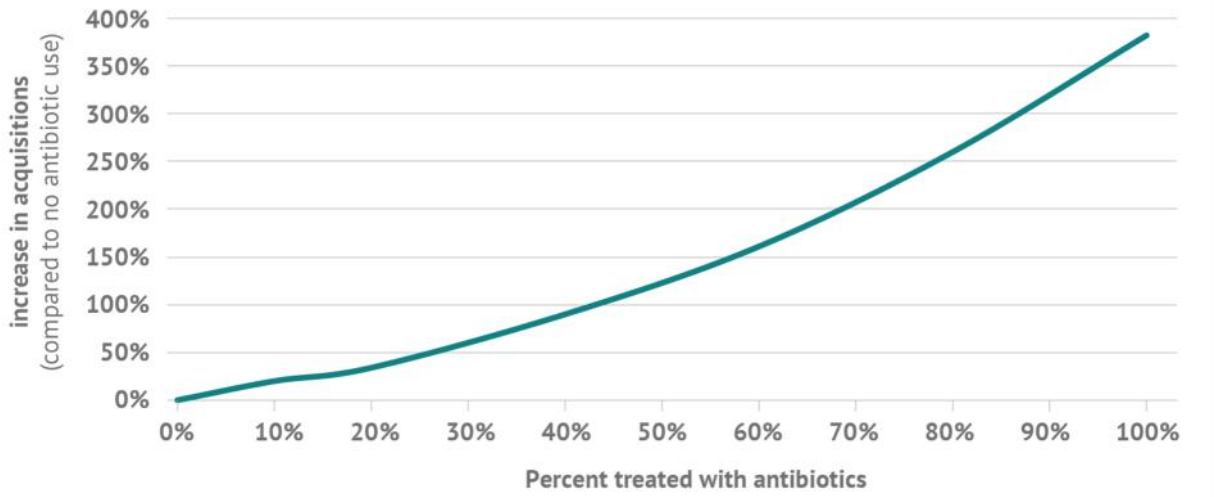


Key:
Red line: % resistance in blood isolates (based on surveillance data)
Black line: % colonization in hospitals (based on modelling)
Grey line: % colonization in the community (based on modelling)

Our models show that the incidence of resistant infections is highly sensitive to infection-control measures and antibiotic use, and therefore implementing appropriate measures in these areas can reduce projected increases. The importance of antibiotic stewardship is clear from Figure 4, which

shows that an increase in the proportion of patients treated with antibiotics leads to an increase in resistance.

Figure 4: The proportion of hospitalized patients colonized with antibiotic-resistant bacteria rises as more patients receive antibiotics



The interval from early establishment of resistance to widespread need for new antibiotics may be brief in some countries.

There are few data on the current number of infections caused by resistant organisms, or the number of new cases in any given time (incidence rate). Most of the large surveillance systems that track antibiotic resistance, such as the ECDC's EARS-Net, do not directly measure the number of infections caused by resistant organisms in each country. Rather, they collect samples of pathogens and report the percentage of resistant organisms that were found in them. However, it is the number of infections that are resistant to treatment that is needed by policymakers to gauge the magnitude of the public health problem and guide the allocation of resources for prevention and treatment. Pharmaceutical companies can also use such predictions to estimate the potential market size for new antibiotics as a factor determining their investments in R&D.

There are no published estimates of the number of antibiotic-resistant bacterial infections worldwide. However, there are some regional estimates. The ECDC estimated that in 28 European countries in 2007 there were 386,000 inpatient bloodstream, lower respiratory tract, urinary tract, and skin and soft tissue infections caused by six resistant organisms.[44] In 2013 the CDC estimated that in the US at least two million people had an infection caused by a resistant pathogen.[39] As these reports focused on high-income countries, we aimed to develop methods for estimating infections that could be applied to all countries. This is important because levels of AMR in low-income countries are reported to be high, and AMR surveillance in these countries is generally weak. An important finding is that resistance data from these countries are limited or lacking. While there is a great deal of uncertainty about our estimates for low- and middle-income countries, our work provides a starting point for assessing the global burden of antibiotic-resistant bacteria. To make reliable estimates, improved surveillance data from low- and middle-income countries are urgently needed.

We focused on infections caused by two specific types of resistant bacteria (*E. coli* and *K. pneumonia)* based on the clinical impact of these infections, and the limited number of safe and effective treatment options available to address them. We based our estimates on data from multinational and national AMR surveillance systems, WHO's 2014 global report on AMR surveillance, and published articles.[45] Our estimates indicate that there were a total of 2.8 million (1.5–4.1 million) resistant 3GC-resistant *E. coli* and *K. pneumoniae* infections in the EU in 2014. We verified our estimates using data from seven EU countries that monitor the actual number of antibiotic-resistant infections (not just the percentage of resistant organisms from patients).

We used data from four large antibiotic resistance surveillance systems to develop models to predict the future spread of antibiotic resistance in individual countries. Resistance generally develops and spreads in a typical pattern. Using prior data collected in countries over time, we constructed mathematical models of how quickly resistance spread. Based on this information, countries were classified into three categories according to the speed of the spread of bacteria resistant to selected antibiotics: slow, intermediate or fast. Knowing that a country has a typical pattern can help us predict what might happen with existing and emerging resistant bacteria. For example, we found that if a new resistance mechanism becomes established in *E. coli*, within five years we can expect that 2.5 per cent of *E. coli* isolates will carry this resistance mechanism in countries where resistance spreads slowly (e.g., because of good sanitary conditions and infection control practices, and low antibiotic use). In contrast, in countries where resistance spreads rapidly, 32 per cent of isolates will be resistant within five years. The pace of spread dictates the demand for antibiotics that are effective against the new resistance mechanism. Our findings underscore that the interval from early establishment of resistance to widespread need for new antibiotics may be brief in some countries.

Deaths from some resistant bacteria, such as carbapenem-resistant *K. pneumoniae,* may double by 2050.

Combining our estimates of the current number of infections with the summary estimates of all-cause mortality (see below), we estimate that in the EU in 2014, there were 26,400 (14,700–38,100) deaths among patients with bloodstream infections caused by 3GC-resistant *E. coli* and *K. pneumoniae*, and 5,200 (2,900–7,600) deaths among patients with bloodstream infections caused by carbapenem-resistant *K. pneumoniae*. We predict that in 2050 these numbers will rise by only 2 per cent for 3GC-resistant *E. coli* and *K. pneumonia* but will double to 10,800 (6,000–15,600) for carbapenem-resistant *K. pneumoniae.*

It is important to note that we calculated all-cause mortality, that is, the number of deaths among patients with these infections. It is not known whether the infection was the cause of death. Thus our results are not comparable to those of the AMR Review, which calculated attributable mortality – that is, the number of patients who died of a resistant infection but would not have died had the infection been antibiotic-susceptible. We chose to focus on all-cause mortality because it is an objective outcome, with fewer of the methodological problems associated with calculating attributable mortality.

Estimating the value of antibiotics

Health technology assessments should evaluate new antibiotics in a way that captures the full range of benefits of these important medicines.

Antibiotics are used to treat infectious diseases. They differ from most other medicines, particularly those directed at non-communicable diseases, in that they reduce transmission when a patient is effectively treated but additionally overuse reduces the effectiveness of these drugs over time. In this section we discuss three distinctive characteristics and sources of value provided by antibiotics: enabling, option/insurance and diversity value.

Antibiotics have become necessary in modern medicine to enable invasive surgical or immunosuppressive medical procedures that depend on preventing infection in the patient. Procedures such as organ transplantation, cancer chemotherapy, hip or knee replacement surgery, transrectal biopsy or appendectomy require the routine use of prophylactic antibiotics that are effective.[46,47] We call this the **enabling value of antibiotics**.

By keeping a stock of unused antibiotics that are not affected by resistance, lives could potentially be saved. To make this clear, Rex makes an analogy between the insurance value of antibiotics and the value of fire prevention:

> In this regard, antibiotics and infection control bear a striking resemblance to the firefighting infrastructure: the microbiology laboratory serves as the smoke detector, medical personnel are the firefighters, and antibiotics are the water supply. All of these elements have to be established before the fire (infection), since buildings burn (and patients die) far more quickly than infrastructure can be built. [48]

This is referred to as **option or insurance value**.

The introduction of antimicrobials with diverse and novel mechanisms of action can help existing and future antibiotics to remain effective by reducing selection pressure.[49] This is referred to as **diversity value**. It depends on the number of existing therapeutic options and the extent to which these can be displaced by a new antibiotic.

Some examples of valuation are included in Appendix D.

Like other biomedical technologies, antibiotics are subject to health technology assessment (HTA) procedures with the aim of evaluating their clinical efficacy, cost-effectiveness, safety, and legal and ethical implications,[50,51] thereby assisting decision-making agencies reach clinical, economic, management and policy decisions that can have an impact on the health of entire populations. Current HTA procedures may not fully recognize the economic value of new antibiotics to patients and society, although this is changing.

In the European AMR Action Plan that was launched in June 2017, the European Commission committed to "develop new or improved methodological HTA approaches and foster methodological consensus-building".[52] The French Comité économique des produits de santé has given special consideration to new antibiotics « with a new active ingredient » [« *à base d'une nouvelle substance active* »] which allows the manufacturer special latitude in negotiating price.[53] However, the French guidance does not provide supporting information, so it is not possible to know the reason for this special dispensation or form an independent assessment of its appropriateness. Moreover, the

specific exemption for antibiotics is couched in terms which are highly specific to the French reimbursement framework.

DRIVE-AB recommends that new antibiotics should be evaluated in a way that captures the full range of benefits of these important technologies. This includes performing a sensistivity analysis at the population level of the impact of resistance to the new antibiotic, both initially and over time. The direct costs and benefits associated with treating one patient with an antibiotic, where relevant, should also take account of the indirect benefits from avoided onward transmission, and diversity benefits from the protective effects on existing antibiotics currently in use.

Recommendation: 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, the development of HTA processes to better capture the societal value of antibiotics in coverage and reimbursement decision-making.

Push and pull incentives

Methods: The DRIVE-AB innovation incentives have been selected via a multi-stage process. A literature review was undertaken to identify both published and grey literature containing theoretical or existing economic incentives for stimulating any type of biopharmaceutical innovation (see Appendix B). Focus groups and a further literature review gathered potential incentives from other industries such as defence. SMEs were consulted through a face-to-face meeting and a survey. DRIVE-AB members (including academics, industry and public health policy experts) were then asked to assess each potential incentive mechanism against different criteria including the incentive's ability to stimulate antibiotic innovation and its impact on sustainable use and equitable availability. On the basis of this evaluation a short-list of plausible and feasible incentives was developed, extensively reviewed by DRIVE-AB academic and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners and presented at high-level internal and external stakeholder meetings. Feedback from stakeholders was then integrated into the design of the models prior to further internal review and model refinement.

DRIVE-AB finds four incentives best suited to fill the antibacterial pipeline and ensure the effectiveness and availability of new antibiotics over time.

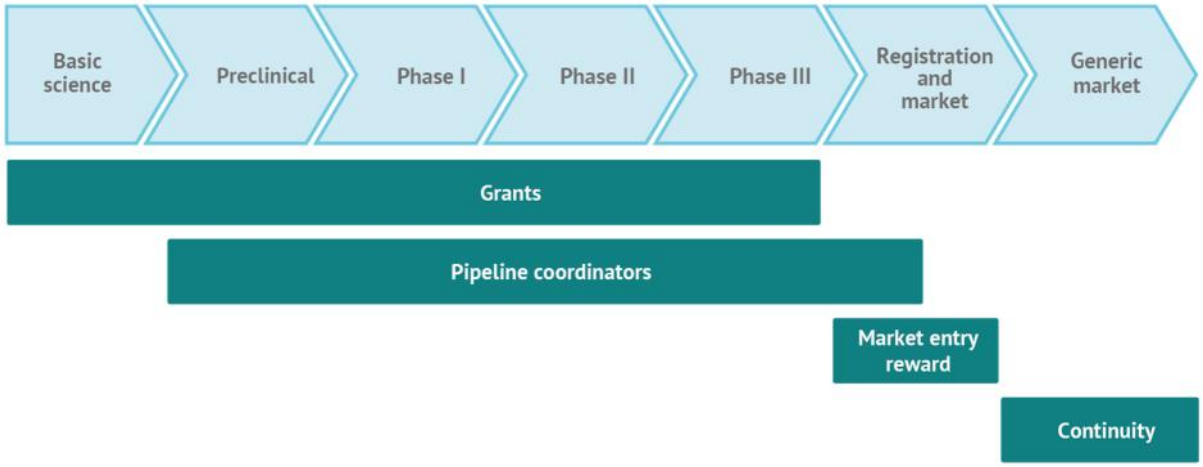
There is no "one size fits all" solution to incentivizing antibiotic innovation in a global market with a variety of unmet needs, healthcare systems and access requirements. A menu of incentives is required that can be adapted to the local context, and yet still achieve the same goal of stimulating antibiotic innovation. We reviewed 35 incentives designed to stimulate greater innovation within pharmaceutical R&D as well as incentives from other industries. For an incentive to be considered promising, it had to be rated as effective by all three groups of voting members (academic, industry and policy) for stimulating innovation, and able to build in equitable availability and sustainable use mechanisms. On the basis of this review, we found four incentives best suited to fill the antibiotic pipeline and ensure that critical antibiotics continue to be accessible:

- **Grants**: non-repayable funds to academic institutions, companies and others, paying for R&D.
- **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 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.

Innovation incentives can be categorized as either "push" or "pull". Push incentives pay for the ongoing R&D. Pull incentives provide rewards to developers for delivering products with characteristics specified by the funder. Both types are important for stimulating antibiotic R&D. Grants and the pipeline coordinator are push incentives. Market entry rewards and the long-term supply continuity model are pull incentives, since they reward successful development or continued

availability of a priority antibiotic. Each incentive is intended to stimulate different phases of the R&D process (see Figure 5). Each can be implemented in customized ways depending on the health need to be addressed. These models do not operate in isolation and are designed to be complementary to maximize the impact on the antibiotic pipeline.

Figure 5: Innovation incentives by R&D phase



DRIVE-AB also assessed a dual-payment, in-patient model based upon disease and pathogen diagnosis and duration of treatment, the Diagnosis Confirmation Model.[54] In this model, if a new antibiotic is prescribed empirically and treatment continued for the full course, indicating it is deemed necessary based on diagnostic results or physician judgment, a price reflecting the full value of the antibiotic would be applied. The full value of the antibiotic would need to be determined by HTA agencies on the basis of clinical benefits for patients and society. If, as a result of the availability of diagnostic results after the initiation of therapy, the decision is made to de-escalate the novel therapy, the price for the first few days' use would be set to a lower price comparable to the de-escalated therapy.

This model reduces financial concerns related to the use of newer antibiotics to address multi-drug-resistant infections when the patient's diagnosis is still uncertain but with risk factors that warrant appropriate empiric coverage that is not achieved with alternative antibiotics. The model has not been included by DRIVE-AB as one of the recommended innovation incentives because the market entry reward was determined to be better aligned with the overall goals, including equitable availability and stewardship. Specifically, some DRIVE-AB members were concerned that a relatively low price for empiric therapy might incentivize inappropriate empiric treatment with novel antibiotics. Relatedly, some members were concerned that the full duration price might need to be high in order to achieve an attractive return on investment, and that this might inhibit access. With appropriate care, the model could be tested in well-developed health systems that are able to provide access to diagnostics and that have stewardship systems in place to support appropriate use and de-escalation. Conversely, the model is not feasible in markets with limited healthcare infrastructure.

Grants

Methods: DRIVE-AB has assessed calls for grant applications in the AMR field from 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 throughout the antibiotic R&D pipeline, and how they address the challenges faced by SMEs. We have also simulated grant financing for clinical trials (see Appendix C). 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.

A significant amount of push funding is channelled towards antibacterial R&D. Greater coordination could help focus investments on public health priorities.

Push incentives seek to overcome two major R&D bottlenecks: scientific challenges and clinical development costs. R&D grants are an important push mechanism to stimulate basic and applied research in AMR. The OECD estimates that $547 million (€451 million) are invested annually in antibiotic R&D push mechanisms, almost all of which are provided as grants.[55] Yet there is little transparency with many national investments, making this figure uncertain.

In the US, the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) are the largest public funders of antibiotic research and development. The NIH funds projects through a variety of mechanisms including: grants awarded to universities and institutes for basic and early-applied scientific research, cooperative agreements and contracts. Small businesses (as defined by the US government) are specifically eligible for small business innovation research (SBIR) and small business technology transfer (STTR). All NIH grant applications are competitive, subject to a peer review process, and may be broadly or narrowly focused in objectives and scope. BARDA does not fund research in basic science but instead focuses on the development of medical countermeasures to bio-terrorism and antibiotic resistance.

European national strategies for AMR and antibiotic-related R&D investments vary by country. For example, the Medical Research Council (MRC, UK) has launched an initiative called “Tackling AMR”, which had four themes: 1) understanding resistance mechanisms; 2) development of therapeutics and diagnostics; 3) understanding the real-world interactions – the threat of AMR in the indoor and built environment; and 4) behaviour within and beyond the healthcare setting.[56] The French National Agency for Research (ANR) generally has a very broad approach to basic science grants, but the government sought to address development and commercialization gaps by investing in the ASTRID Programme.[57] ASTRID has similarities with NIH SBIR/STTR grants and the BARDA model. It was created to encourage public-private partnerships and technology transfer from academic research to industry, and to support R&D of technologies, including biotechnology, with national defence and public health potential.

In Japan, the Agency for Medical Research and Development (AMED) was created in 2015 using the NIH as a role model.[58] Priorities for research in infectious diseases were set very broadly with a reference to common epidemiological risks in East Asia. Calls for research funding were part of a

wider e-ASIA Joint Research Programme (JRP),[59] which fosters research among publicly funded institutions of the Association of Southeast Asian Nations (ASEAN) and eight other countries: Australia, Japan, New Zealand, China, India, the Republic of Korea, Russia and the United States.

At the supranational level, there are notable funding and coordinating initiatives in the EU and the US: the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR),[60] the Innovative Medicines Initiative's (IMI) programme New Drugs 4 Bad Bugs (ND4BB),[61] and the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X).[26] While JPIAMR and, in part, IMI fund research conducted exclusively in member states, CARB-X has global outreach and does not restrict access to funding according to the developer's geographical location. JPIAMR is mostly focused on research regarding antimicrobial resistance, with the aim of translating results to new prevention and intervention strategies to improve public health.

The advantages of grant funding reside in the opportunity for targeted approaches to R&D, where the objectives of the research programme can be tailored to tackle public health needs, and to focus research on areas that create major scientific and technological bottlenecks. It enables a wide range of researchers to be incentivized, ranging from research teams at universities, research institutions and SMEs to those in large pharmaceutical companies. Our analyses of antibiotic grants demonstrate that *communication* between the grant-giving agencies is occurring, for example through the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)[62] and JPIAMR. But this has not yet resulted in *coordination*, where funders target common goals and work together to identify R&D gaps. JPIAMR has succeeded in getting its 26 member countries to agree to a Strategic Research Agenda, but funding calls explicitly tie national financing to nationally selected priorities.

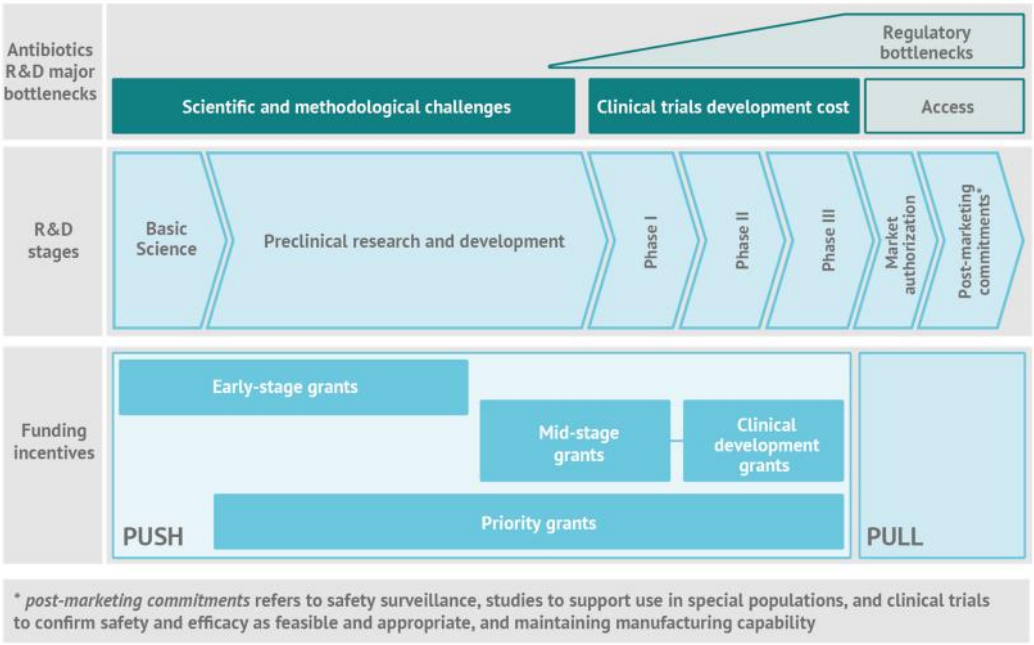
Proposed grant mechanisms

DRIVE-AB proposes a model of four related and partially overlapping grant incentives with the aim of stimulating R&D of new antibiotics (Figure 6):[63]

- Early-stage grants
- Mid-stage grants
- Clinical development grants and
- Priority grants

The intention here is not to replace the existing grant-giving mechanisms but to recommend enhancements.

Figure 6: **Push-funding incentives, R&D phases and major R&D bottlenecks**



Early-stage grants target basic and applied scientific research, and drug discovery and early development activities. These are divided into two main groups. The first group has broad research objectives, mainly focused on basic and early, applied scientific research. Through this funding mechanism, research would be targeted towards public health needs (e.g. identification and investigation of new antibiotic resistance mechanisms as they emerge, principles of drug penetration and efflux). The main recipients of these grants would be academic research groups and research institutes. Such research grants should foster collaboration among research groups, the training of young scientists, and cooperation between academia and SMEs if there is a need and mutual benefit. Examples of these types of grants include NIH grants for academic research, MRC, ANR and JPIAMR. The second group of grants supports drug discovery activities at universities, non-profit research institutions, SMEs and drug discovery units of large pharmaceutical companies. The funding priorities should mainly be based on the WHO critical pathogens priority list but also allow for funding of general innovative approaches for future public health needs (an example of a funding mechanism could be NIH SBIR/STTR or the French ASTRID Programme). SMEs report that the NIH SBIR/STTR mechanisms are effective in stimulating SMEs, whereas the EU's requirements in JPIAMR and IMI for large consortia may slow and increase the cost of the research. EIB's InnovFin Infectious Diseases Finance Facility provides a range of financial products to companies developing vaccines, drugs, medical devices and diagnostics for combating infectious diseases.[27] SMEs report that InnovFin has a low appetite for risk, making it difficult to secure funding for early-development projects.

Mid-stage grants are designed to help project advancement from the preclinical stage, toxicology and manufacturing to the end of phase I clinical trials. They are targeted towards R&D of treatments (and diagnostic tools) against pathogens on WHO's priority pathogens list (PPL). The main recipients of these grants should be SMEs, industry, public-private consortia and non-profit research groups and institutes. Although the current trend in the EU is to oblige mid-stage research to move towards a collaboration and consortium approach, this should not be the primary operational mode. Developers should not have to collaborate and should be allowed access to needed funding on their own account. It is also important to emphasize two aspects of mid-stage R&D grants: 1) a developer should be able to apply for a mid-stage grant at later phases of preclinical R&D (toxicology and/or manufacturing stage); 2) after successfully accomplishing phase I clinical trials, the developer should be able to proceed directly to clinical development (phases II and III) by utilizing clinical development grant funding. The bureaucratic application barrier should be removed by streamlined progression to clinical development and accelerated access to the EU clinical trial network, e.g. as in COMBACTE-NET.

Clinical development grants are designed to support projects through clinical development phases II and III, by utilizing the clinical trial support grant financing mechanism (see below). These grants aim to progress antibiotics towards clinical development by offsetting the opportunity costs that arise when a developer has competing projects in its portfolio and/or limited financial resources. In addition, this incentive should help developers attract investors by reducing the financial risk of clinical trials.

These grants would be targeted towards public health needs defined through a TPP for one or more pathogens on WHO's PPL, and for clinical development of innovative/novel antibiotics and AMR therapeutics. The developer could apply for this financing mechanism directly, and be subject to peer review, or could proceed from previous mid-stage grant funding conditional on successfully accomplishing a phase I and review process.

The amount of financial support for clinical trials would be determined according to cost estimation (which is mainly determined by the intended clinical indication and number of patients). Additional stipulations attached to clinical development grants should include:

1) If the developer receives an award in the form of the pull funding such as the market entry reward, the reward should be reduced by the full amount of clinical trial grants received.

2) The developer should adhere to all grant contractual obligations including regulatory, sustainable use and monitoring requirements.

Priority grants target the development of innovative/novel antibiotics and AMR therapeutics across all phases of R&D. These grants should be strictly focused on antibiotic-resistant bacteria that pose imminent threats owing to rising incidence, and should ideally support the development of innovative antibiotics and/or AMR therapeutics that will defy cross-resistance. The panel of experts led by WHO has already compiled the PPL and assessed the antibiotic R&D pipeline to identify the gaps and inform the funding agency or agencies about the priority public health needs. This grant scheme should have an option for a long-term duration (10 years or more, to support research from the preclinical stage to the completion of phase III clinical development). The contract arrangement between the funding agency and the developer should stipulate instalment payments based on successful accomplishment of pre-agreed milestones (e.g. successful termination of one R&D stage and technological readiness to proceed to the next stage). To support phases II and III of clinical trials, priority grants should have flexible funding via a clinical trial support grant.

Priority grants should ideally focus on candidates that are unlikely to be subject to existing resistance mechanisms or that have a low propensity for resistance development, most likely achieved by targeting a new binding site and new mode of action, and representing a new chemical class that was not previously commercialized. This includes innovative approaches and technologies and is not limited to small-molecule antibiotics. However, candidates with the potential to provide treatment options to patients lacking acceptable options should also qualify.

Additional grant financing

Further targeted funding is required to increase the number of candidates entering the pipeline and the numbers progressing to registration in this high-attrition R&D area.

The imprecision of the current estimate of grant financing into antibiotic R&D makes it difficult to estimate exactly how much more should be invested. Existing financing could also be more effectively allocated, leading to better outcomes. On the basis of our feedback from developers (particularly SMEs) and our analysis of the pipeline, we estimate that additional annual global push funding in the range of $200 million to $500 million (€170 to €412 million) would particularly benefit early-stage research (to increase the number of molecules entering preclinical research), and help

attract investors to support clinical development (by sharing the financial risks of clinical trials with high attrition rates).

The AMR Review recommended a Global Innovation Fund of $2 billion (€1,650 million) over five years to support basic and non-commercial research in drugs, vaccines and diagnostics across all microbes. Our recommendation is not to create a new fund, but to utilize the existing grant mechanisms that already function well today. Our analyses also point to the need for sustainable financing over a longer period than five years. The entire pipeline is currently sparsely filled. It will take time and continuous investments to develop it into a pipeline that sustainably brings new antibiotics to market. It is also evident that, without a "pull" incentive (e.g., market entry reward) to compensate for the lack of a viable market, increasing grant funding will have a negligible effect in incentivizing private-sector companies to develop new antibiotics.

Recommendation: 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) to absorb and effectively deploy more capital. Given 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 to target pathogens that pose most urgent public health threats (e.g. WHO's priority pathogens list (PPL) for the discovery phase and TPPs for the development phase).

Pipeline coordinators

Methods: This section is based on our analysis of the antibiotic pipeline and stakeholder interviews with different types of developers (large, medium and small pharmaceutical companies and non-profit developers). It also draws on the experience of product development partnerships in managing R&D for diseases that mainly affect developing countries.

There are notable gaps in antibiotic R&D for products that are a public health priority because of insufficient investment. More effort is needed to coordinate the allocation of R&D resources to fill priority gaps.

While it may be possible to use incentives such as market entry rewards to stimulate greater innovation for novel antibiotics against predefined high-priority pathogens, such incentives may not be the most cost-effective in terms of stimulating other types of necessary antibiotic innovation. For instance, companies may focus on pathogens that occur in high-income countries because there are well established supply chains, healthcare distribution systems and infrastructure, as well as internal capacity to service these well-established markets. Infections caused by certain pathogens may be more commercially attractive, even with the introduction of a market entry reward.

Reviewing the current antibiotic pipeline demonstrates that not all pathogens are equally attractive for developers. Most development activity is concentrated around four pathogens (*Acinetobacter baumannii*, *Pseudomonas aeruginosa, Enterobacteriaceae* and *Staphylococcus aureus).* We have not identified any products under development for clarithromycin-resistant *Helicobacter pylori* or fluoroquinolone-resistant *Campylobacter*, and identified only one in preclinical development for fluoroquinolone-resistant *Salmonellae.* The likely reason is the extent of the paying market, based on the geographic area of need. For *H. pylori*, public health measures exist to stop infection, making the lack of antibiotics only important to countries with weak health systems. Correspondingly, drug-resistant *Salmonellae* is largely confined to India.[64]

In some instances, there may be less costly options than market entry rewards. For example, companies may have already invested in developing potential antibiotics but then abandoned them because of the lack of an attractive market, meaning that a partially developed product now resides in the public domain. GARDP has initiated the Antimicrobial Memory Recovery Initiative to identify these forgotten or abandoned antibiotics and stimulate the development of promising candidates.[65] Other resources with a similar objective include the Shared Platform for Antibiotic Research and Knowledge, and AntibioticDB.com.[65-67]

For some bacteria, alternative treatments may also be successful, such as faecal microbiota transplantation in the case of C. *difficile*. Incremental improvements may also be beneficial. For example, reformulations of existing antibiotics to tolerate higher temperatures or to create oral paediatric formulations are also needed.

These are examples where *targeted* and proactive public R&D investments are required, supporting the need for an additional incentive to fill R&D gaps for unmet public health needs. For these a pipeline coordinator is needed to closely track the antibiotic pipeline (or subsets thereof), identify gaps, and actively support R&D projects to fill these gaps.[68] The difference between a pipeline coordinator and a traditional funding organization is the active involvement of the pipeline

coordinator in R&D management, the ability to organize finance for identified gaps (using both direct invitations to identified organizations and open calls for proposals) and the use of multiple forms of financing (including forgivable loans, milestone payments, equity investments and grants).

Pipeline coordinators are common in R&D of specific relevance to low- and middle-income countries. Organizations called product development partnerships (PDPs) are non-profit R&D organizations with a focus on developing new medicines, vaccines or diagnostics to meet the needs of patients in these countries. They are usually virtual R&D organizations, pursuing portfolio management through investments in R&D projects at universities or research institutes, and in the private sector. They are funded by grants from development agencies and philanthropic bodies, and the resulting technologies are priced to ensure accessibility.

The key functions of a pipeline coordinator include the following:

- **Technical gap analyses** based on unmet public health need for a **proactive selection** of relevant projects within the pipeline coordinator's funding portfolio;
- **Financing with active oversight** and technical advice to selected projects; funding tools may include forgivable loans, milestone payments, guarantees on loans given by third-party financing institutions, and equity in companies;
- **Portfolio management** across the specified clinical pipeline;
- **Coordination** with other key supporting actors and organizations (e.g., JPIAMR, CARB-X, BARDA, GARDP, IMI/ENABLE) to catalyse and mobilize funding;
- **Partnering and deal-making**: relationship brokering to assist companies with potential products meeting public health needs that want to exit to find suitable partners.

There are already three organizations that operate like a pipeline coordinator for antibiotics – BARDA, CARB-X and GARDP – each within its own well-defined area. BARDA focuses on clinical development, CARB-X on preclinical development, and GARDP instead takes a therapeutic approach, focusing initially on neonatal sepsis and sexually transmitted infections. Each takes a proactive gap-filling stance to ensure a robust pipeline within its mandate. Stakeholders have repeatedly acknowledged the important role that these organizations play in developing antibiotics.

DRIVE-AB recommends that funders enable these three organizations to fulfil their goals. BARDA, as a US governmental body, is understandably closely tied to the specific needs of the United States, and other governments are not likely to fund BARDA directly. CARB-X, however, has a more diversified funding base including BARDA, Wellcome Trust and others. GARDP, born out of DND*i*, has a strong focus on the unmet public health needs of low- and middle-income countries.

Recommendation: To ensure that progress is made on all identified priority pathogens, targeted portfolio-based approaches such as BARDA, CARB-X and GARDP – i.e. pipeline coordinators – should be supported and expanded.

Reviewing 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 political coordination, like the G20's Global R&D Collaboration Hub on AMR.

Market entry rewards

Methods: DRIVE-AB has conducted a literature review of novel antibiotic incentive model proposals and performed intensive internal review and stakeholder interviews with developers, payers, venture capital firms and others (Appendix B). Once there was broad agreement on the key components and parameters, we performed a detailed simulation of market entry rewards, evaluating the impacts of both fully and partially delinked market entry rewards, tightly-focused or broadly-inclusive market entry rewards, and the effect of increased market sizes. We have also engaged in a national pilot design of a delinked model, allowing us to begin to assess the operational impacts of implementing this model.

The current market incentives are not stimulating innovation sufficiently for emerging and unmet public health needs.

Why a market entry reward?

Since the 1980s, only three new classes of antibiotics have reached the market.[4,6] Developers of all types have told us that without some intervention to incentivize private investment, the current business model for antibiotics will not deliver the level of innovation needed to address AMR. There are many reasons for this. The development of new antibiotics is primarily focused on the treatment of diseases caused by bacteria resistant to existing antibiotics. The uptake curve for safe and effective novel antibiotics is generally slow for a number of reasons: there may be limited data on resistance patterns; new drugs are often set aside to preserve effectiveness; resistant infections may be relatively rare; and appropriate diagnostics may not be available or routinely used. The cumulative developer return on investment for novel antibiotics is relatively low, especially when compared with many other profitable therapeutic areas.

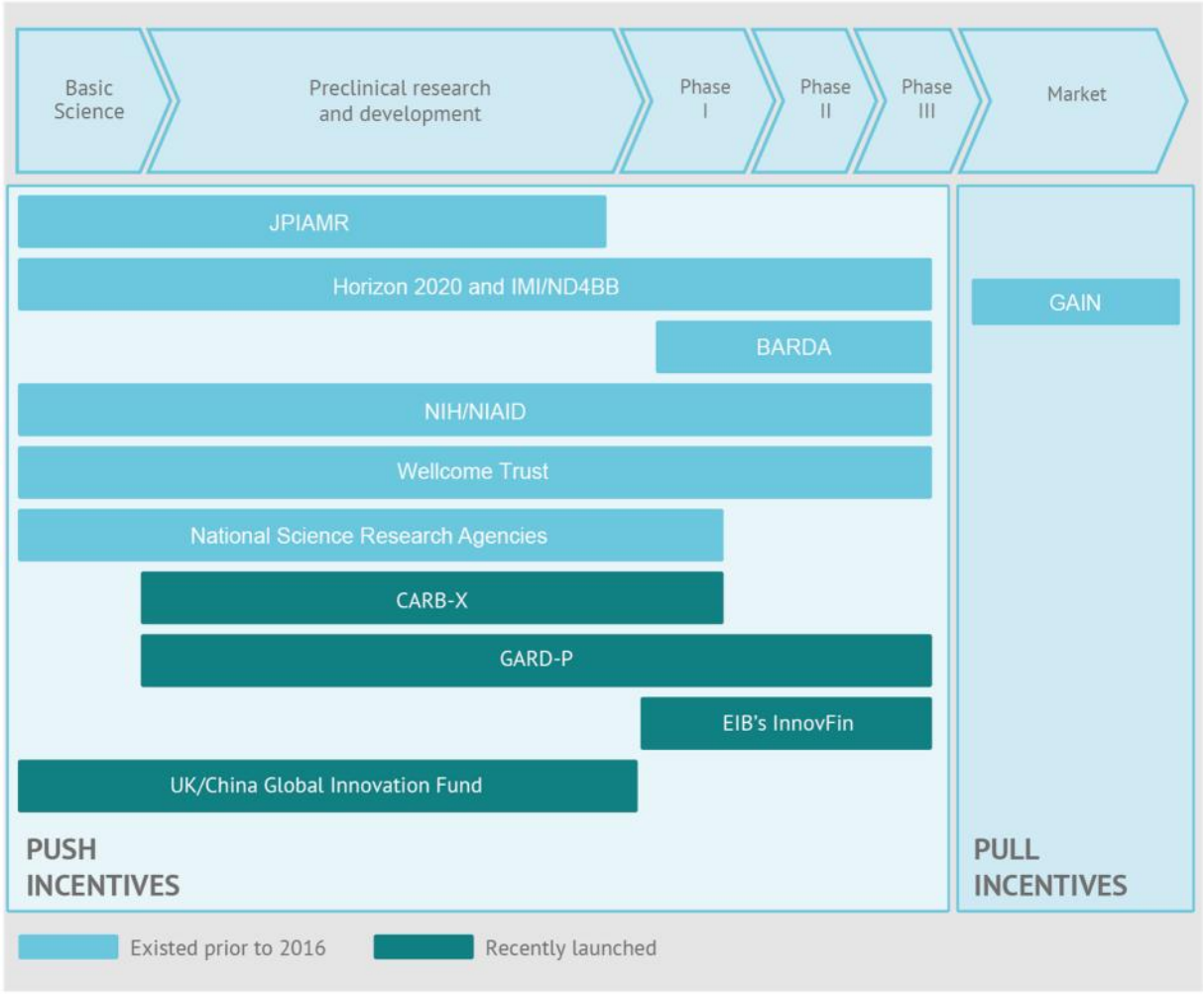
Global annual sales of antibiotics are about $40 billion (€33 billion).[69-71] These revenues are spread across many antibiotics, including primarily older generic antibiotics. Only about 10 per cent of this spend is attributed to patented antibiotics. Novel antibiotics targeting resistance are a subset of the existing market.

Some antibiotics have significant earnings decades after the initial product launch and patent expiry. However, in the past decade it has become unusual for a new antibiotic to achieve more than modest revenues for the reasons stated above. For example, fidaxomicin (a pathogen-specific, innovative antibiotic for *C. difficile*, which is a CDC urgent-level threat) was approved in the US in 2012 and had American and European sales of less than $75 million (€62 million) in 2015.[72,73] As stronger antibiotic stewardship measures are implemented, the market size for novel antibiotics will be largely determined by the growth of antibiotic resistance. In countries with low rates of resistance and strong antibiotic stewardship routines, such as Norway, physicians leave new antibiotics on the shelf for a "rainy day", strictly limiting volume use and consequent revenues to the developer.[74]

The high direct and opportunity costs of antibiotic R&D and low revenues dissuade investors and developers. As of August 2017 there were 41 antibiotic candidates under clinical development, but, as stated earlier, this pipeline can be expected to deliver only one new class of antibiotics for a critical priority pathogen within the next five years.[37] In response to the dwindling pipeline, there has been a significant increase in push funding for antibiotic innovation (Figure 7). However, pull

incentives are largely missing. Push incentives could theoretically cover all of the R&D costs, but if the market is limited there will still be little private-sector interest. Revenues, leading to an attractive return on investment, are required as this will drive private investment in antibiotic R&D and pull products through clinical development to market approval. Most of the current public funding for antibiotic R&D is via push mechanisms (BARDA, CARB-X, GARDP, InnovFin). The failure to implement a meaningful pull incentive in the short to medium term threatens the viability of the existing push mechanisms that either finance companies directly (including BARDA, CARB-X and InnovFin) or partner with companies (GARDP). To a large extent, these push mechanisms seek to use public funding as leverage to attract subsequent private investment for clinical development and commercialization. If investors and pharmaceutical companies continue to exit antibiotic R&D because of perceived market unattractiveness, significantly more public funding will be needed to cover the costs and risks of clinical development and the commercialization of antibiotics.

Figure 7: Major publicly funded incentives, by R&D phases



One pull mechanism has recently been implemented: in the US, Generating Antibiotic Incentives Now (GAIN), signed into law in 2012, extends the existing regulatory exclusivity of new antibiotics for an additional five years. Stakeholders report that while GAIN has had a positive impact, it is generally insufficient to stimulate the types of innovation required to address AMR. The additional regulatory exclusivity runs concurrent to any existing patent life, and given the slow uptake curve of antibiotics

and the time value of money as a pull incentive, this additional exclusivity will do little to improve the business case for investing in antibiotic R&D.[75]

A successful antibiotic business model must reward high investments in innovative antibiotics for the treatment of relatively few patients. DRIVE-AB evaluated 15 unique pull incentives. A market entry reward to stimulate innovation for serious unmet or emerging public health needs was selected because it was considered the most promising by three stakeholder groups (academic, industry and public health), could provide an attractive return on investment for the private sector, and could also encourage sustainable use and equitable availability. Similar proposals have been advocated by others including the AMR Review, Chatham House, the Boston Consulting Group and the Duke-Margolis Center for Health Policy.[32,33,48,76]

A market entry reward is a payment for delivering the desired antibacterial innovation, with strings attached to support sustainable use and equitable availability.

What is a market entry reward?

A market entry reward is a single payment or series of payments to a pharmaceutical developer for successfully achieving regulatory approval for an antibiotic that meets specific predetermined criteria to address a defined public health need. It is embodied in a contract between the payer and the developer that starts at regulatory approval and ends at intellectual property (IP) expiry (that is, generic entry). A market entry reward is a voluntary programme – the developer decides if it will apply for the reward during the clinical development phase of the antibiotic. The main goal of the reward is to encourage greater R&D risk-taking. To be effective in stimulating innovation, a market entry reward should be:

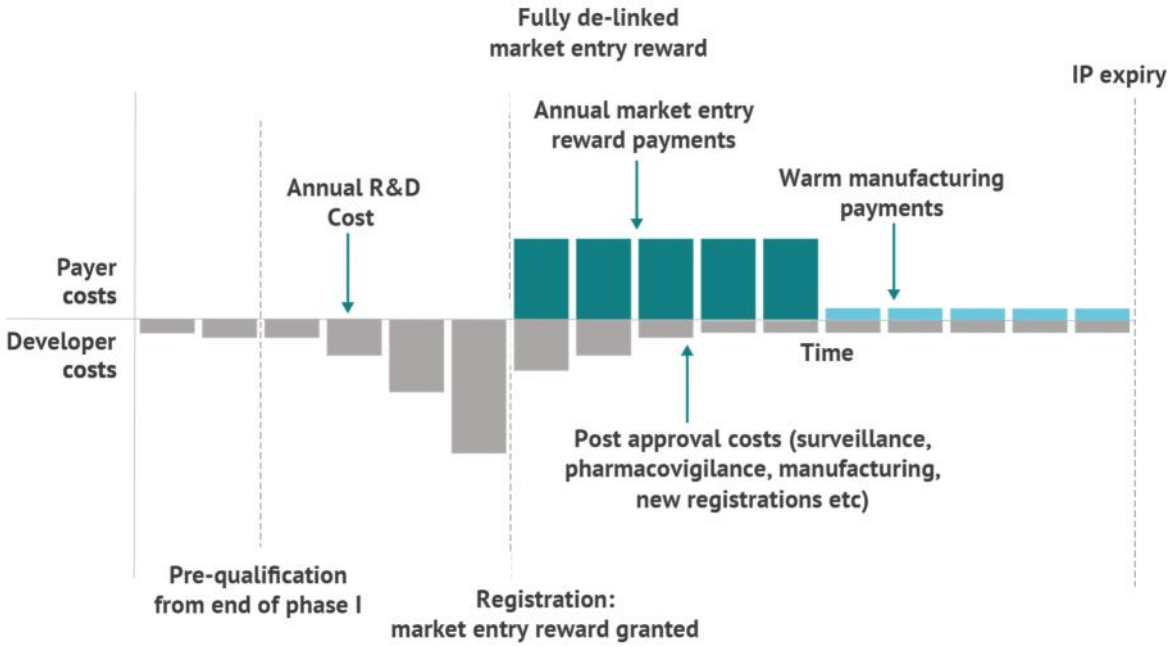
- **Targeted:** market entry rewards should focus on existing and predicted future key public health priorities, through predefined TPPs. They should reward those antibiotics that are predicted to bring the greatest value to society. They should also reinforce the sustainable use and equitable availability of the antibiotic.
- **Sustainable:** Funding must be predictable and reliable. Developers must have confidence that a market entry reward will be available when products secure marketing authorization many years in the future. Given that it can take a decade or more to develop a new antibiotic, the eligibility criteria should remain in place for at least ten years after the criteria are published to promote long-term investments. Once approved, funding should be ring-fenced and not subjected to budget authorizations and annual appropriations that may decrease a reward's reliability and credibility. Although this is difficult, it has been achieved before, for example in the case of US Highway Trust Funds.[77]
- **Transparent:** Funders should transparently evaluate and award market entry rewards on the basis of unambiguous, predefined and transparent criteria.
- **Sufficient:** Net present value (NPV) is a metric commonly used to quantify the time-adjusted value of an investment and thus determine its long-term profitability. The reward must sufficiently increase an antibiotic project's NPV to demonstrate a sufficient return on investment. For the purposes of the simulation, a NPV threshold between $200 million and $500 million (€170 million and €412 million) was used.
- **Supportive**: To support other AMR policies, recipients of the reward must accept a set of conditions, defined by the payer, that support sustainable use and access plans. These conditions are related to product-related communications, global regulatory activity, surveillance and supply.

There are many ways to design a market entry reward. The main structural components that are subject to variation are the payment schedule, the degree of delinkage and the ownership of intellectual property.

Payment schedule (single vs staged payments): Rewards can be paid as one lump sum or spread out over time (e.g., five or ten years) following registration of an antibiotic. Given the time value of money and the risk-adjusted valuation methodology used by the pharmaceutical industry, a single large payment to a developer immediately after regulatory approval is worth more than the same amount paid over time. However, for the payer staged payments are preferable to avoid single, large costs contained in one budget cycle. Additionally, a lump-sum payment limits the ability of the payer to budget the complete cost, ensure developer compliance with contractual conditions or respond in case the antibiotic is withdrawn from the market (owing to post-approval safety or effectiveness concerns). Market withdrawal is a risk to the payer, especially given recent regulatory efforts to allow for smaller and shorter clinical trials for antibiotics. The best solution to this dilemma may be payments spread out over the lifetime of the IP, with larger payments in the first five years and smaller payments to maintain the manufacturing facilities. A staged payment reward is optimal for balancing risk and ensuring a continued relationship between the payer and developer, optimizing product development opportunities and ensuring continued long-term supply. Companies are more likely to comply with performance-linked payments over time, rather than with contractual conditions over many years after a single lump-sum payment has been made.

Delinkage (full or partial): The level of delinkage refers to how much of the developer's revenues are derived from the reward or from antibiotic unit sales. A reward can be designed to be 'fully' delinked or 'partially' delinked (see Figures 8 and 9[ix]).

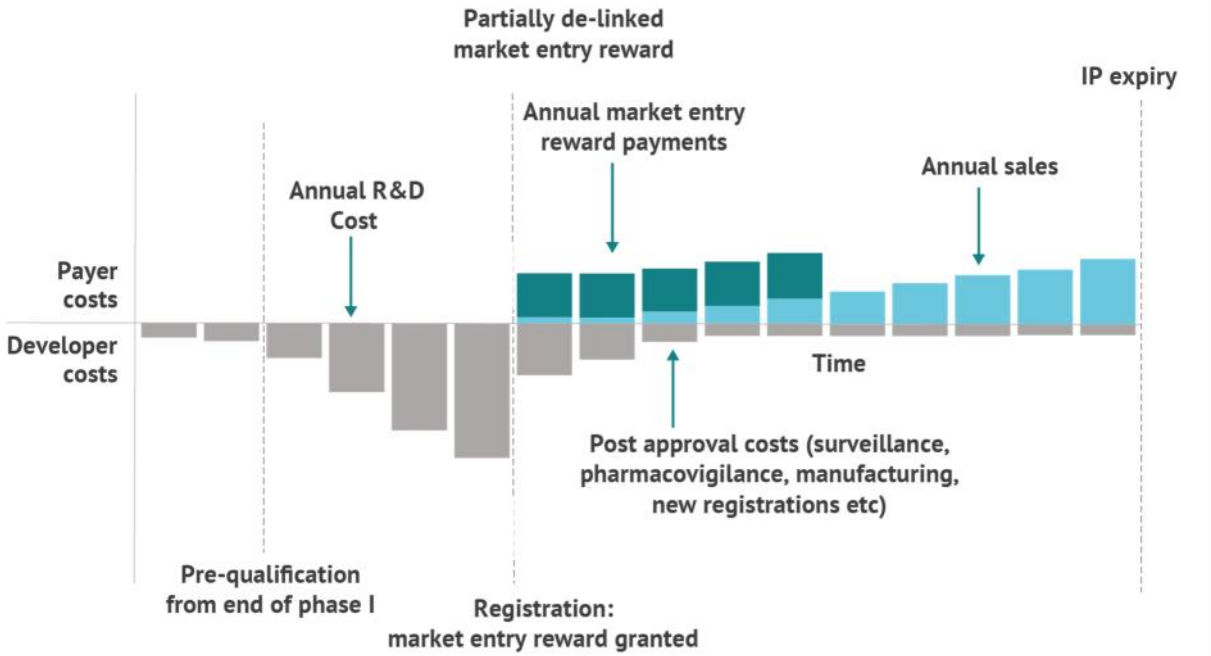
Figure 8: A fully delinked market entry reward



[ix] All figures are illustrative and not drawn to scale and exclude supplementary costs such as developer investments in post-market-entry R&D (life-cycle management), costs associated with maintaining a licence, and product communications.

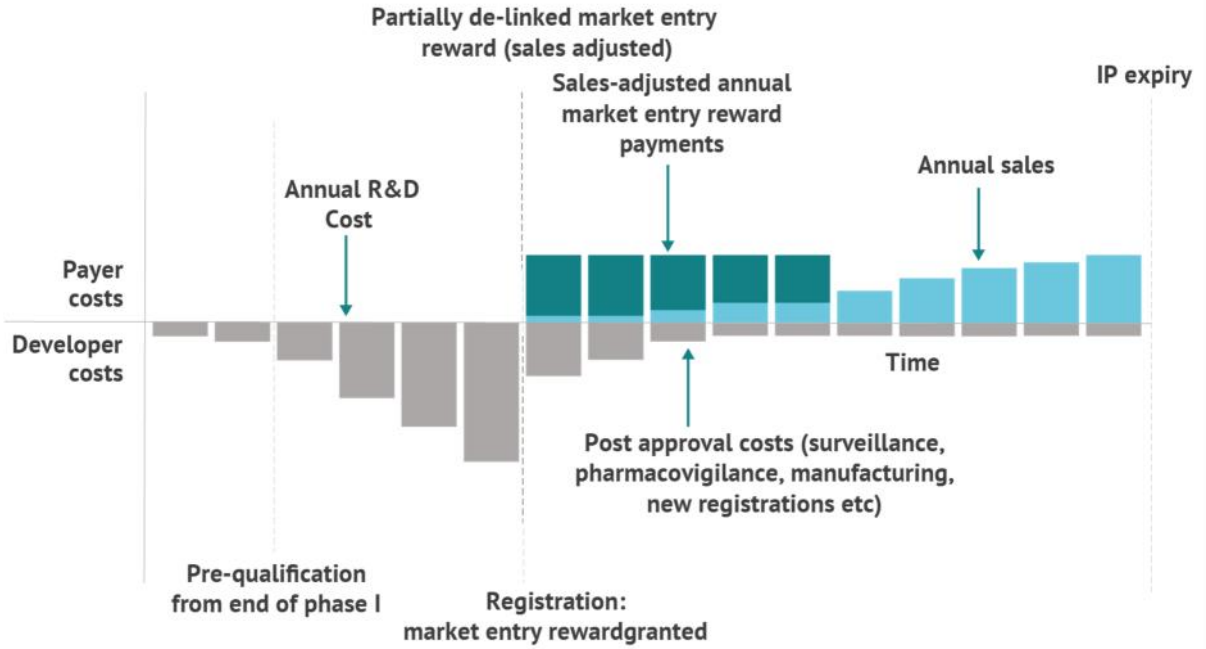
In a fully delinked market entry reward, *all* developer revenues associated with the eligible antibiotic would come from payments over the lifetime of the IP; the antibiotic would be supplied at cost price to the payer (e.g. the national government). However, the cost price may be cheaper than the price of commonly prescribed generic antibiotics. Therefore, a higher price would need to be charged to the healthcare provider to ensure that the newest antibiotics are not cheaper than older ones – a perverse incentive to overprescribe newer antibiotics. The payer would retain the revenues earned from the national healthcare providers. The price paid by the healthcare provider to the payer (e.g. national government) should be set in a way that reinforces stewardship without hampering access. Fully delinked payments could be paid out over multiple years, including small payments closer to the expiry of the IP to maintain "warm" manufacturing facilities.

Figure 9: A partially delinked market entry reward



In a partially delinked model, the developer's revenues would derive from the reward payments and unit-based sales; the developer would set the price as negotiated with the payer(s) and would agree to conditions on sustainable use and equitable availability. It preserves some flexible market-based elements, which lowers the payer's upfront financial commitment and risk, and allows developers to operate within their existing business model. A partially delinked reward could also be adjusted according to sales of the antibiotic. A cap on revenues could be agreed so that sales revenues are subtracted from the annual reward payment for a given year, and any excess sales revenues would reduce the following year's reward (see Figure 10).

Figure 10: A partially delinked market entry reward (sales-adjusted)



All three models (fully delinked, partially delinked and partially delinked sales-adjusted) are based upon the concept of delinkage, which has never been tested to our knowledge. Understanding the operational ramifications of delinkage is crucial to any successful implementation. Assisted by DRIVE-AB, Norway began the process to design a national delinked model. This experience offers lessons on the operational challenges of implementing a delinked model (see Box 2).

Box 2: Operational lessons from the design of a national delinked model[78]

Norway is a small country of five million people with some of the lowest rates of antibiotic resistance in the world. It barely uses novel antibiotics, making the market unattractive for developers. Yet in the rare case of multi-drug resistance, Norwegian citizens expect the government to secure access to effective antibiotics. Therefore, Norway is an interesting case for a delinked model – not to stimulate innovation (the country is too small to do this on its own) but to secure a predictable supply if/when needed. **Although the goals for implementing a delinked model may vary (i.e., to stimulate innovation or to secure access), the operational aspects of implementing delinkage are identical..**

A project group of representatives from the directorate of health, the regulatory and reimbursement agency, the hospital procurement agency and hospitals gathered to design an incentive to secure access to important, novel antibiotics. To a large extent the process outlined in the long-term supply continuity model was followed. But the assessment of partial and fully delinked models is important evidence that should be taken into account when considering market entry rewards.

The stakeholder project group perceived little value in implementing a fully delinked model, given that antibiotics are generally already used responsibly and sparingly in Norway. The power of the pharmaceutical industry to over-promote an antibiotic in Norway is considered marginal, and the cost of implementing a dedicated delinked system for only a handful of medicines was considered too bureaucratic and costly. Rather, solutions where a developer could receive a “top-up” payment (i.e., a partially delinked model) would be simple to implement and administer.[78]

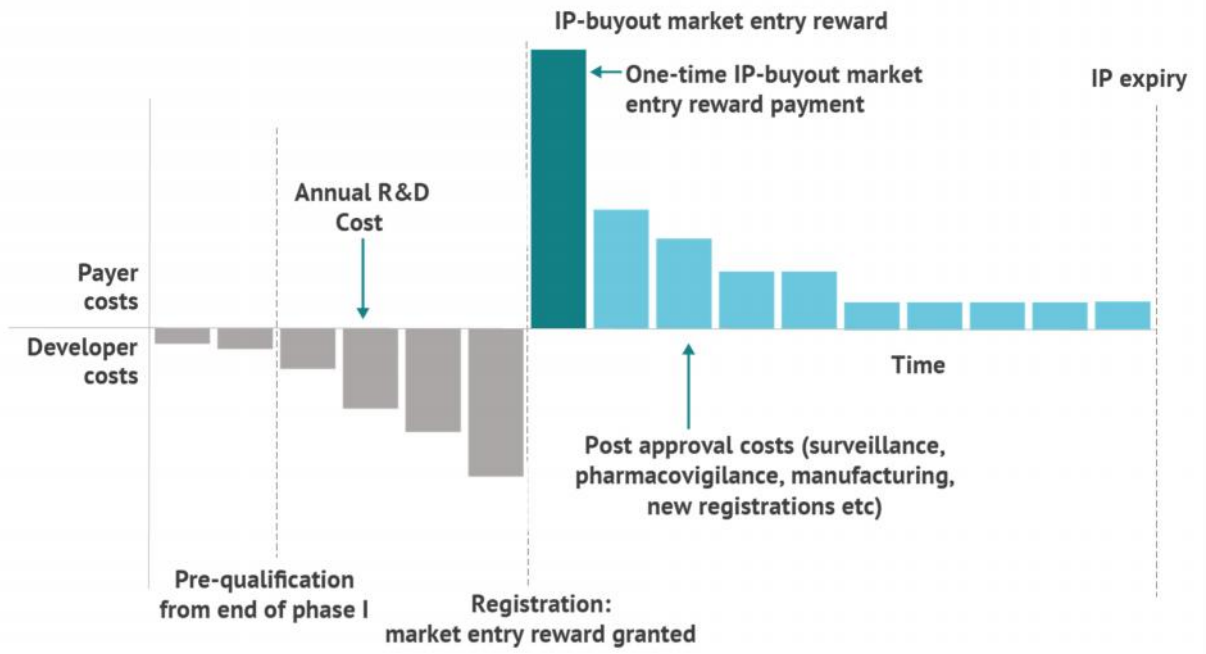
Table 3: Comparison of market entry reward models proposed

	Fully delinked	Partially delinked	
		Standard payments	Sales-adjusted payments
Proportion of developer revenue from antibiotic sales	None	Some	Some
Size of market entry reward	$$$$	$$$	$$$
Size of annual payment	Standard	Standard	Sales-adjusted
Unit price to hospital/insurer	Set by payer	Negotiated	Negotiated
Implications for national reimbursement systems	New processes for pricing and reimbursement for a few antibiotics High risk of cross-border price arbitrage with markets without market entry reward	Works with existing reimbursement procedures	Works with existing reimbursement procedures
Impact on sustainable use	Contractual requirements to ensure the developer engages in sustainable use Eliminates any sales incentive for the antibiotic	Contractual requirements to ensure the developer engages in sustainable use	Contractual requirements to ensure the developer engages in sustainable use
Impact on equitable availability	Contractual requirements to ensure the developer engages in equitable availability	Contractual requirements to ensure the developer engages in equitable availability	Contractual requirements to ensure the developer engages in equitable availability
Impact on private-sector financing	Some SMEs have reported that this would appear as a revenue cap and reduce the attractiveness of private-sector funders (e.g. venture capital firms)	Would increase the attractiveness for private-sector funders	Some SMEs have reported that this would appear as a revenue cap and reduce the attractiveness of private-sector funders (e.g. venture capital firms)

Intellectual property (IP) buyout: Another variation of a market entry reward involves the purchase (or exclusive licence) of the developer's IP on the novel antibiotic by the payer or designated entity in exchange for the market entry reward (see Figure 11). The payer then takes full responsibility for production, supply, distribution, pharmacovigilance and additional regulatory applications to extend the geographic availability of the antibiotic. The argument is that IP buyouts may be advantageous because the antibiotic can be distributed in a way that maximizes public access and sustainable use.[79] The counter-argument is that this transfers the risk and cost of services (such as almost all regulatory approvals, product communications, medical and regulatory support, production, distribution and pharmacovigilance) to the payer. Not only will this cost hundreds of millions of US dollars, but there are currently no instances of a government entity manufacturing a medicine or vaccine and supplying the world. The developer will expect to be paid the full value of the antibiotic at registration, including the development costs. An IP buyout could also risk other pipeline assets further upstream (e.g., for platform technologies), which would further complicate a buyout or increase the price.

However, some developers have stated that they are positive about this model, particularly SMEs which do not possess global distribution networks.

Figure 11: IP buyout reward



Eligibility for a market entry reward can be "tightly focused" or "broadly inclusive". Yet if it is perceived as too difficult to achieve, it may result in more companies exiting antibacterial R&D.

Which antibiotics should be eligible for a market entry reward?

Determining which types of antibiotics are eligible for a market entry reward is a central design decision. The aim is to stimulate the "right" kind of innovation, i.e., those antibiotics that society values but that otherwise would not be developed, without making the goal so onerous that developers walk away from what they see as an unachievable TPP. DRIVE-AB developed a simulation model to determine the optimal size of rewards for different delinkage models across different product profiles. For products with expected global revenues above $2–2.5 billion (€1.65–2.06 billion) over the lifetime of the IP, the simulation found that a reward in addition to this would have a limited impact on the likelihood of a developer making the necessary investment to bring a novel antibiotic to market.[x] Two types of profiles were simulated to assess the required reward to increase pipeline output for each: "tightly focused" and "broadly inclusive".

[x] Putting this figure into context, a novel antibiotic that achieves increasing global sales reaching $90 million (€74 million) in the third year after launch, and peak-year sales of $400 million (€330 million) in its tenth (and assumed final) year of IP-protected sales, would have accumulated sales of approximately $2.3 billion (€1.9 billion) over those ten years. However, under existing market conditions of limited prices and highly restricted use, achieving this level of sales is unlikely for a new antibiotic reserved for treating only patients with specific multi-drug-resistant infections.

A **tightly focused design** would provide rewards only for "innovative" antibiotics, meaning those candidates thought to be free of cross-resistance to existing classes, most likely with a novel chemical scaffold, novel molecular target/novel binding sites, or associated novel mode of action, in conformance with the predefined TPPs. It is anticipated that such a reward would be triggered infrequently. For example, with the existing pipeline it would apply to about two antibiotics within the next five years. (There are also promising alternative technologies in the pipeline that could qualify for a reward, but their market launch is expected to come later.) The simulation indicates that without any intervention four new classes of antibiotics (range of two to eight) matching tightly-focused TPPs would receive marketing authorization during the next 30 years. If this definition is applied historically, based on unmet public health threats at the time, potentially only three antibiotics[xi] (not used solely for tuberculosis) would have received this award in the last twenty years.

A **broadly inclusive design** would provide rewards for antibiotics from both new and known classes that represent significant therapeutic improvements as defined through TPPs. The first-in-class antibiotic is not always the best-in-class. For example, for both first- and third-generation cephalosporins, it is the follow-on antibiotics that are included in WHO's Essential Medicines List (2017).[80] Follow-on antibiotics may have an improved efficacy, spectrum or safety profile. A broadly inclusive reward would incentivize incremental innovation, potentially leading to therapeutic improvements that would not be developed if only the first-in-class antibiotic was rewarded. As a result of the expanded eligibility profile, a broadly inclusive reward would be triggered relatively more frequently. For example, with the existing pipeline it would apply to about ten antibiotics within the next five years. The simulation indicates that without any intervention 14 known-class antibiotics (range of four to 26) offering therapeutic improvements would receive marketing authorization during the next 30 years.

Of course, the two types can also be combined where the value of the market entry reward varies depending on the characteristics of the antibiotic. For example, bigger rewards could be given for antibiotics meeting the tightly focused criteria, and smaller ones for the broadly inclusive. This would encourage risk-taking to pursue new classes but still incentivize diversity and improvements to existing classes. A limit should be placed on the number of known-class antibiotics incentivized, to avoid a proliferation of similar products.

The benefits and limitations of each approach are summarized in the Table 4.

Table 4: Strengths and weaknesses of a tightly focused vs broadly inclusive market entry reward

Type	Strengths	Weaknesses
Tightly focused	Creates clarity via a focus on innovation May drive R&D investment to take new risks by incentivizing innovation Increases the diversity of antibiotics to slow the selection of resistance Focuses public investment on innovation and the highest public	Owing to high discovery challenges and development risk with low probability of success, this may be non-incentivizing, leading to divestment and exit from this therapy area across all phases of R&D A high bar for innovation increases the risk of failure, which may discourage private capital investment in antibiotics in favour of other therapeutic areas

[xi] Linezolid, daptomycin and fidaxomicin.

	health need	Leads to a R&D focus on a few pathogens and TPPs
Broadly inclusive	Gradation of reward still incentivizes new classes, but this approach also acknowledges the clinical need for and benefits of incremental improvements May pull through current pipeline and prevent short- and long-term disinvestment	Availability of smaller rewards for incremental improvements may not shift focus or promote significant new risk-taking in R&D More funding likely to berequired overall than for tightly focused reward May appear as a generous subsidy to a highly profitable industry Once a reward is in place, it would be difficult to make the requirements more stringent

Whether a tightly focused or broadly inclusive reward is chosen, the payer should undertake an assessment of prequalification status for eligibility for a reward at the end of phase I or II clinical trials. On the basis of available early data that indicate an acceptable probability of meeting the TPP at registration, this will give both the developer and the payer greater certainty. Prequalification would not be a guarantee for obtaining the reward. It provides an opportunity for payers to engage formally with industry to facilitate the development of novel antibiotics and better understand the future budget requirements for the antibiotic pipeline. Prequalification would also provide an opportunity for payers and developers to discuss sustainable use and equitable availability criteria. Prequalification may also encourage more private capital investments to help push an antibiotic through the expensive late clinical trials, as it would indicate that a level of due diligence had been undertaken, leading to a positive external assessment of the antibiotic. Moreover, a prequalification process would provide for broad dissemination of knowledge about technical progress in the field.

A tightly focused market entry reward of $1 billion (€850) per antibiotic (in addition to unit sales revenues) has the potential to bring 18 (13–23) new antibiotic classes to the market in the next 30 years.

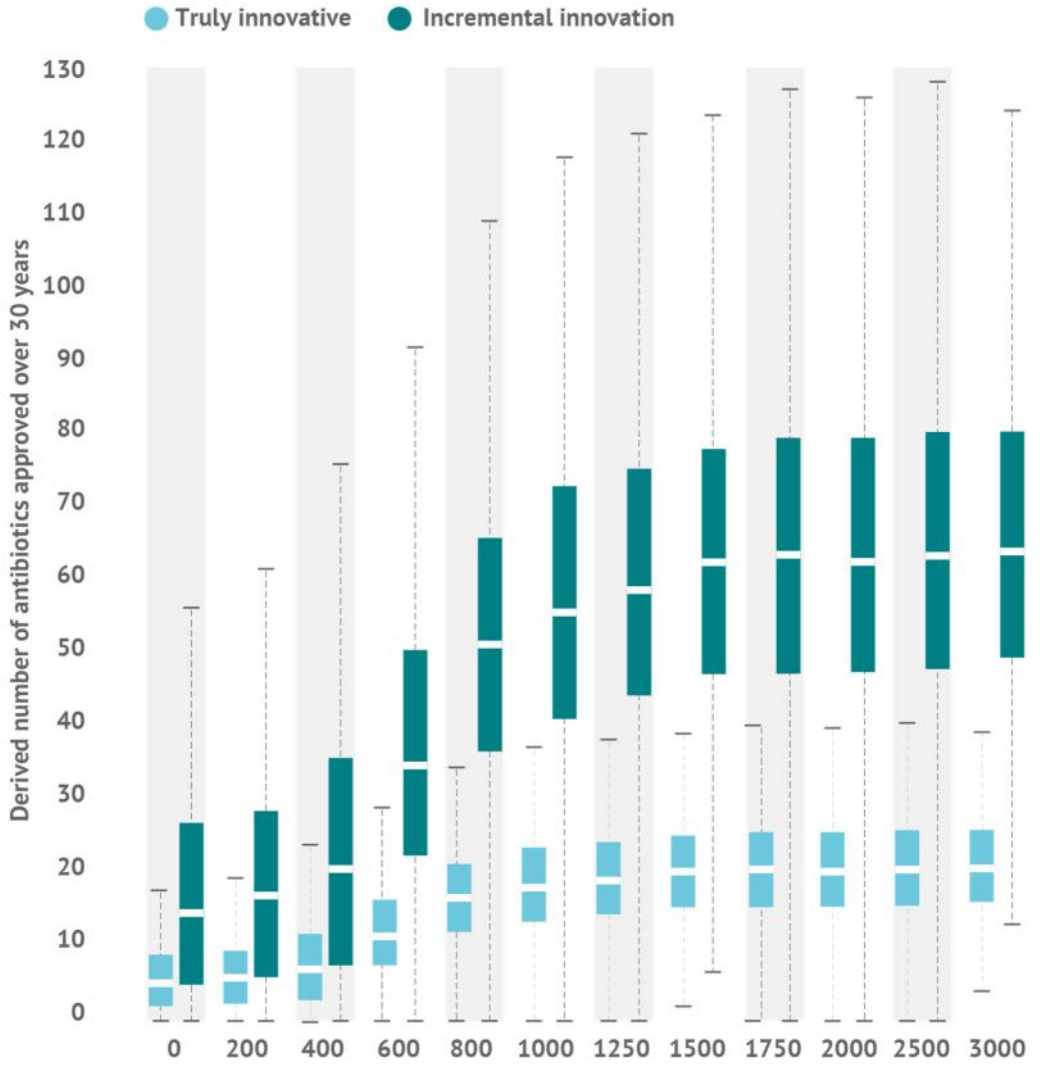
How much should the total market entry reward payment per antibiotic be?

Figures 12 and 13 show the results of the simulations for different reward categories. These show that the number of new antibiotic classes would more than quadruple to about 18 (range 13–23) by the introduction of a tightly-focused reward scheme with total payouts of $1 billion (€850 million) for a partially delinked reward, or $1.25 billion (€1.03 billion) for a fully delinked reward. The number of new classes plateaus at about 20 new approvals (range 13– 24) in 30 years, if rewards increase to $1.5 billion and $1.75 billion (€1.2 billion and €1.4 billion) respectively. Thus a tightly focused market entry reward between $1.5 billion and $1.75 billion would make almost all applicable projects in the pipeline profitable (i.e., those that have not failed for scientific reasons).

For a broadly inclusive reward, new approvals would more than triple to 55 known-class antibiotics with therapeutic improvements (range 41–73) and with a partially delinked reward of $1 billion, or a fully delinked reward of $1.25 billion. A plateau of 62 new known-class approvals (range 47–78) is reached if rewards increase respectively to $1.5 billion and $1.75 billion. This increase in rewards provides up to about four new classes in both partially and fully delinked models. The value of increasing the amount of the reward to ensure that the tail-end (about four) novel antibiotic classes

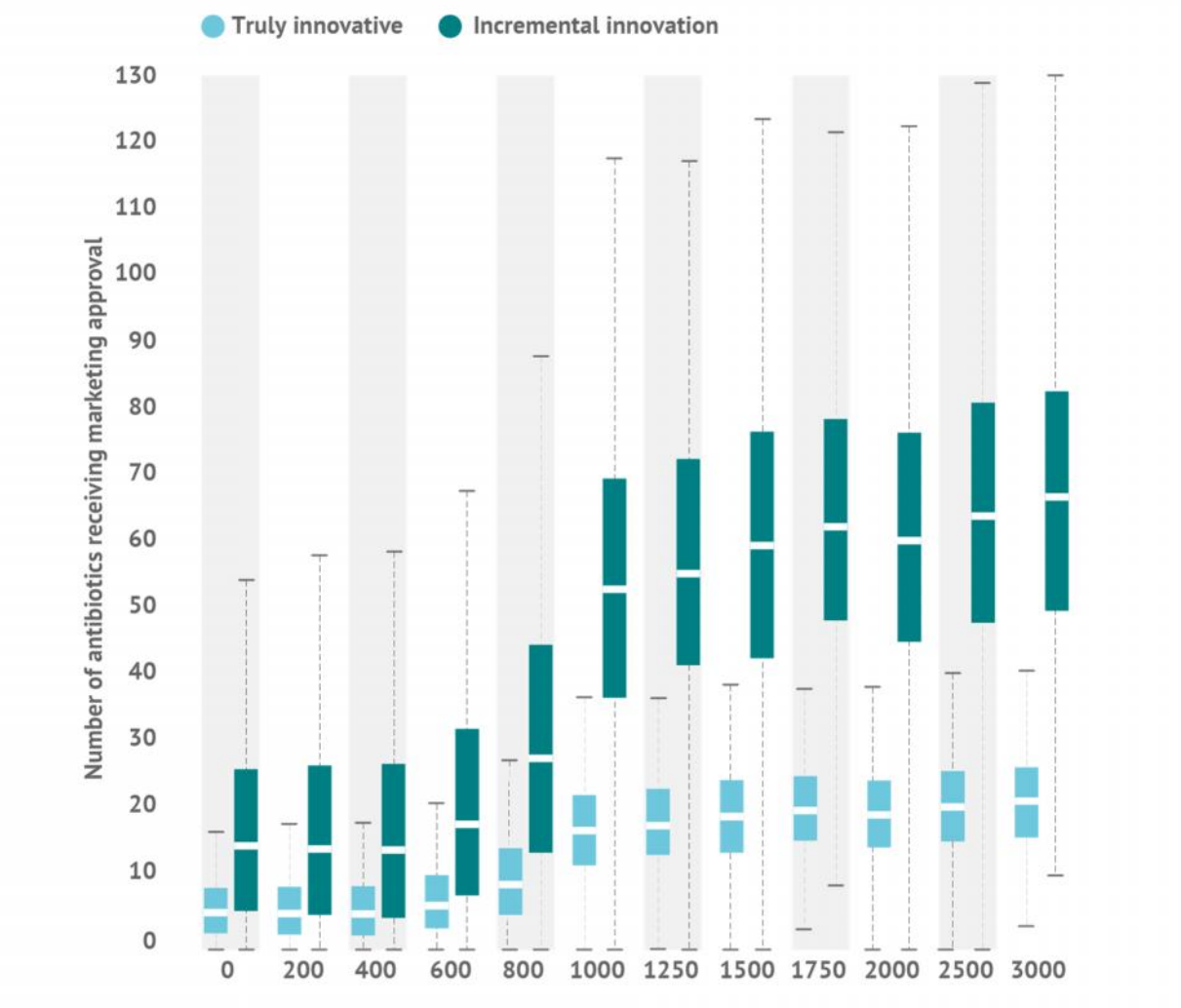
reach the market is questionable as it significantly increases the overall expenditure. Arguably, these last classes are the most scientifically ambitious, with the smallest patient populations (or patient populations that are difficult to recruit for clinical trials), and thus require larger reward values to achieve the NPV threshold. Other mechanisms (such as a pipeline coordinator) may be more cost-effective for bringing these types of products to market.

Figure 12: Market approvals by antibiotic types obtained with *partially* delinked rewards



Note: Antibiotics are placed into two categories depending on the scientific difficulty: "truly innovative" and "incremental innovation". In order to simulate the market entry of antibiotics some simplifications were needed regarding the actual complicated process of antibiotic innovation. This particularly relates to the ability to discover and develop new classes or other truly innovative antibiotics. For the simulation, it was assumed that "truly innovative" antibiotics enter preclinical development at a rate of 0.5–3 per month, while the more common "incremental innovation" antibiotics achieve a rate of 3–8 per month.

Figure 13: Market approvals by antibiotic types obtained with *fully* delinked rewards



Note: See Figure 12.

Market entry rewards must be bound by sustainable use and equitable availability obligations on the developer.

What contractual conditions should be tied to a market entry reward?

To extend the effectiveness of new antibiotics, in exchange for receiving a reward a developer must accept a set of conditions defined by the payer, including sustainable use and equitable availability and supply (see sections below).

These conditions should be detailed in the reward agreement between the payer and the developer. In cases of noncompliance with the terms and conditions of this agreement, the payer could reduce or stop annual reward payments.

The eventual conditions attached to the acceptance of a reward will affect the size and structure of the reward. The primary objective of a reward is to incentivize investment in innovative antibiotic R&D; additional conditions should not be so numerous or onerous that they make the reward unattractive to developers or too difficult to administer effectively, whether from an industry or a public payer perspective.

While the significant public investment in a reward offers an opportunity to promote key public health goals, it is important to recognize that this incentive model and any conditions applied operate in the context of broader efforts to combat AMR by actors from both the public and private sector. The rewards should be designed to complement these efforts to improve sustainable use, equitable availability and public health.

DRIVE-AB recommendations on market entry rewards

DRIVE-AB recognizes that countries vary in resistance levels, stewardship programmes, regulatory capacity, and health system financing and structure. Therefore, governments may see different pull solutions as meeting their needs. Developers have also stated clearly that if the bar is set too high (i.e., in the case of tightly focused rewards) without other incentives being in place to stimulate incremental improvements, the private sector will lose interest and may exit antibiotic R&D. Therefore, any design decisions regarding implementation of a market entry reward also need to reward antibiotics in known classes that offer significant public health benefits.

DRIVE-AB has calculated that $800 million–1.5 billion (€680–1,236 billion) would deliver on average 16–20 innovative new antibiotics over 30 years (Figure 12). An award amount of $1 billion (€850 million) is recommended as the most efficient choice because the value of increasing the amount of the reward to ensure that the tail-end antibiotics reach the market significantly increases the overall expenditure. This amount is similar to the values recommended by others including the United Kingdom's AMR Review ($800 million–1.3 billion (€680 million–1.07 billion), in addition to unit sales) and the Boston Consulting Group ($1 billion, again in addition to unit sales, but gradually refunded dependent on those sales).

Yet no level of precision can be claimed regarding these values. The exact amount needed to motivate a company to invest varies greatly from company to company. Some stakeholders argue for a higher market entry reward amount, and others state that a billion dollars is excessive. Therefore, the parameters have been set to provide a reasonable return on investment for the developer but one that is far lower than the profits achieved by the top-selling drugs in 2016. DRIVE-AB recommends a partially delinked market entry reward for several reasons: it will minimize disruptive effects to existing national systems such as reimbursement; it is compatible with 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. However, some DRIVE-AB members argue that a partially delinked model leaves in place a strong incentive for the manufacturer to oversell the antibiotic, with a detrimental impact on sustainable use. This is a risk that must be closely monitored.

To properly test the ability of a market entry reward to drive antibiotic innovation, a coalition of countries would need to implement a market entry reward scheme lasting a minimum of 20 years (i.e., one complete discovery and development cycle). 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. A 20-year period seems appropriate, not because this will enable the problem to be solved, but to learn from the implementation and fix any unintended consequences. The ability of the market entry reward to incentivize antibiotic innovation should be revisited every five years by performing an in-depth pipeline analysis to assess the rate of change.

This does not necessarily need to be one pooled market entry reward but can represent many national or regional market entry rewards of varying designs. Initially a pilot in two or three countries to test the operational ramifications is appropriate.

It should be noted that other incentives are being established to stimulate the development of new antibiotics for tuberculosis, such as the Life Prize. These incentives are independent of market entry rewards, and novel antibiotics should be able to receive both, so long as they comply with the specified requirements.

Recommendation: 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 fully operational, a partially delinked market entry reward of $1 billion (€850 million) per antibiotic for innovative antibiotics meeting predefined target product profiles (TPPs) is recommended. 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. This 20-year period is recommended not because this will enable the problem to be solved, but to learn from the implementation and fix any unintended consequences. Twenty years is the right amount of time to determine the impact of the market entry reward on innovation. Any shorter assessment will be biased by the existing antibiotic pipeline.

Incentivizing clinical trials for "difficult" or uncommon indications

Methods: DRIVE-AB has assessed the need for alternative reward models for late-stage clinical trials focused on "difficult" indications. We have reviewed relevant literature, conducted interviews when in depth information was deemed necessary, and undertaken a mapping of the indications for which novel antibiotics in the US have gained registration since 2000. Finally, a focus group discussion was organized within the DRIVE-AB team, which included contributions from both academia and industry representatives.

More data on the efficacy of novel antibiotics in rare infections or those involving critically ill patients are needed. These are most likely to be achieved through direct grant funding and improved clinical trial networks.

Clinical trials for "difficult" indications (i.e. those that are rare and/or involve critically ill patients, or for which no clear development/regulatory pathway has been established) present special problems because of the small number of patients available to participate in clinical trials, and often also the urgency of life-saving treatment. Rapid diagnostic tests are frequently not available. Patients may suffer from multiple morbidities, have a compromised immune system or suffer from other conditions that preclude them from participation in a clinical trial.

Since 2000 the most common clinical development programmes have been for regulatory submissions leading to indications in skin and skin structure infections, community-acquired pneumonia, complicated intra-abdominal infection and complicated urinary tract infections. These infections are also among the most prevalent, and clear regulatory guidance, including well-defined end points and other parameters, are well established by major regulatory agencies.[81] Less common indications, such as endocarditis, osteomyelitis or meningitis, are rarely studied for registration purposes. Yet providing data for these infections as well as the efficacy for specific patient groups (such as children) is of great importance, particularly where off-label prescribing is common. The absence of data means physicians have to rely on their own judgment, and can also make it difficult for a hospital to be reimbursed for the treatment.

We assessed the possibility of incentivizing "difficult" indications as a requirement or top-up payment to a market entry reward. We concluded that this would have a low impact at a very high cost because of the multiple challenges related to conducting clinical trials for these specific indications. Adding a requirement to conduct clinical trials for "difficult" indications to a market entry reward would be too onerous. Directing industry to focus especially on these indications may significantly delay bringing the antibiotic to the market. Providing top-up payments was calculated to be more costly than allocating targeted grants to gather this evidence.

Stakeholder interviews revealed that direct grants to academics or developers would be a better solution to increase empirical evidence on the safety and efficacy of new antibiotics for uncommon infections and vulnerable patient groups. Investigator-initiated trials on drugs already on the market, not funded by pharmaceutical companies, are an important source of post-approval information and should also be considered when funding research.

Clinical trial networks have been suggested to achieve the desired efficiency in designing and implementing clinical research. Several promising models exist already, such as the European Clinical

Research Alliance on Infectious Diseases (ECRAID).[82] Challenges that need to be addressed include the funding and recruitment of staff and the sustainability of such networks, since the number of antibiotics in the clinical pipeline is low. Lessons can be learnt from successful networks for other types of research such as cancer. A problem with networks in this area, particularly focused on specific types of resistant bacteria, is that centres do not wish to be known for having high rates of infections due to resistant bacteria. This is a fundamental paradox without an obvious solution.

Recommendation: 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 them. Continued emphasis should be placed on improving clinical trial networks to facilitate the rapid identification of eligible patients.

Long-term supply continuity model

Methods: DRIVE-AB has performed an interrupted time-series analysis of changes in the number of prescriptions in the US after the introduction of one or more generic version to market. We have engaged in a national Norwegian pilot design of the long-term supply continuity model, allowing us to begin to assess the operational impacts of implementing this model.[78] We have interviewed individuals regarding joint procurement processes.

Some critical antibiotics will be seldom used. Other incentives are needed to maintain a predictable supply of these antibiotics.

It is important that antibiotics meeting an unmet health need continue to be manufactured and available for patients who need them. This includes antibiotics in their post-market-entry reward life-cycle when IP rights have expired and is also applicable to other critical antibiotics that are in use today.

The market entry reward is designed to bring antibiotic therapies to market that meet unmet public health needs, but also to conserve these important antibiotic therapies through sustainable use measures. If they are effective, at the close of a reward contractual period consumption of many of these antibiotic therapies should be modest. Our research indicates that, at least in the US market, generic entry does not affect the consumption trend of the antibiotic, i.e., consumption does not appear to significantly increase with the introduction of additional manufacturers (and hence reduction in price).[83] We do not have data to assess if this is also the case in low- and middle-income countries.

The end of the market entry reward duration coincides with the generic availability of the product. There are two primary risks associated with this transition. The modest market may be unattractive for both generic and the original manufacturers, so they may decide that (1) there is insufficient profit to continue manufacture of the product, leaving no supplier; or (2) the market could be improved via marketing and promotion, with the result that they attempt to increase unit sales in ways that may be detrimental to public health.

The ESCMID Study Group for Antibiotic Policies and ReAct identified 36 older, systemic antibiotics that still may be medically useful today but are ‘forgotten’, i.e., no longer used and difficult to obtain.[84] These modest markets are not attractive for manufacturers and therefore supply becomes limited to a few manufacturers, and the active pharmaceutical ingredients may only be supplied by one provider. This creates supply insecurity and potential supply failure. In other therapeutic areas generic manufacturers have attempted to capitalize on medicines that are considered important but rarely used, and have increased the price by many multiples.

For these reasons, development of a new model is recommended – the Long-Term Supply Continuity Model, which can support a predictable supply of important but rarely used antibiotics. A country or group of countries would agree to annual payments to one or more manufacturers to ensure the predictable supply of an antibiotic. There are similarities to a market entry reward since a government is paying a delinked reward for the supply of an important antibiotic. This payment would be bound to sustainable use obligations. A long-term supply continuity reward need not be announced many years in advance as it is based on current resistance profiles and needs. The contractual manufacturers would be determined in a competitive tender, and equitable availability would need to be tailored to the specific antibiotic. This model is a pull mechanism, in that it pays for

delivery of a specific outcome and creates a market. It is not intended to incentivize antibiotic innovation but to maintain access to important antibiotics.

Implementation of a long-term supply continuity model would follow a series of steps: (1) select vulnerable, important antibiotic therapies; (2) determine the value of maintaining access to these therapies; (3) tender out the predictable supply of these therapies in line with standard sustainable use and equitable availability provisions. The contract period should be long enough (minimum five years) to warrant continued investment in supply.

Selection of potential antibiotic therapies

The selection of antibiotic therapies suitable for a long-term supply continuity model should be determined by well-defined and transparent criteria, including placement within national antibiotic treatment guidelines, national resistance profiles and expected incidence of applicable infections. The aim is to identify those antibiotic therapies that are considered important and necessary but may be subject to supply uncertainty owing to unprofitable markets. Likely candidates for this model may be antibiotics supported by a market entry reward that is about to expire.

Health technology assessment

The second step is to determine the value of a predictable supply of the antibiotic therapy, which can serve as the basis for determining the value of the delinked payments. Since this process occurs around generic transition, no health technology assessment would normally be performed. Rather the value of the product would have been assessed at market launch. One way to determine the societal value of predictable access to this antibiotic therapy would be to update the previous HTA performed in line with current resistance patterns and alternative costs of treating patients, to determine the antibiotic's enabling, insurance and diversity values. However, this would require a fundamental shift in the way HTAs are completed for antibiotics.

Tendering

Most countries require that contracts of this magnitude be assigned via competitive tendering processes. In this case, the optimal condition is likely to be the choice of at least two manufacturers (with independent supply of active ingredients) in case of unforeseen supply problems. Other sustainable use measures, such as adherence to environmental guidelines, can be assured via the tendering process. The same standard contractual language regarding sustainable use for market entry rewards should also apply to the long-term supply continuity model.

Joint procurement processes could also be used as a way to build equitable availability into these models as well as giving manufacturers more predictable demand to cover the costs of maintaining a production facility. Typical joint procurement models, such as that of the European Union, allow countries to express an interest in participating in a common Request for Proposal (RfP). The RfP is a competitive tender whereby vendors are selected on the basis of their proposals, which typically include product price information. Participating countries are not obliged to purchase the product, nor the vendor(s) to supply the product. Rather, national contracts are then negotiated on the basis of the terms provided by the selected vendor(s), i.e., there is no supranational pooled funding. To date, the main intent of such EU tenders has been to ensure access to products that are small in volume or difficult to purchase, i.e., to consolidate a market. In the case of rarely used antibiotics with unstable demand, low- and middle-income countries should also be invited to participate in the joint procurement process.

Recommendation: **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.

Building in sustainable use

Methods: DRIVE-AB has performed stakeholder interviews with national governments, regulatory agencies, developers, academics, civil society and others.[85] We have also performed an in-depth analysis of the Single Convention on Narcotics, including interviews with relevant agencies in eight national governments.[86]

It is vital that any innovation incentive promotes the sustainable use of applicable antibiotics to ensure the longevity of the public-sector investment and continued benefit to patients.

We define sustainable use as the implementation of policies targeting a range of actors to ensure the long-term effectiveness of a specific, novel antibiotic. Though resistance is not preventable, its development can be slowed. "Sustainable" use differs from "responsible" or "appropriate" use which has been defined by the World Health Organization as "*the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug related toxicity and the development of antimicrobial resistance*".[2] Whereas responsible use measures contribute to the sustainable use of an antibiotic, other factors such as the use of the antibiotic in non-human populations and discharges from the production of antibiotics also influence the sustainable use of a specific antibiotic. Sustainable use measures must balance the need for access with the avoidance of excess use of the antibiotic. These measures should not impede clinically appropriate access in any country. Sustainable use does not equal no use.

Many initiatives exist to encourage the sustainable use of antibiotics, varying by country and setting. Many high-income countries have sophisticated measures in place. These include extensive hygiene and stewardship programmes, as well as guidelines and protocols that limit the use of new antibiotics to those patients whose treatment has failed on alternatives, or who require specific efficacy against multi-drug-resistant bacteria. The development of National Action Plans that are aligned with the WHO Global Action Plan will encourage wider implementation of such initiatives globally.

Industry has also made efforts to facilitate elements of sustainable use. More than 100 companies and associations signed a declaration at the World Economic Forum meeting in Davos in January 2016. Further commitments were contained in the Industry Roadmap for Progress on Combating Antimicrobial Resistance (September 2016).[87] These include reducing the environmental impact from the production of antibiotics, examining companies' promotional activities, sharing surveillance data with public health bodies, and improving access. Subsequently, the AMR Industry Alliance has brought together a range of pharmaceutical, biotechnology and diagnostics companies pledged to put into action the principles set out in the Davos Declaration and IFPMA Roadmap, including commitments to support appropriate use and stewardship.

There are many different actors with a role to play in ensuring sustainable use of antibiotics, including patients, healthcare providers, governments, civil society, academia and the

pharmaceutical industry, among others. However, for sustainable use policies that are tied to recommended innovation incentives, the primary stakeholders are national governments, funders and developers. Healthcare providers are, of course, also critical but are considered in the context of responsible use below.

For sustainable use activities that are within the control of developers, these obligations should be contractually agreed between the funder and developer, with annual reporting. This allows both parties to customize the agreement for the antibiotic, such as including different provisions for community-distributed antibiotics. General, standardized obligations agreed in advance bring valuable certainty for developers, allowing for weighing the relative merits of participation in the market entry or supply continuity rewards and minimizing unexpected risks. These contractual terms should follow the antibiotic (in the event of acquisition or out-licensing).

National governments are in control of sustainable use policies. Here we recommend national commitments to clear, measurable sustainable use policies, with annual reporting. For sustainable use activities that must be performed by national governments, we recommend non-binding agreements between countries and a coordination body such as the G20's Global R&D Collaboration Hub on AMR. It is important that the agreements are at least initially non-binding since sustainable use provisions need to be tested and amended. Binding agreements such as treaties can be complicated to implement, with unintended consequences. For example, we evaluated the introduction of a globally agreed system for controlling the use of antibiotics akin to the controlled drug regimen that exists for narcotics.[85] This would allow for stringent controls on the sale and consumption of antibiotics, which could be especially valuable for antibiotics deemed critical. However, such a system was rejected as we concluded that it would be costly, detrimental to access, challenging to implement, and no more effective than introducing national stewardship measures already included in many countries' national AMR plans.

Sustainable use policies for grants and pipeline coordinators

Sustainable use can begin to be built in during early-stage product development through stipulations in grants and other funding sources. Despite the early uncertainty surrounding the eventually approved product and the environment in which it will be launched, there are two certainties with any antibiotic candidate: resistance to the antibiotic will develop; and the greater the consumption, the faster resistance will develop. Yet funders should consider the stage of development and the potential implications of building too many restrictions or conditions into their grants – they can have important downstream effects on the attractiveness of these products for further private investment, undermining one of the primary objectives of these grants: to incentivize additional private investment.

Grant recipients should be required to contribute to diagnostic development by making clinical samples, isolates and/or the molecule available to diagnostic manufacturers at the close of the grant

period. However, diagnostic manufacturers are likely to be interested only in late-stage candidates (clinical trials phases II and III) to allow for greater certainty that the antibiotic will make it to market.

Recommendation: 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.

Sustainable use for market entry rewards and long-term supply continuity model

Table 5 contains the DRIVE-AB recommended sustainable use obligations for developers associated with a partially or fully delinked pull mechanism. These are general, standardized recommendations that will require refinement depending on the design of the pull mechanism, target product profiles and regulatory context.

The conditions attached to the acceptance of an incentive will affect the size and structure of the incentive. It is important that sustainable use obligations are not so numerous or complex that they make the incentive unattractive to developers or too difficult to administer, from both an industry and a public-payer perspective. This may have the effect of disincentivizing the private sector from pursuing the market entry reward.

Additionally, some of these obligations may become superfluous as the broader policy and regulatory context changes over time. For example, stringent national regulations are being introduced regarding the discharge of antibiotic residues from factories. In time the World Health Organization's Global Development and Stewardship Framework may also make some obligations redundant.

Table 5: Recommended sustainable use obligations for developers

Domain	Recommendation
Non-human use	Active ingredients for human use may not be sold for veterinary medicines (unless product is classified by the World Organization for Animal Health's veterinary antimicrobial list as critically or highly important).
Marketing and promotion[1]	All materials sent to the appropriate regulator or coordinating body at least 90 days prior to use, with the body able to notify the developer if it deems the materials inappropriate. Appropriate communications include to healthcare stakeholders responsible for infection control, guideline and formulary development, distribution and stocking as well as regulatory authorities. This is like the US government's requirements for the Limited Population Antibacterial Drug (LPAD) requirements. **Alternative view:** Some DRIVE-AB members argue that there should rather be no industry product communications, mirroring existing off-label restrictions, with defined exceptions ("safe harbours") for the dissemination of use-related information (to be supported by greater efforts by public health bodies to inform practitioners etc.).
Environmental	Review and apply antibiotic discharge framework across supply chain (including

safeguards	active pharmaceutical ingredients (APIs)). Work with stakeholders to develop a practical mechanism to transparently demonstrate that supply chains meet the framework standards. Work with experts to establish science-driven, risk-based targets for discharge concentrations of antibiotics and good-practice methods to reduce the environmental impact of manufacturing discharges. This is largely consistent with the AMR industry Roadmap.
Disclosure of sales unit data and resistance detection	Conduct time-bound collection and reporting (as packs and and standardized reporting of active ingredients) of product volumes (adjusted for redistribution) by country and supply-channel and health-system level (as feasible and relevant to the country context) and if company becomes aware of cases of resistance rapidly inform relevant national authorities (including ministry of health, medicine regulator and focal point for emerging public health threats).
Perverse incentives (that encourage volume sales)	No volume-based remuneration of staff related to the specific antibiotic. Identification and elimination of inducements that may encourage use of the product including but not limited to hospital dispensing kickbacks and payments/benefits-in-kind to prescribers.
Contribution to diagnostic development[2]	Request-based provision of clinical samples, isolates and/or the molecule (where appropriate) to diagnostic manufacturers to facilitate the expedient development and validation of susceptibility tests.

Notes:
[1] The aim of both recommendations is the same – to discourage promotion that may lead to inappropriate use of novel antibiotics; the difference is the implementation. The legality and context of the country must be taken into account to tailor this recommendation.
[2] We considered a stipulation that the developer couple the new antibiotic with one or more rapid diagnostics. However, we decided against this owing to the different expertise required by antibiotic and diagnostic developers. Also, it may be undesirable to incentivize the development of solitary diagnostics coupled with specific antibiotics. Rather, it may be more useful to develop diagnostics across multiple infections. Ensuring that patients are appropriately diagnosed is a country-level obligation.

National governments and developers play different roles in sustainable use. National commitments will not vary according to the design of the pull mechanism but rather according to the type of antibiotic, for example for use in the community or hospitals. Again, these are general, standardized recommendations that will require refinement with use. Funders may ensure that countries are able to comply (or are working towards compliance) with sustainable use commitments prior to gaining access to the novel antibiotic. Some low- and middle-income countries may require technical and financial assistance to comply.

The high-level commitments of each government are largely in line with a country's existing commitments, including:

- Active implementation of its National Action Plan on AMR, in line with commitments to WHO, including effective surveillance systems for both antibiotic consumption and resistance patterns;
- Immediate reporting of adverse events and instances of resistance to the regulator and coordinating body;
- Compliance with the antibiotic-specific guidance document (see below); if this has not been developed, the country should put forward a plan describing how it will ensure appropriate use of the novel antibiotic, addressing the domains described below.

For each antibiotic covered by a market entry reward, DRIVE-AB recommends that WHO (or another expert body) develop specific policy guidance on sustainable use. This would be similar, for example,

to the guidance developed for the use of bedaquiline for drug-resistant tuberculosis.[87] The policy guidance should include specifications outlined in Table 6.

Table 6: Recommended sustainable use commitments to be detailed in an antibiotic-specific guidance document

Domain	Recommendation
AMR stewardship programmes	Define which facilities should gain access to the antibiotic, including a minimum requirement for AMR stewardship programmes
Antibiotic-specific stewardship controls	Define which healthcare workers should gain access to the antibiotic (for example, allowing the antibiotic to be given only by specifically authorized and trained staff)
Surveillance and monitoring	Define the minimum surveillance systems to monitor consumption levels of the specific antibiotic, and implementing systems to address occurrences of inappropriate prescribing, and report occurrence of resistance
Diagnostics	Detail which diagnostic tools can be used and, where possible, link reimbursement to the use of diagnostics
Disposal	Define methods to dispose of the antibiotic appropriately (potentially as hazardous pharmaceutical waste)
Environmental safeguards	Define methods to treat hospital waste water to eliminate antibiotic residues

Recommendation: 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 for both developers and governments.

Measuring responsible clinical use

Methods: DRIVE-AB has developed quality indicators and quantity metrics by a systematic and stepwise method combining findings from the scientific literature and stakeholder opinion. The perspectives of the medical community, public health, patients, antibiotic developers, regulators and governments were taken into account.

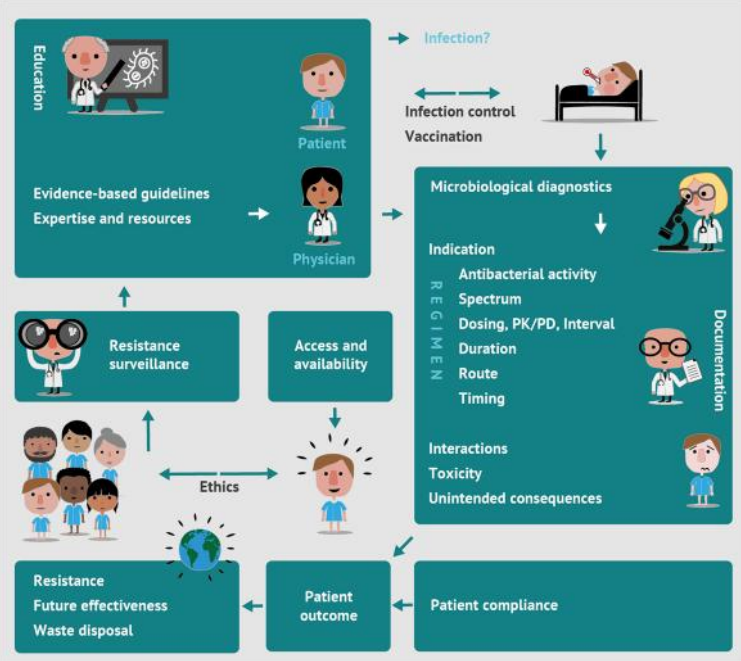
Implementing responsible use measures in clinical settings is critical to ensure the sustainable use of important antibiotics. A common framework including a clear definition of and measurement tools for responsible use is needed.

This section focuses on responsible clinical use, which is a specific component of sustainable use.

While all antibiotic use drives the emergence and dissemination of resistance to some degree, a major aggravating force is the inappropriate use of antibiotics in clinical settings.[89] Reducing unnecessary or inappropriate use of antibiotics in hospitals, care homes and the community is necessary to slow the pace of the emergence and spread of resistant bacteria and ensure the longevity of the investment in market entry rewards. Although antibiotic stewardship programmes have increased in recent years, there is no consensus on the definition or measures of responsible antibiotic use.

A framework of responsible use is needed to achieve a common definition and measurement tools. DRIVE-AB worked to reach consensus on a definition of responsible human antibiotic use. A total of 22 key elements and their associated best-practice descriptions were developed that, taken together, describe what responsible antibiotic use in a clinical setting should entail. This definition is applicable to existing and newly developed antibiotics. The definition takes account of diverse socioeconomic settings and can be applied to healthcare settings around the world. An infographic showing the 22 elements (in black characters) is shown in Figure 14. A distinction was made between individual patient-level and societal elements of responsible antibiotic use.

Figure 14: Responsible antibiotic use



Qualitative and quantitative measures of antibiotic use are valuable tools to give insight into how patterns of use drive resistance. DRIVE-AB made a clear distinction between indicators of quality and measures of quantity of antibiotic use. A quality indicator reflects the degree to which antibiotic use is correct or appropriate, while a quantity metric reflects the volume or the costs of antibiotic use. Therefore, the quality indicator has a value on its own, while the quantity metric only gains value when comparisons are made between e.g. wards, hospitals or countries.

DRIVE-AB developed generic quality and quantity indicators to measure the appropriateness of antibiotic use. Quality indicators can be used for implementation in antimicrobial stewardship policies, for identification of targets for improvement, for evaluating the effects of antibiotic stewardship interventions, for application in clinical studies, and for educational purposes.

DRIVE-AB developed 51 quality indicators for the inpatient (hospital) care setting and 32 quality indicators for the outpatient setting. These generic quality indicators provide a guideline for “best practices” that healthcare providers can use to assess responsible use. These measures are intended to be universally applicable, regardless of infectious disease type, geographical or socioeconomic setting. Among the outpatient quality indicators, a distinction was made between 20 general practice indicators, 11 Outpatient Parenteral Antimicrobial Therapy (OPAT) indicators and one indicator common to both categories.

Quantity metrics of antibiotic use describe the extent and profiles of use and trends over time that require further qualitative investigation. They enable regional, national and international benchmarking. DRIVE-AB identified twelve generic quantity metrics for measuring antibiotic use for inpatients and six for outpatients. During the consensus procedure, the need to combine different quantity metrics to optimize interpretation of the volumes of antibiotic use was emphasized. In both settings Defined Daily Dose (DDD) was found to be the most commonly used numerator, and combination with at least one other metric was recommended.

Building in equitable availability

Methods: DRIVE-AB performed an assessment of the geographic spread of antibiotic sales between 1999 and 2014 based on data from IMS Health. We also identified a list of antibiotics currently under patent and reviewed selected low- and middle-income country national marketing authorizations to gain a better understanding of where the antibiotics were registered. At the same time, we assessed lists of countries with marketing authorization by antibiotic, as reported by EFPIA partners. We interviewed members of the Center for Disease Dynamics, Economics, and Policy's (CDDEP) Global Antibiotic Resistance Partnership (GARP) in India, Kenya, Nepal, Nigeria and South Africa, and representatives from the Medicines Patent Pool.

The need for novel antibiotics to treat multi-drug-resistant pathogens is global. Yet low- and middle-income countries are predominantly the last countries where patented antibiotics receive marketing authorization, delaying patient access to new antibiotics to address AMR.

DRIVE-AB defines equitable availability as ensuring that innovative antibiotics over time are registered and priced affordably across all countries with a public health need for them.

Our analysis of the geographic availability of patented (or recently off-patent) antibiotics that received their initial marketing authorization between 1999 and 2014 demonstrates wide variation in the geographic reach achieved.[83] This analysis is based on IMS Health sales data and not marketing authorizations. The older antibiotics (those that have been on the market for more than 15 years) can have utilization data in more than 70 countries across five different geographical regions. Others on the market for 10 years have been consumed in as many as 65 countries. With a single exception, all antibiotics that have been consumed in more than 40 countries originate from large, multinational pharmaceutical companies.

An analysis of specific countries' list of products with marketing authorization confirms that low- and middle-income countries are unlikely to have marketing authorizations for most patented antibiotics.[88] For example, only five out of twelve antibiotics currently under patent in high-income countries have marketing approval in India. The same five have marketing approval in South Africa. Yet five of the remaining antibiotics had only been registered in Europe in 2011, 2015 (n=3) and 2017. The remaining two have been removed from the European market.

Among poorer countries, some antibiotics may be registered in a few countries but not in neighbouring countries, for example in Kenya but not Tanzania, or in Bangladesh but not Burma. Cambodia and Tanzania are examples of countries that do not appear to have marketing authorization for any of the patented antibiotics. This reflects a number of factors, including manufacturers not seeking regulatory approval for less attractive markets, as well as domestic hurdles to achieving regulatory approval.

An analysis of marketing authorizations awarded to large pharmaceutical companies demonstrates that more than 100 countries, across every continent, can be reached within a decade.[89] The remaining countries are those with small purchasing power, e.g. lower-income countries such as Cambodia and Mozambique or remote, middle-income countries such as Kiribati and Tonga.

The available data suggest that equitable availability in terms of countries where the product is registered can be achieved in a significant number of countries within the patent lifetime of an

antibiotic, but this may be achievable only by large, multinational pharmaceutical companies. Small to medium-sized companies will need to seek out-licensing agreements with other companies, which may decrease the attractiveness of a market entry reward.

DRIVE-AB recommends that developers who receive a market entry reward be contractually bound to the equitable availability obligations listed in Table 7. Since these stipulations are untested, a flexible approach is recommended.

Table 7: Proposed equitable availability obligations

	Obligation	Rationale / Evidence
1	**Companies must submit an access plan** to the regulator or coordinating body, identifying countries with highest need for the antibiotic and setting out the company's approach to enhancing access, including regulatory approval, distribution and pricing. Highest need may be difficult to assess but should be based on the burden of disease and resistance levels reported from national surveillance systems. For countries with weaker surveillance systems suitable proxy data may be used and the resistance situation assessed in the context of other therapy options. The access plan should be based on the principle of providing early access to the antibiotic to patients with limited treatment options. A company's approach may be to manufacture and distribute the antibiotic on its own, or to seek assistance from other companies or organizations such as GARDP or the Medicines Patent Pool, which can facilitate agreements with generic producers. The contents of the access plan are negotiated between the coordinating body and the company. The plan should be ambitious but realistic. If a market entry reward is awarded, the access plan is made public.	In interviews with representatives from CDDEP's GARP, there was universal agreement that the newest antibiotics should be launched with care in countries with weaker healthcare systems, and potentially restricted only to tertiary hospitals with AMR stewardship programmes. Rollout in these countries (which may have great need for the antibiotic) should be customized with the buy-in of local experts.
2	**Countries or other healthcare providers not included in the access plan can submit a letter of interest** to the company to be included in the product rollout. Unmet public health need will play a primary role in determining the country-by-country rollout.	There is strong evidence that if the onus to register for access is placed only on countries, high-need countries may miss the opportunity because of insufficient capacity or other challenges. Therefore, this is a secondary option for countries with weak/non-existent surveillance and healthcare, whereas Step 1 should be based on the national epidemiological data.
3	**The company must commit to provide all necessary data to WHO to develop antibiotic-specific policy guidance** for the novel antibiotic (with similar intent to WHO's guidance on bedaquiline for drug-resistant tuberculosis).	In interviews with representatives from CDDEP's GARP, there was agreement that guidance must accompany regulatory approval so that physicians can make informed decisions regarding alternative antibiotics. Today the pharmaceutical company is the main provider of this information.
4	**The company commits to implement the final access plan and monitoring activities**, including the reporting of any adverse	The regular assessment of local-unit use data compared with

	events and instances of resistance immediately to the coordinating body and respective regulatory authority. The company commits to provide annual reporting against the contract, including data to assess both sustainable use and equitable availability (e.g. country-level annual unit sales). The non-profit, independent Antimicrobial Resistance Benchmark is encouraged to assess the company over time for making the antibiotic available sustainably. The company commits to respond to the Benchmark's enquiries in a timely manner.	epidemiological and other surveillance data will be critical to perform analyses of under- or overuse of the antibiotic.

From our analysis of the current pipeline, most antibiotic candidates are being developed by SMEs. The market entry reward will assist SMEs by demonstrating to their investors that the market can be profitable, but profitability may be compromised if they must build a global regulatory and distribution network. Large pharmaceutical companies may be uninterested in licensing these products if they are not commercially attractive, or there are high risks and added controls associated with their commercialization. Therefore, large companies may expect to be paid to perform this service, which will decrease the attractiveness of the reward. SMEs may need support to develop an adequate geographic access plan. Some organizations such as GARDP have experience in facilitating access and may be willing to help meet these obligations. Demonstrating realistic pathways in these access plans is important to build confidence without distracting investors.

The Medicines Patent Pool could be an option for some antibiotics. It facilitates generic manufacturing of patented technologies for specified geographic areas. Its mandate is currently limited to medicines and technologies related to HIV/AIDS, hepatitis C and tuberculosis. Generic manufacturers will only be interested in producing novel antibiotics if the market is sufficient to achieve a reasonable profit. This excludes any antibiotic specifically developed as a last resort, also bound by sustainable use obligations.

Expectations regarding the access plan should be adjusted to the developer and the type of antibiotic. Yet all developers must be sufficiently challenged to ensure widespread access across all country income groups. Access shortfalls should be regularly assessed, and mitigating measures taken to increase access.

Expanding equitable access globally to both novel and off-patent antibiotics will require significant investments, not only by countries in strengthening health systems to ensure appropriate use of novel antibiotics, but also by donors, to put in place supportive mechanisms. For example, this might include funding for technical assistance to procure and expand appropriate access to novel antibiotics, support to expand the mandate of the Medicines Patent Pool to include novel antibiotics, or facilitating assistance by GARDP with launching novel antibiotics in low- and middle-income countries.

The design of equitable availability measures for new antibiotics will need some refinement since developers may not be able to find interested partners or generic manufacturers willing to launch or produce novel antibiotics in small or challenging markets. Generic manufacturers may not be able to implement the sustainable use conditions for licensed antibiotics.

Recommendation: 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. 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.

Financing and governance

Methods: DRIVE-AB has performed multiple stakeholder interviews with national policymakers and philanthropic funders, and participated in key intergovernmental meetings. We have also assessed different forms of governance including gathering information from interviews with the International Space Station and CERN.

We estimate the cost of implementing our recommendations to start at $800 million (€680 million) per year in 2018, increasing to $1 billion (€850 million) per year in 2019, and then to $1.2 billion (€1.02 billion) in 2021.

Magnitude of financing needed

Recent reports have given differing estimates of the amounts of financing needed to stimulate antibiotic innovation. The United Kingdom's AMR Review recommended $16 billion (€13.2 billion) over ten years for promoting the development of new antimicrobials, including making better use of existing ones, as well as $2 billion (€1.65 billion) over five years for a global innovation fund supporting basic and non-commercial research in drugs, vaccines and diagnostics.[32] The Boston Consulting Group recommended an additional $400 million (€330 million) per year in push funding and a market entry reward of $1 billion (€850 million) per commercialized antibiotic therapy meeting a specified TPP (in addition to unit sales, but gradually paid back dependent on those sales).[33]

On the basis of current research DRIVE-AB recommends *additional* grant financing of $250 million (€206 million) per annum. On the basis of the assumptions used in the simulator, reflecting the existing R&D metrics and market environment, DRIVE-AB supports a partially delinked market entry reward with a total global payment of $1 billion per antibiotic, divided into five yearly payments of $200 million (€170 million) but with a maximum duration of the lifetime of the IP. If a tightly focused reward is implemented, there are seven potentially qualifying antibiotics currently in the clinical pipeline for both "critical" and "high" priority pathogens.[xii] (There are also nine biologics such as antibodies that we exclude since their medical relevance as a therapeutic option is not yet clear.) Six of the seven antibiotic candidates are currently in phase II clinical trials and the last is in phase III.[37] While one could argue that these antibiotics are close to market and could reach marketing approval without a market entry reward, they would not do so with provisions for sustainable use and equitable availability, and might seek premium prices that a market entry reward would obviate. These are the antibiotics most suitable for a market entry reward pilot where the payout could be negotiable. With standard attrition rates, two of the seven could reach the market in the next one to five years.[13] With these financing amounts, therefore, total global public-sector financing could resemble the forecast in Table 8. (This is in addition to philanthropic and private-sector investments.)

Table 8: Estimated total global public-sector costs to incentivize antibiotic innovation, 2018–22 ($ millions)

	2018	2019	2020	2021	2022
Existing grant financing[55]	550	550	550	550	550
Additional push	250	250	250	250	250

[xii] Afabicin (Debio 1450), Brilacidin, CG400549, Gepotidacin, Lefamulin, POL7080, Zoliflodacin (ETX0914).

financing					
Market entry reward(s)	0	200	200	400	400
Total	**800**	**1 000**	**1 000**	**1 200**	**1 200**

Note: Some grant financing would be repaid on award of a market entry reward. The amounts for the pilot market entry rewards could be negotiable.

The above costs do 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.

We project that at least $1.2 billion (€1.02 billion) per year will be necessary every year after 2022 (depending on how many awards are made). Antibiotic resistance will always be a problem. In order to provide an adequate stream of antibiotics, these investments will need to continue initially for 20 years, as previously recommended.

The global annual financing can be divided up by countries in multiple ways – for example, according to gross domestic product, population or antibiotic consumption. Yet, to start the process, it may be simplest to gather commitments from willing countries. If the three big markets – Europe, Japan and the US – divided the market entry reward cost into three parts based on GDP or population, this could be an expedient way to start a pilot.

Multinational coordination options

Financing this magnitude of investment requires multinational collaboration; no single government can bear this load. Multinational collaboration can take multiple forms but can be simplistically divided into two types: (1) where a new organization is created with a specified mandate; or (2) where countries agree to pursue the mandate independently but with increased coordination. To assess which type of organization is most suitable for antibiotic innovation coordination, the identified characteristics need to be assessed against existing coordination mechanisms – namely, financing magnitude, existing financing, financing source and sustainability. Table 9 describes examples of multinational collaboration according to these characteristics.

Table 9: Examples of multinational collaboration

Organization and year of origin	Type of collaboration and financing source	Annual contributions to pooled fund	Recurring, binding financing commitments
CEPI (2016)	Voluntary collaboration with contributions from two philanthropic foundations and three countries to date. Country financing is mostly from development aid budgets but also science and technology funds.	$~125 m (2017)	No
CERN (1954)	Convention ratified by 22 member states containing financing commitments for operational costs. Labour costs for the scientists are not included but paid for nationally. Building costs, for example, building the Large Hadron Collider, are also excluded and paid for through voluntary donations.	CHF1,117 m (2014)	Yes
GAVI Alliance (2000)	Voluntary collaboration with contributions from philanthropic foundations and countries. Country financing is mostly from development	$4,426 m (2015)	No

	aid budgets.		
International Space Station (1998)	Many bilateral agreements with the United States where countries commit to pay for the provision of scientists, maintenance of ISS parts and other expenses. There is no pooled financing.	None	Yes
NATO (1949)	Treaty ratified by 28 countries with financing commitments for operational costs. Equipment and troop costs are paid nationally.	€2,179 m (2017)	Yes
The Global Fund Against AIDS, Tuberculosis and Malaria (2002)	Voluntary collaboration with contributions from philanthropic foundations and countries. Country financing is mostly from development aid budgets.	$2,189 m (2015)	No
The Green Climate Fund (2010)	Initiated under a framework of the UNFCCC by its 24 member states as a voluntary funding mechanism. Focus is on developing countries, with financing coming mainly from development aid budgets.	$1,757 m (2015)	No

All initiatives (in Table 9) with the exception of the newer ones – CEPI (the Center for Epidemic Preparedness Innovations) and the Green Climate Fund – have proved sustainable for at least a decade, but the assortment is biased towards existing and successful initiatives. Several initiatives have failed, such as the proposal made in 2012 for a binding convention to finance neglected disease R&D, which WHO member states have not endorsed. The sample in the table is also biased towards initiatives that have pooled funds. Many other initiatives function through collaboration towards common goals, such as the Sustainable Development Goals and the Paris Climate Agreement.

The financing sources of the newer initiatives are supplied mainly through development aid (CEPI, GAVI Alliance, the Global Fund and the Green Climate Fund), which can be applied more flexibly than national health budgets. Development aid cannot generally be applied to antibiotic innovation since the main objective is not to promote the economic development and welfare of developing countries.

The Global Fund to Fight AIDS, Tuberculosis and Malaria also provides an instructive example. It is a pooled fund that raises $10–12 billion (€8.25–9.9 billion) in three-year replenishment cycles. These funds are used to support the relevant programmes in recipient countries, including significant funding for the procurement of life-saving health commodities. Although the Global Fund enjoys broad government and civil society support, is funded mainly through development aid and is generally regarded as a success, there is always a high degree of uncertainty around replenishment.

The two initiatives bound by treaties or conventions with financing commitments were both agreed more than 50 years ago. In an interview with participants in CERN, it was mentioned that any attempt to establish CERN today would be unlikely to result in a convention, since there are many difficulties with this format, including practical problems (all employees enjoy diplomatic status and rights) and rigidity in modifying the agreement. The newer initiatives, such as the Green Climate Fund, have shied away from binding financial commitments.

For antibiotic innovation, most governments finance research grants through ministries of science, education and/or health. These grants may also be coordinated or pooled regionally. For example, JPIAMR grant financing is coordinated regionally but paid out nationally. IMI financing is both coordinated and pooled regionally. The push financing is spread among many established R&D programmes, and none of the financing is provided through a long-term, binding legal agreement.

Under the current business model, pull financing occurs through revenue from antibiotic sales. Where insurance is provided publicly, the ministry of health pays these costs (perhaps with co-payments from patients). Even in the United States, where a large proportion of the insurance is provided privately, the government still pays a significant portion of drug costs through Medicare and Medicaid. Pull financing has always been nationally or sub-nationally provided.

Governance models

Applying the characteristics of these models to antibiotic innovation suggests possible ways forward for the financing and governance of market entry rewards. Since there are already so many effective push mechanisms in place, it would be counterproductive to disrupt their ongoing work. However, additional push investments are needed for R&D against priority pathogens. Many of the existing organizations (such as CARB-X, GARDP, JPIAMR or IMI) have the potential to absorb greater targeted investments and distribute them effectively. Therefore, the central questions are how to ensure that the various push mechanisms work in a synergistic fashion and how the pull mechanism(s) should be implemented. DRIVE-AB has assessed different types of governance models including the creation of a new organization, as well as greater coordination of existing organizations.

Some within DRIVE-AB have advocated the creation of a new international body with strong control mechanisms, including controlling the intellectual property for all antibiotics awarded a market entry reward. This organization would then assume responsibility for global distribution arrangements, including manufacturing, sales, obtaining regulatory approvals and overseeing post-marketing surveillance. The main strengths of this option are simplicity (one body provides one global reward) and the potential for tightly controlling the distribution of critical, last-resort antibiotics.

We have already noted above that stringent controls contained within the Single Convention on Narcotics have not managed to stop overconsumption (mainly in high-income countries) and under-consumption (in low-income countries).[85] We also know that the IP buyout model is more expensive than a partially or fully delinked scheme (since the purchaser must thereafter pay for services, such as regulatory approval, manufacturing, distribution and pharmacovigilance, that are otherwise included in a partially or fully delinked scheme).

In addition, given the magnitude of financing needed for the pull mechanism and the sources of this financing, it appears unlikely that countries would be willing to create such a body. The challenges of raising the level of funding needed for antibiotic innovation and establishing a new mechanism for funding and governance should not be underestimated. The budgets of ministries of health already have competing priorities within healthcare that they find difficult to satisfy, and the health budget itself must compete with other highly political budget allocations, for education, science and the many other demands on the public purse. Since the funding required to implement an effective scheme is significant, it is unlikely that national governments will be willing to cede control of these funds to an independent, multinational organization. The political opportunity cost might be too high.

Another option is increased coordination based on existing organizations. A group of countries would agree to non-binding, non-pooled commitments. The sum of these commitments would equal the total amount of financing needed. Each partner would be responsible for determining the best financing method. However, to be successful, the coalition of countries must agree to implement a common set of principles, including:

- The amount of total aggregate funding to be made available over 20 years;
- A combined commitment to support pull as well as push incentives;
- A percentage breakdown of each country's financial commitments;
- Antibiotic innovation priorities, i.e., lists of priority pathogens and antibiotic profiles, standard sustainable use and equitable availability policies;
- Resourcing a coordinating secretariat to facilitate joint processes and monitor implementation.

Each government would determine the best way to satisfy this financial commitment. All countries may not be able to contribute financially, but all could commit to sustainable use measures for the resulting new antibiotics.

There is significant flexibility in implementing this proposal, which can be done rapidly. Countries can select the pull mechanism that best fits their local healthcare system. For example, the US may select a variation on the market entry reward designed for public and private insurers, as proposed by Duke-Margolis.[34] Like-minded countries can decide to pool funds, in the style of the IMI. This may encourage smaller countries to participate by lessening administrative burdens. If they are all working on the same principles, the aggregate of the parts should be the same as for a single global body.

Even when variations on a market entry reward are implemented, standard contract language of sustainable use and equitable availability can be agreed. It is normal that companies (even small ones) register their antibiotics in the major high-income markets. The same access plan can be utilized for all market entry reward submissions.

The strength of multinational coordination is that there is no need for one pooled fund, although we believe that a single pooled fund to distribute the reward would be beneficial in Europe. Regulatory approval is already undertaken regionally for European countries. Since the reward payments start after regulatory approval, a mechanism is needed to trigger the payments. We believe that the European Investment Bank (EIB) in coordination with the European Medicines Agency (EMA) could be a potential implementer. We do not believe that every European country will contribute to a market entry reward fund at the EIB, but all will need to agree to follow the sustainable use provisions.

The weaknesses of multinational coordination are that it creates a greater administrative burden on the developer and accountability is distributed.

Recommendation: 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.

Germany, as the lead of the G20 in 2017, launched the Global R&D Collaboration Hub on AMR with a Berlin-based secretariat with financing 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. This high-level coordination should act to align public funding towards important investment opportunities. It is not intended to be an extensive new organization or to create a new pooled fund, nor will it 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.

National financing mechanisms

There are many methods to raise national funds to cover the financial commitments, including those listed in Table 10. Financing mechanisms can also be designed to support sustainable use provisions by, for example, de-incentivizing consumption by animals. Each reward financing mechanism requires review by countries taking part in delivering market entry rewards, to establish which mechanism best aligns with their national financing priorities.

Table 10: Possible financing mechanisms

Financing mechanism	Strengths	Weaknesses
Import tax on antibiotic active pharmaceutical ingredients (APIs)	Supports sustainable use by making the resulting antibiotic slightly more expensive	China and India manufacture a large proportion of the world's antibiotic APIs – so the tax may be perceived as disproportionately targeting these two countries.
National tax on veterinary antibiotic sales	Supports sustainable use by making veterinary antibiotics more expensive.	As countries continue to ban the use of antibiotics as growth promoters and utilize different infection control mechanisms, the income from this tax could diminish over time.
National tax on medicine sales	This would give the perception that the pharmaceutical industry is contributing to paying for the innovation costs.	The tax is likely to be simply passed on, raising the overall costs of medicines.
Annual fee on healthcare insurance policies	Aligns well with the global public good of having effective antibiotics available as a necessary part of any healthcare plan.	For European countries, simply agreeing to a fixed sum per resident is likely to be easier.
Pay or play – large pharmaceutical companies which do not invest sufficiently in antibiotic R&D would pay a fee into a designated fund	It is politically appealing that industry uses its profits from other therapeutic areas to finance antibiotic R&D.	It is likely that the additional cost would simply be passed on through the price of other medicines. Additionally, it incentivizes industry to perform research (to the required threshold) but not necessarily to bring new, high value antibiotics to market.
Transferrable exclusivity voucher – an award auctioned	Depending on the duration of exclusivity offered, this would	For national insurers this will always be more expensive than

Financing mechanism	Strengths	Weaknesses
off to a developer giving extended market exclusivity to an already marketed medicine	be likely to generate significant funds. It does not require ongoing government appropriations.	paying directly for the incentive, since the insurer must also cover the profit margin to the developer. This can also force specific patients (which could be few in number or paying out-of-pocket) to continue to pay higher prices for an important medicine.

Regional (European) financing mechanism

For the European Union, we see another potential financing mechanism, through the European Investment Bank (EIB). The bank is already actively investing in antimicrobial R&D through its InnovFin programme. Our proposed model is a variation on the "megafund" idea championed by Andrew Lo and Roger Stein.[90] A megafund is a very large financial fund that invests and takes equity in a diversified portfolio of assets. Once these assets are commercialized, a portion of the revenues is ploughed back into the fund, thereby making the fund revolving and sustainable.

The EIB typically does not invest directly in companies but rather acts through private fund managers, allowing them to offer preferential terms within the scope of the scheme. There appears to be interest from the EIB to increase its investments in health technologies generally, which presents an opportunity for antibiotic R&D. If the EIB takes equity by investing in the R&D of healthcare technologies (with diversified risk profiles across many different therapeutic areas), some of these products are likely to be very successful and generate high revenues. If a small portion of this investment portfolio is dedicated to antibiotic R&D (without the expectation that these products will have high revenues, and allowing for riskier investments), this facilitates greater antibiotic R&D funded directly from the revenues of other therapeutic areas. In other words, those treatments that are enabled by antibiotics (such as oncology medicines) will start paying directly for antibiotic innovation. Alternatively, these revenues could potentially pay the European share of the market entry reward.

This fund would be financed either by a one-time payment by member states or through debt raised on the capital markets. The fund would invest in a wide portfolio of biopharmaceutical and other health-related products. It is important that the portfolio is diversified, i.e., not restricted to one therapeutic area, and includes attractive market opportunities. The fund would invest across the entire biopharmaceutical pre-launch value chain covering both R&D. The aim is to make the fund the most desirable source of external financing for biopharmaceutical activities. This would be achieved by offering better terms than private venture capital.

Greater antibiotic innovation is facilitated by allocating a percentage (10–15 per cent) of the fund to financing of antibiotic R&D aimed at unmet public health needs. This percentage is aspirational, and if there are too few high-quality antibiotic R&D projects, the funding could be used on other therapeutic areas. Antibiotic innovation investments would also be given on preferential terms, including grants for early-stage research and loans at low interest rates for development activities. Investments for non-antibiotic R&D would be in the form of either equity or royalties, thereby ensuring a financing stream back to the fund. The fund would require two governing bodies: (1) a

financial governance body to ensure that the portfolio is sufficiently diversified and adheres to good financial practices; and (2) an expert governance body on biopharmaceutical R&D to identify the attractiveness, risk and potential of the various biopharmaceutical R&D projects, as well as priorities within antibiotic innovation. This second expert group could be implemented through a pipeline coordinator.

We have heard concerns that this type of fund could increase the price of medicines overall. However, we do not believe this to be the case. Since the EIB has access to large amounts of capital, has the highest credit rating, and is motivated by the desires of member states, we believe that this could lower drug prices generally, since it tempers the private-sector funds' profitability demands.

Recommendation: 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 to invest their monies in improved national infection control and stewardship programmes. The European Union's 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 which further EU policy goals. DRIVE-AB sees potential that a group of like-minded European countries can commit to pilot a European-based market entry reward paid out by 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. The European Commission's Joint Action on AMR and Healthcare-Associated Infections could be utilized to assist in the implementation of this pilot.

Appendices

Appendix A: About DRIVE-AB

The Innovative Medicines Initiative (IMI) is the world's largest public-private partnership in healthcare. IMI seeks to improve the environment for pharmaceutical innovation in Europe by engaging and supporting networks of industrial and academic experts in collaborative research projects. The EU contributes €1 billion to the IMI research programmes, which is matched by in-kind contributions worth at least another €1 billion from the member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA). The European Union's 2011 Action Plan against the Rising Threats from Antimicrobial Resistance called for research to help develop new antibiotics. The result was IMI's "New Drugs for Bad Bugs" (ND4BB) programme launched in 2012.[61] DRIVE-AB ("Driving Reinvestment in R&D and Responsible Antibiotic Use") is part of IMI's ND4BB programme and was mandated by the EU Commission to deliver costed implementable solutions to incentivize antibiotic R&D while supporting sustainable use and access. DRIVE-AB derived from a 2013 IMI call for proposals, was launched in October 2014 and ended in December 2017.[91] It was funded by IMI with in-kind support from EFPIA partners equivalent to one-third of the total €9.4 million funding awarded.

DRIVE-AB was a multidisciplinary consortium composed of 16 public and seven private/EFPIA partners from 12 countries. The public partners included the British Society for Antimicrobial Chemotherapy (BSAC), Chatham House, the Centre for Anti-Infective Agents (CEFAIA), Heidelberg University, the London School of Economics and Political Science, the Norwegian Institute of Public Health, Radboud University Medical Centre, Tel Aviv Sourasky Medical Center, the University of Antwerp, the University of Geneva, the University of Lorraine, the University of Rijeka Medical Faculty, the University of Strathclyde,the University of Tübingen, Uppsala University and Wageningen University. The EFPIA partners were Astellas Pharma Europe LTD, AstraZeneca AB, Merck Sharp & Dohme (replaced Cubist Pharmaceuticals GmbH), GlaxoSmithKline PLC, F. Hoffmann-La Roche Ltd, Pfizer Limited and Sanofi-Aventis Research & Development.

What were the objectives of DRIVE-AB?

Three key objectives for DRIVE-AB were set before the start of the project:

1: Create the building blocks of economic models (Work Package (WP) 1)
- *Objective 1A: Define "responsible" use of antibiotics (WP1A)*
- *Objective 1B: Set, communicate and revise public health priorities (WP1B)*
- *Objective 1C: Develop antibiotic valuation models (WP1C)*

2: Create, test and validate new economic models (WP2)

3: Manage the project and its stakeholder platform (WP3)
- *Objective 3A: Coordinate and manage the project (WP3A)*
- *Objective 3B: Manage stakeholder platform and external communication (WP3B)*

What did each WP achieve?

Detailed outputs from all work packages are available on the DRIVE-AB website, and planned publications are listed in the next section. In summary:

WP1A provided a common terminology and framework for shared understanding of responsible and sustainable antibiotic use. It also delivered broadly accepted metrics to monitor responsible use which could be used to inform stewardship programmes, improve use of existing antibiotics and prevent inappropriate use of newly developed molecules (see section *Measuring responsible clinical use*).

WP1B used a novel approach to describe early signals for new emerging AMR, developed a novel methodology to predict the spread of resistant organisms, and validated and calibrated these predictions on the basis of updated data and preventive measures (see section *Predicting the spread of antibiotic resistance*).

WP1C provided novel approaches to evaluating antibiotics that capture their value to patients, society and the healthcare system. Among more immediate applications, these methods will inform health technology assessment agencies in determining the value of new antibiotics from the payer perspective (see *Estimating the full value of antibiotics*).

WP2 developed the parameters governing the operation of incentive models and quantitatively tested new models through the development of a simulator. The clear guidance given for implementing this evidence will provide a persuasive argument to undertake the necessary system changes at the national or supranational level. The long-term impact should be increased financing to re-ignite and maintain the necessary levels of antibiotic R&D over time while ensuring rational use.

WP3A provided the scientific and administrative leadership and integrated programme management essential to the project's success, including setting up and managing the steering committee and project management office. The project steering committee was composed of all WP leaders and was the main governing body of the project. As in all IMI projects, each WP is co-led by a public and a private representative.

WP3B set up and managed a multidisciplinary stakeholder platform to engage with all stages of the DRIVE-AB project and support the implementation of new models.

We would like to acknowledge the participation and hard work of all the people who were involved in the DRIVE-AB project over the years (in bold are highlighted the work package leaders, who were all also members of the Steering Committee over the lifetime of the project):

Work Package	Last name	First name	Organization
WP1A	**Gyssens**	**Inge**	**Radboud University Medical Centre, Nijmegen**
WP1A	**Eisenstein**	**Barry**	**Merck Sharp & Dohme**
WP1A	**Hermsen**	**Elizabeth**	**Merck Sharp & Dohme**
WP1A	Adriaenssens	Niels	University of Antwerp
WP1A	Baillon-Plot	Nathalie	Pfizer

WP1A	Goossens	Herman	University of Antwerp
WP1A	Hulscher	Marlies	Radboud University Nijmegen Medical Centre
WP1A	Huttner	Benedikt	University of Geneva
WP1A	Kullberg	Bart-Jan	Radboud University Nijmegen Medical Centre
WP1A	Le Maréchal	Marion	University of Lorraine
WP1A	Milanic	Romina	University of Rijeka Medical School
WP1A	Monnier	Annelie	Radboud University Nijmegen Medical Centre
WP1A	Oualim	Abdel	Sanofi-Aventis
WP1A	Pulcini	Céline	University of Lorraine
WP1A	Schouten	Jeroen	Radboud University Nijmegen Medical Centre
WP1A	Stanic Benic	Mirjana	University of Rijeka Medical School
WP1A	Tebano	Gianpiero	University of Lorraine
WP1A	ten Oever	Jaap	Radboud University Nijmegen Medical Centre
WP1A	Versporten	Ann	University of Antwerp
WP1A	Vlahović-Palčevski	Vera	University Hospital Rijeka, Croatia
WP1A	Zanichelli	Veronica	University of Geneva
WP1B	**Carmeli**	**Yehuda**	**Tel Aviv Sourasky Medical Center**
WP1B	**Longshaw**	**Chris**	**Astellas**
WP1B	**Murillo**	**Nathalia**	**Sanofi-Aventis**
WP1B	Almagor	Jonathan	Tel Aviv Sourasky Medical Center
WP1B	Benenson	Itzhak	University of Tel Aviv
WP1B	Bernhard	Alisa	University Hospital Tübingen
WP1B	Beryl	Primrose	University Hospital Tübingen
WP1B	Brennan Benson	Paul	Astellas
WP1B	Carrara	Elena	University Hospital Tübingen
WP1B	Cohen Percia	Shimrit	Tel Aviv Sourasky Medical Center
WP1B	Cona	Andrea	University Hospital Tübingen
WP1B	Dane	Aaron	AstraZeneca
WP1B	Fallach	Noga	Tel Aviv Sourasky Medical Center
WP1B	Gilchrist	Kim A.	GlaxoSmithKline
WP1B	Kattula	Deepthi	University Hospital Tübingen
WP1B	Kleiman	Ivgeny	Tel Aviv Sourasky Medical Center
WP1B	Levi	Gal	Tel Aviv Sourasky Medical Center
WP1B	Luxemburger	Christine	Sanofi-Aventis
WP1B	Sen	Shuvayu	Merck Sharp & Dohme
WP1B	Shamsrizi	Parichehr	University Hospital Tübingen
WP1B	Silberschein	Erez	Tel Aviv Sourasky Medical Center
WP1B	Tacconelli	Evelina	University Hospital Tübingen
WP1B	Tadmor	Galit	Tel Aviv Sourasky Medical Center
WP1B	Temkin	Elizabeth	Tel Aviv Sourasky Medical Center
WP1B	Tenenboim	Izhak	Tel Aviv Sourasky Medical Center
WP1B	Vilken	Tuba	University Hospital Tübingen
WP1B	Witt	Joyce	Tel Aviv Sourasky Medical Center
WP1C	**Laxminarayan**	**Ramanan**	**University of Strathclyde**
WP1C	**Rex**	**John**	**AstraZeneca**
WP1C	Bedford	Tim	University of Strathclyde
WP1C	Bhatti	Taimur	Roche
WP1C	Colson	Abby	University of Strathclyde
WP1C	Cooke	Roger	University of Strathclyde

WP1C	Dhillon	Harpal	Merck Sharp & Dohme
WP1C	Donnelly	Sheryl	Merck Sharp & Dohme
WP1C	Drabik	Dusan	Wageningen University
WP1C	Goeschl	Timo	Ruprecht-Karls-Universität Heidelberg
WP1C	Joly	Florence	Sanofi-Aventis
WP1C	Leporowski	Axel	Ruprecht-Karls-Universität Heidelberg
WP1C	McBeth	David	University of Strathclyde
WP1C	Megiddo	Itamar	University of Strathclyde
WP1C	Millar	Robyn	University of Strathclyde
WP1C	Morton	Alec	University of Strathclyde
WP1C	Sen	Shuvayu	Merck Sharp & Dohme
WP1C	Watt	Maureen	Astellas
WP1C	Wesseler	Justus	Wageningen University
WP2	**Årdal**	**Christine**	**Norwegian Institute of Public Health**
WP2	**Ciabuschi**	**Francesco**	**Uppsala University**
WP2	**Findlay**	**David**	**GlaxoSmithKline**
WP2	**Rankin**	**Richard**	**GlaxoSmithKline**
WP2	**Røttingen**	**John-Arne**	**Norwegian Institute of Public Health**
WP2	Aagaard	Helle	Uppsala University/ReAct
WP2	Aftab	Friha	NIPH/University of Oslo
WP2	Anderson	James S.	GlaxoSmithKline
WP2	Antonisse	Ad	AstraZeneca
WP2	Baraldi	Enrico	Uppsala University
WP2	Bradshaw	David	Astellas
WP2	Callegari	Simone	Uppsala University
WP2	Cars	Otto	Uppsala University/ReAct
WP2	Charbonneau	Claudie	Pfizer
WP2	Domeij	Bengt	Uppsala University
WP2	Edwards	Suzanne	Unige
WP2	Gouglas	Dimitrios	Norwegian Institute of Public Health
WP2	Guthrie	Mark	Roche
WP2	Hallerbäck	Peter	AstraZeneca
WP2	Holland	Silas	Merck Sharp & Dohme
WP2	Jasovsky	Dusan	Uppsala University/ReAct
WP2	Johnsen	Jostein	Norwegian Institute of Public Health
WP2	Kållberg	Cecilia	Norwegian Institute of Public Health
WP2	Leach	Ross	Unige
WP2	Lindahl	Olof	Uppsala University
WP2	Lum	Ka	Roche
WP2	Martinsen	Lene	Norwegian Institute of Public Health
WP2	McDonald	John	Astellas
WP2	McKeever	Steve	Uppsala University
WP2	Morel	Chantal	Unige and London School of Economics and Political Science
WP2	Mossialos	Elias	London School of Economics and Political Science
WP2	Nwokoro	Ejike	Norwegian Institute of Public Health
WP2	Okhravi	Christopher	Uppsala University
WP2	Outterson	Kevin	Boston School of Law/Chatham House
WP2	Payne	David	GlaxoSmithKline

WP2	Peacocke	Elizabeth	Norwegian Institute of Public Health
WP2	Peterson	Stefan	Uppsala University
WP2	Plahte	Jens	Norwegian Institute of Public Health
WP2	Renwick	Matthew	London School of Economics and Political Science
WP2	Savic	Miloje	Norwegian Institute of Public Health
WP2	Schaper	Paul	Merck Sharp & Dohme
WP2	Storehagen	Live	Norwegian Institute of Public Health
WP2	Waluszewski	Alexandra	Uppsala University
WP2	Wood	Susan	Astellas
WP2	Zorzet	Anna	Uppsala University/ReAct
WP3A	**Harbarth**	**Stephan**	**University of Geneva**
WP3A	**Hackett**	**Judith**	**AstraZeneca**
WP3A	Bettiol	Esther	University of Geneva
WP3A	Howell	Jenny	AstraZeneca
WP3A	Huttner	Angela	University of Geneva
WP3A	Jantarada	Fabricio	University of Geneva
WP3A	Jensen	Jörgen	AstraZeneca
WP1A	Knirsch	Charles	Pfizer
WP3A	Legros	Stéphane	University of Geneva
WP3A	Mastrangelo	Dana	AstraZeneca
WP3A	Mok	Juliana	AstraZeneca
WP3B	**Theuretzbacher**	**Ursula**	**CEFAIA**
WP3B	**Mahoney**	**Nicole**	**Merck Sharp & Dohme**
WP3B	**Nolet**	**Brigitte**	**Roche**
WP3B	Brown	Nicholas	British Society for Antimicrobial Chemotherapy
WP3B	Clift	Charles	Chatham House
WP3B	Dar	Osman	Chatham House
WP3B	Ewers	Robert	Chatham House
WP3B	Goodall	Johnathan	AstraZeneca
WP3B	Guise	Tracey	British Society for Antimicrobial Chemotherapy
WP3B	Heymann	David	Chatham House
WP3B	O'Brien	Seamus	AstraZeneca
WP3B	Piddock	Laura	British Society for Antimicrobial Chemotherapy
WP3B	Pooni	Kam	Astellas
WP3B	Ross	Emma	Chatham House
WP3B	Trottier	Andre	Roche
WP3B	Wells	Victoria	British Society for Antimicrobial Chemotherapy

What were the project lessons learned?

DRIVE-AB was a public-private partnership including 23 partners from large pharmaceutical companies, academia and civil society – in other words, a contrasting mix of people with different experience, expertise, visions and perspectives. This was the strength and the originality of the project, but also represented its major challenge.

As the project developed, DRIVE-AB had to adapt to a fast-moving environment owing to political timelines and the high momentum around AMR policy discussions, to which it contributed. This placed much pressure on participants to deliver and raised the interests at stake considerably since the project was conceived in 2013. Under these circumstances, we were also faced with the

challenging task of weighing data and evidence from all DRIVE-AB participants to find realistic and pragmatic solutions to the project's key questions and present them in a timeframe that was relevant for policymakers.

In May 2017, ReAct, which was participating in DRIVE-AB through the partner Uppsala University, decided to withdraw, citing conflict of interest and governance issues. We regretted that ReAct decided to leave the DRIVE-AB partnership. We believe that it contributed positively to the conversations and development of DRIVE-AB's research. When ReAct left we lost an important voice within the project to represent civil society. Although we were aware that aligning such a diverse group of partners behind all recommendations would be difficult, DRIVE-AB was committed to building consensus. All partners were consistently included in meetings and were encouraged to comment on major documents and report drafts. As in all collaborative research-based projects, publications authored by named individuals followed a standard process, including circulation to all WP members and the steering committee for feedback, often with numerous iterations to include participants' positions. When no consensus was achieved, publications were authored with a disclaimer stating that they did not represent the view of all DRIVE-AB partners. In those few instances where there were no named authors (for example, policy briefs), all drafts were circulated and feedback incorporated. We also attempted to reflect diverging views when space was limited, and reflected them in detail when there was no space limitation (as is the case in this final report and many other publications).

As the project developed, as well as ReAct leaving, diverging views were expressed on certain topics on which partners of this consortium have visions that are far apart. We acknowledge the procedural complexities of this public-private multi-stakeholder project and that some improvements could have been made. In terms of fostering consensus, we recognize that a more formal process could have been put in place earlier in the project. At the same time, we are unsure whether a more formal process would have been more successful in aligning people's visions. To ensure that this report reflects the views of different stakeholders, we have clearly distinguished areas where there were different views or no consensus (e.g. see section on market entry rewards and sustainable use). Conference presentations discussing DRIVE-AB's conclusions reflected this diversity of views.

DRIVE-AB's Research Articles

The following articles have been published or submitted or are in preparation under the auspices of DRIVE-AB.

WP1A - *Define "responsible" use of antibiotics*

WP1A posters presented at the Brussels final conference in September 2017 are available here:

http://drive-ab.eu/events/drive-ab-project-events/drive-ab-final-conference/drive-ab-final-conference-downloads-and-resources/drive-ab-final-conference-posters/

Submitted manuscripts:

Introduction: DRIVE-AB's definitions and indicators to monitor responsible antibiotic use. Stephan Harbarth and Judy Hackett

Towards a global definition of responsible antibiotic use: results of an international and multidisciplinary consensus procedure. Monnier AA, Eisenstein BI, Hulscher ME & Gyssens IC, the DRIVE-AB stakeholders

Variation in antibiotic use among and within different settings: a systematic review. Zanichelli V, Monnier AA, Gyssens IC, Adriaenssens N, Versporten A, Pulcini C, Le Maréchal M, Tebano G, Vlahović-Palčevski V, Stanic Benic M, Milanic R, Harbarth S, Hulscher M, Huttner B

Quality indicators for responsible antibiotic use in the inpatient setting: a systematic review followed by an international consensus procedure. Monnier AA, Schouten J, Le Maréchal M, Tebano G, Pulcini C, Stanic Benic M, Vlahović-Palčevski V, Milanic R, Adriaenssens N, Versporten A, Huttner B, Zanichelli V, Hulscher ME & Gyssens IC, the DRIVE-AB stakeholders

Metrics for quantifying antibiotic use in the hospital setting: results from a systematic review and consensus procedure. Stanić Benić M, Milanič R, Monnier A, Gyssens IC, Adriaenssens N, Versporten A, Zanichelli V, Le Maréchal M, Huttner B, Tebano G, Hulscher M, Pulcini C, Schouten J, Vlahović-Palčevski V, the DRIVE-AB stakeholders

Quality indicators assessing antibiotic use in the outpatient setting: a systematic literature review followed by a global consensus procedure. Le Maréchal M, Tebano G, Monnier AA, Adriaenssens N, Gyssens IC, Huttner B, Milanic R, Schouten J, Stanic Benic M, Versporten A, Vlahović-Palčevski V, Zanichelli V, Hulscher M, Pulcini C, the DRIVE-AB stakeholders

Quantity metrics assessing antibiotic use in the outpatient setting: a global consensus procedure. Versporten A, Gyssens IC, Pulcini C, Schouten J, Milanic R, Monnier A, Stanic M, Tebano G, Le Maréchal M, Zanichelli V, Huttner B, Vlahović-Palčevski V, Goossens H, Hulscher M, Adriaenssens N, the DRIVE-AB stakeholders

Manuscripts in preparation:

1. Barriers and enablers of responsible systemic antibiotic use from the patient's perspective: a systematic review by Zanichelli V, Tebano G, Pulcini C, Huttner B

2. Views and experiences of currently or recently hospitalized patients with regard to barriers or facilitators to responsible antibiotic use: an international qualitative descriptive study by Zanichelli V, Monnier A, Hulscher M, Huttner B
3. Barriers & facilitators of responsible antibiotic use from the government, payers, regulators and R&D perspective by Monnier A, Tebano G, Hulscher M, Gyssens IC

WP1B - *Set, communicate and revise public health priorities*

Output: Website with worldwide map showing current and projected number and rate of infections with selected MDROs, freely available for users

Publications in print:

Friedman ND, Temkin E, Carmeli.Y (2016). The negative impact of antibiotic resistance. *Clinical Microbiology and Infection* 22, 416-422

Nithya BR, Gladstone BP, Rodríguez-Baño, J, Sifakis F, Voss A, Carmeli Y, Burkert FR, Gkolia P, Tacconelli E (2017). EpideMiology and control measures of outBreaks due to Antibiotic-Resistant orGanisms in EurOpe (EMBARGO): a systematic review protocol. BMJ Open *7*, e013634. In collaboration with COMBACTE-MAGNET

Gladstone BP, Cona A, Shamsrizi P, Vilken T, Kern WV, Malek N, Tacconelli E (2017) Antimicrobial resistance rates in Gram-positive bacteria do not drive glycopeptides use. PLOS ONE 12(7): e0181358. In collaboration with COMBACTE-MAGNET

Planned publications

- Publications submitted and under review
  1. Tacconelli E, et al. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics
  2. Almagor Y, et al. The impact of antibiotics and antibiotic stewardship on transmission of resistant bacteria in hospitals

- Publications in progress
  1. Estimating the worldwide number and incidence of 3GC-resistant and carbapenem-resistant *E. coli* and *K. pneumoniae* infections
  2. Epidemiological differences in controlling the spread of carbapenem-resistant bacterial strains in hospitalised patients
  3. Clinical impact of resistance in bacterial infections: a global perspective
  4. A systematic review of the impact of immigrants and refugees on the spread of antibiotic-resistant bacteria
  5. Medical tourism and the risk of infection or colonization with antibiotic-resistant organisms: A literature review
  6. Identification and modelingof antibiotic-resistant bacteria worldwide
  7. Mortality associated with antibiotic-resistant bacteria – the silent killer? Estimating future trends in the spread of antibiotic resistance: the case of third-generation cephalosporin-resistant *E. coli*

WP1C - *Develop antibiotic valuation models*

Publications in print:

Aude Teillant, Sumanth Gandra, Devra Barter, Daniel J Morgan, Ramanan Laxminarayan. 2015. "Potential Burden of Antibiotic Resistance on Surgery and Cancer Chemotherapy Antibiotic Prophylaxis in the USA: A Literature Review and Modelling Study". *The Lancet infectious diseases* 15 (12): 1429–37. doi:10.1016/S1473-3099(15)00270-4.

Planned publications

Itamar Megiddo, Dusan Drabik, Tim Bedford, Alec Morton, Justus Wesseler, Ramanan Laxminarayan. Investing in antibiotics to alleviate future catastrophic outcomes: what is the real option value of having an effective antibiotic to mitigate pandemic influenza?

Alec Morton, Abigail R. Colson, Axel Leporowski, Anna Trett, Taimur Bhatti, Ramanan Laxminarayan. Horses for courses: how should the value attributes of novel antibiotics be considered in reimbursement decision making?

Sumanth Gandra, Anna Trett, Gerardo Alvarez-Uria, Ramanan Laxminarayan. Is the efficacy of antibiotic prophylaxis for surgical procedures decreasing? Systematic review and meta-analysis of randomized control trials

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Christoph Werner, Tim Bedford, Abigail R. Colson, Alec Morton. Risk assessment of future antibiotic resistance – eliciting and modelling probabilistic dependence between multivariate uncertainties of bug-drug combinations

John H. Rex, Axel Leporowski, Dusan Drabik, Abigail R. Colson, Charles Knirsch, Ramanan Laxminarayan. Historical perspectives on antibiotics and implications for a possible post-antibiotic era

WP2 - *Create, test and validate new economic models*

Publications in print:

Okhravi Christopher, McKeever Steve, Kronlid Carl, Baraldi Enrico, Lindahl Olof, Ciabuschi Francesco. Simulating market-oriented policy interventions for stimulating antibiotics development. Proceedings of the 50th Annual Simulation Symposium 2017. Society for Computer Simulation International

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Policy briefs and interim reports:

Policy brief: The necessity for greater antibiotic innovation. Developed for the World Health Assembly 2016 and the launch event of the Global Antibiotic Research and Development Partnership (GARDP), 2016.

Policy brief: The role for non-profit antibiotic developers. Developed for the World Health Assembly 2016 and the launch event of the Global Antibiotic Research and Development Partnership (GARD), 2016.

Report: Incentives to stimulate antibiotic innovation: The preliminary findings of DRIVE-AB. Distributed to participants at DRIVE-AB conference, June 2016.

Report: Identified risks and bottlenecks to antibiotics innovation, 2016.

Report: Solutions from other industries applicable to the antibiotic field. 2016.

Policy brief: The importance of multinational coordination and increased public financing for antibiotic innovation. Developed for the United Nations General Assembly meeting on antimicrobial resistance in September 2016. Also disseminated at the Global Health Security Agenda 3rd Annual Ministerial Meeting, October 2016.

WP2 posters presented at the Brussels final conference in September 2017 are available here:

http://drive-ab.eu/events/drive-ab-project-events/drive-ab-final-conference/drive-ab-final-conference-downloads-and-resources/drive-ab-final-conference-posters/

Planned publications

2. Årdal Christine, Baraldi Enrico, Theuretzbacher Ursula, Outterson Kevin, Plahte Jens, Ciabuschi Francesco, Røttingen John-Arne. Insights into early stage antibacterial development in small and medium sized enterprises: a survey of targets, costs, and durations
3. Årdal C, Baraldi E, Findlay JD. Financing antibiotic research through a mega-fund
4. Storehagen L, Aftab F, Årdal C, Savic M, Røttingen J-A. Should antibiotics be controlled medicines? Lessons from the controlled drug regimen
5. Bhatti T, Lum K, Holland S, Sassman S, Findlay D, Outterson K. A Perspective on Pull Incentives for Novel Antibiotics: No One-Size-Fits-All
6. Årdal C, Storehagen L. Ensuring equitable availability of novel antibiotics
7. Okhravi C, Callegari S, McKeever, S, et al. Simulating antibacterial innovation rewards
8. Edwards S, Morel C. Sustainable use obligations for market entry rewards
9. Guthrie M, Bhatti T, Holland S. Incentivizing appropriate use of novel antibiotics with the Diagnostic Confirmation Model

Savic M, Årdal C. Push incentives to stimulate research and development of new antibiotics

Christine Årdal, Jostein Johnsen, Karianne Johansen. Designing a delinked antibiotic pilot – lessons from Norway

Cecilia Kållberg, Christine Årdal, Hege Salvesen Blix, Elena Martinez, Eili Klein, Morten Lindbæk, Kevin Outterson, John-Arne Røttingen, Ramanan Laxminarayan. Factors influencing the introduction of new antibiotics approved between 1999 and 2014

Cecilia Kållberg et al. Quantitative assessment of factors influencing the introduction of new antibiotics.

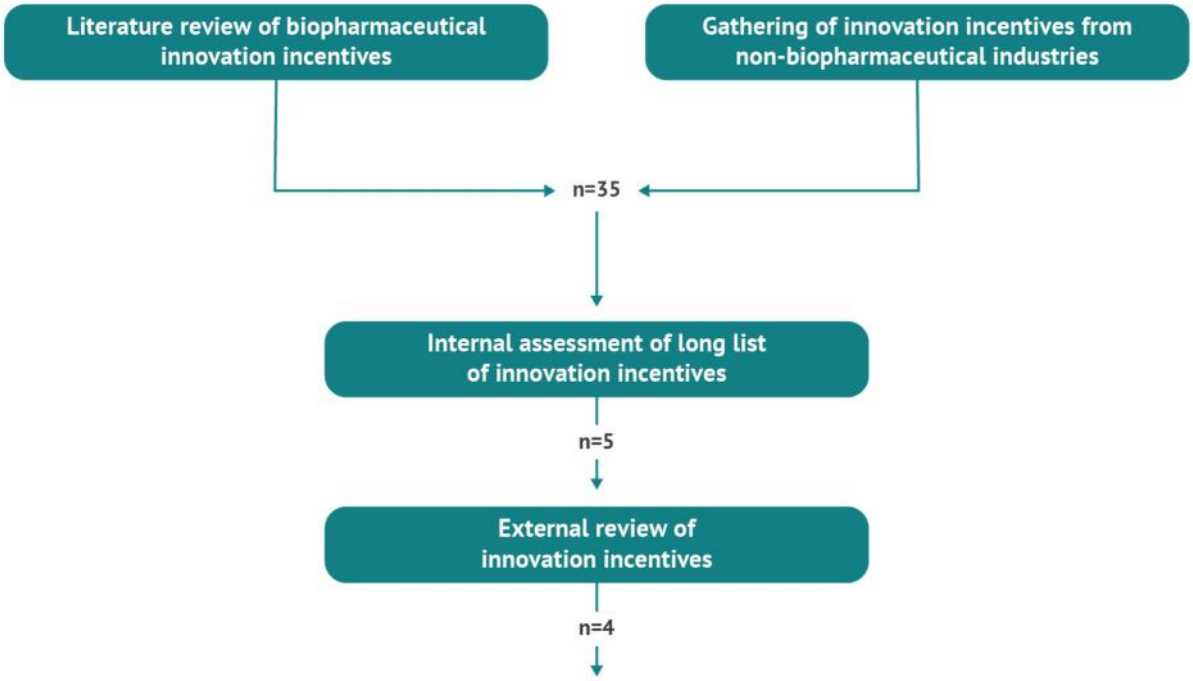
Cecilia Kållberg et al. Impact of generic transition on antibiotic sales between 1999 and 2014

Appendix B: Incentives to stimulate antibacterial innovation: the DRIVE-AB short-list

Methods

The DRIVE-AB innovation incentives have been selected via a multi-stage process (Figure 15). A literature review was undertaken to identify both published and grey literature containing theoretical or practical economic incentives for stimulating any type of biopharmaceutical innovation. Incentives were also extracted from WHO's Consultative Expert Working Group on Research and Development: Financing and Coordination,[92] and DRIVE-AB team members were asked to supplement the list with any additional models.

Figure 15: Selection process of DRIVE-AB innovation incentives



At the same time, an analysis of potential incentives used in non-healthcare-related industries was performed. A literature review was conducted and three focus group meetings were held, in France, Norway and Sweden.[89]

The incentives from these two sources were combined and duplicates removed. Each incentive was boiled down to core concepts. Many existing incentives combine multiple mechanisms – for example, orphan drug legislation is a combination of several mechanisms including extended exclusivities and tax exemptions. This long-list was compared against a set of core antibiotic bottlenecks.[7] If the incentive did not aim to remedy at least one bottleneck, it was discarded. Those incentives identified as potentially useful to improve sustainable use or equitable availability (but not innovation) were shared with the DRIVE-AB team members working on these tasks. This resulted in a list of 35 incentives.

Sixteen DRIVE-AB members were then asked to assess these 35 innovation mechanisms. The group consisted of five academics, six employees of large pharmaceutical companies and five individuals working for non-profit or governmental policy-related organizations. All have significant expertise in their respective fields. Pharmaceutical industry employees were allowed to answer the survey on behalf of their company rather than provide an individual assessment. Each member received a pre-

reading document giving a brief description of the incentive, the advantages and disadvantages, as well as an online survey to complete. All participants except two (one academic and one policy expert) voted in the online survey, but one participant (from industry) only voted on half of the incentives. The votes were tallied and presented at an internal meeting, which discussed in detail 17 incentives (those broadly supported, those with no clear consensus, and two with little support but that were strongly supported by individuals in the group). For an incentive to be included, it had to have support from both industry and non-industry members. This resulted in a short-list of four prioritized incentives. Project members were then asked if there was any additional incentive that they strongly advocated should be included in the external stakeholder assessment. One model was put forward by an industry member.

DRIVE-AB then organized a high-level stakeholder meeting in Amsterdam to present, discuss and refine promising new economic models for the discovery and development of novel antibiotics. There were 45 participants, primarily from Europe and North America, representing large and small pharmaceutical companies, a product development partnership, academia, the public health sector and civil society. All received a pre-reading document before the meeting. The Chatham House Rule regarding disclosure applied to the meeting discussion. Short-listed incentives were presented in detail. Presentations included a brief description of the incentive, a preliminary assessment including the type of R&D the model is intended to incentivize, its impact on sustainable use of antibiotics, and its impact on availability of the resulting antibiotic. Stakeholders were then asked to complete a short survey and discuss the incentive.

Results

DRIVE-AB team members assessed 35 potential innovation incentives. The online survey asked members to determine to what extent the incentive was expected to stimulate greater innovation in antibiotic R&D in a sustainable fashion. Additionally, they were asked to assess (1) where the incentives would most likely work well, including at which stage of R&D, with what type of actor, and with what type of technology; and (2) what impact the incentives would have on sustainable use and equitable availability.

No incentives were deemed by the majority of internal experts to “strongly” stimulate greater antibiotic innovation. Five incentives received four or more votes that they could “strongly” stimulate innovation, and five more received nine votes that they could “strongly” or “moderately” stimulate it. These ten incentives were discussed in depth by the internal group. After this discussion four incentives were selected for further analysis (see Table 11) as representative of the group’s consensus. Thirty incentives were excluded from further consideration or combined with another mechanism. Table 12 provides a brief description of the incentives and rationale for exclusion or merger.

The DRIVE-AB short-list of innovation incentives presented to stakeholders in June 2016 included: (1) grants, (2) non-profit antibiotic developer, (3) market entry rewards, (4) insurance licence, and (5) diagnosis confirmation model.[94] Each incentive/model is designed to stimulate different types of antibiotic innovation as well as different stages of the R&D process. Grants were excluded from the presentation owing to time constraints and since the concept is already well understood. They are therefore not included in the results here. Table 11 gives a brief description of each model, as well as the scores from the internal assessment.

The external stakeholder feedback is described below for each model.

Non-profit antibiotic developer

A non-profit antibiotic developer is an independent organization that manages and finances a portfolio of antibiotic discovery and development projects through to commercialization. It is not a profit-seeking organization but one that would reinvest any profits back into its development work. However, it may partner with and finance profit-seeking companies to further develop specific antibiotic candidates. Such an arrangement is a product development partnership (PDP), similar to those established for neglected diseases.

Stakeholders judged this proposal neutral in terms of stimulating innovation (it neither strongly nor weakly stimulates). However, private-sector participants thought otherwise. Excluding the private sector, the other stakeholders were slightly more positive but still neutral about the incentive's ability to stimulate innovation. The proposal was generally judged favourably in terms of compatibility with national regulatory and reimbursement systems and promoting both sustainable use and equitable availability. In the discussion, it was acknowledged that this proposal already performed well for neglected diseases. However, it was questioned whether this model could develop novel products through to marketing approval. Some suggested that it could be used to test an existing product for other indications as well as to develop combination therapies. More clarity was needed around the advantages of for-profit companies collaborating with a non-profit antibiotic developer and the financing model.

Market entry reward

A market entry reward is a series of substantial, annual payments made to an innovator who achieves regulatory approval for a new antibiotic meeting specified requirements, including target pathogens. By accepting the payment, the developer contractually agrees to a set of stipulations regarding global availability, regulatory maintenance and sustainable use provisions. There are two versions of this incentive – fully and partially delinked. In a fully delinked model, all developer revenues come from the reward payment(s) whereas in a partially delinked model, revenues are achieved both from the reward payment(s) and unit sales. However, in a fully delinked model the healthcare providers will need to pay a higher unit price to avoid the economic incentive to overuse the antibiotic.

Market entry rewards were judged to strongly stimulate innovation, with the partially delinked version receiving slightly higher support. There were concerns about the financial feasibility of the fully delinked model and thus sustainability and implementation. Stakeholders were sceptical of one global implementation of either model, highlighting the complexity, amount of financing, and level of consensus required. Participants mentioned that it would be difficult to safeguard such a large pot of money from other political agendas.

The fully delinked model was judged to strongly support sustainable use and equitable availability, but there were concerns that the partially delinked model would be less effective in these areas. There were also concerns about the national complexity of the implementation of a fully delinked model, especially the ability of governments to set unit prices of novel antibiotics for their healthcare providers. Setting too low a unit price could have an adverse impact on sustainable use. Finding a "neutral" price could be complicated.

There were concerns regarding a market entry reward's ability to stimulate earlier-phase financing, particularly for small to medium-sized enterprises (SMEs), which normally licensed or sold their products in development prior to regulatory approval.

Insurance licence

An insurance licence is an annual amount paid to a manufacturer to safeguard access to a specific antibiotic, up to a specified volume. If the threshold volume limit (sometimes called the "collar") is exceeded, then the payer would provide an additional amount (either per treatment or a fixed amount to a higher threshold). In a variation of this model (the cap and collar model), there is an additional threshold (the "cap") where there is revenue-sharing between the manufacturer and the payer.

This model was not perceived to stimulate innovation. Yet it was judged to be financially feasible, sustainable, compatible with regulatory and reimbursement systems, supportive of sustainable use policies, and implementable nationally. It was acknowledged that this could be a strong model to ensure national access to critical antibiotic therapies, such as colistin. There was uncertainty about the model's ability to promote global access to antibiotics, and about whether the model could be implemented in low- and middle-income countries.

Diagnosis confirmation model

The diagnosis confirmation model is a diagnosis-driven, dual-pricing model where a premium price is charged if the antibiotic is used for the entire course (based on a confirmed diagnosis or clinical decision) or a lesser price if the antibiotic is used first empirically and then promptly de-escalated after the receipt of the diagnostic/laboratory results.

Only SMEs thought that this model would stimulate innovation; otherwise it was assessed as not stimulating innovation. Some commented that since this model could be implemented today, it was unclear how this would improve antibacterial R&D incentives. The model was judged as financially feasible, implementable nationally, and compatible with national regulatory and reimbursement systems. It was judged poorly for supporting equitable availability. In the discussion, stakeholders questioned if dual pricing was actually necessary. Some commented that hospitals must implement strict controls for budgetary reasons when using any extremely highly-priced products. These controls may be as effective for sustainable use as the dual-pricing mechanism. Some participants stated that diagnostic results were not always clear and that physicians might continue to administer the antibacterial therapy as long as the patient was improving. There was a general concern that the model promoted empiric use of a novel antibiotic. There was a strong critique of the model's impact on equitable availability.

Discussion

Throughout our assessments we have been clear that there is a need for different incentive models depending on the type of infection and patient population. The models need to ensure that risk and royalties are shared between stakeholders. On the basis of this stakeholder evaluation, DRIVE-AB selected four models to further detail and research. Grants and market entry rewards (both partially and fully delinked models) received strong support and clearly needed further development and assessment. The non-profit antibiotic developer was transformed, based upon the feedback, into the pipeline coordinator, with more emphasis on collaboration with the private sector. The insurance licence model was shifted from an innovation to an access incentive, entitled the long-term supply continuity model, to be used to maintain reliable access to important but rarely used generic antibiotics. The diagnosis confirmation model was excluded because of its inability to be paired with any equitable availability models and because market entry rewards were deemed a stronger incentive.

DRIVE-AB finds these four incentives (grants, pipeline coordinator, market entry reward and long-term supply continuity model) best suited to fill the antibiotic pipeline and ensure the effectiveness and availability of new antibiotics over time. There is no "one size fits all' solution to incentivizing antibiotic innovation in a global market with a huge variety of unmet needs, healthcare systems and access requirements. A menu of incentives is required that can be adapted to the local context and yet still achieve the same goal of stimulating antibacterial innovation.

Table 11: DRIVE-AB short-list of incentives presented at external stakeholder meeting

Incentive	Type	Delinked	Type of innovation stimulated	Scores from internal assessment		
				Ability to stimulate innovation	Ability to promote sustainable use	Ability to promote equitable availability
Grants	Push	n/a	Early-phase research and development	Not able (0) Weakly (2) **Moderately (9)** Strongly (3) Don't know (0)	Not able (0) Neutral (5) **If paired (9)** Will promote (0) Don't know (0)	Not able (0) **If paired (7)** Neutral (6) Will promote (1) Don't know (0)
Non-profit antibiotic developer	Push	n/a	Incremental innovation and development with a higher risk profile	Not able (2) **Weakly (5)** Moderately (2) **Strongly (5)*** Don't know (0) *Only from academic and policy experts	Not able (0) Neutral (6) **If paired (7)** Will promote (1) Don't know (0)	Not able (0) **If paired (7)** Neutral (1) Will promote (6) Don't know (0)
Diagnosis confirmation model	Pull	No	Greater diversity of broad- and narrow-spectrum antibiotics with significant improvements	(Not assessed as this incentive was added after February 2016)	(Not assessed as this incentive was added after February 2016)	(Not assessed as this incentive was added after February 2016)
Market entry reward	Pull	Yes	Most pressing public health threats	Not able (0) Weakly (1) **Moderately (8)** Strongly (5) Don't know (0)	Not able (0) Neutral (2) **If paired (8)** Will promote (4) Don't know (0)	Not able (0) **If paired (8)** Neutral (3) Will promote (3) Don't know (0)
Insurance licence	Pull	Yes	Rarely used, emergency antibiotics	Not able (1) Weakly (2) **Moderately (8)** Strongly (2) Don't know (1)	Not able (0) Neutral (1) If paired (6) **Will promote (7)** Don't know (0)	Not able (0) If paired (4) **Neutral (5)** Will promote (4) Don't know (1)

Table 12: Incentives determined to insufficiently stimulate antibacterial innovation and rationale

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
Fund-related mechanism	**Antibiotic Health Impact Fund**: A mechanism where donors create a fund to pay for the actual global health impact of the antibiotic including conservation. The fund runs parallel to the traditional reimbursement system. If a company voluntarily opts into payments from the fund, it agrees to sell the antibiotic at cost price globally. It then receives an annual payment based upon the amount of financing in the fund, divided formulaically by the calculated health impact of the antibiotic. This annual payment continues for the lifetime of the patent.	Not able (0) **Weakly (7)** Moderately (5) Strongly (2) Don't know (0)	In order to function effectively, donors must contribute substantially ($1 billion/€850 million) or more annually) to a pooled fund without any assurances that these funds will generate innovative antibiotics. There is scepticism that governments would be willing to do so on a long-term basis, not only because of the large sums involved but also given that the payout is based upon a ranking of global health impact and theoretically could result in large payments to patented antibiotics that offer little public health benefit. The unpredictability of government funding would be likely to deter private-sector investment. This mechanism is also complicated, requiring significant funds to administer.
Fund-related mechanism	**Antibiotic tax:** A mechanism that imposes a fee or tax on antibiotic use to offset negative externalities, with the proceeds used to fund conservation and R&D for new antibacterials. The tax can be selectively applied, e.g., only to antibiotics used for animals and/or only to antibiotic consumption in high-income countries. One option for implementation is to tax antibiotic active pharmaceutical ingredients.	Not able (3) **Weakly (5)** Moderately (5) Strongly (1) Don't know (0)	This may be an effective financing mechanism for antibacterial R&D and must be paired with a mechanism for utilizing the funds. This was transferred to potential national financing mechanisms.
Fund-related mechanism	**Antibiotic corporate bond**: A mechanism where developers performing antibiotic-related R&D market their corporate bonds as antibiotic-related. The aim is to increase the number of social-impact	**Not able (5)** **Weakly (5)** Moderately (2) Strongly (0) Don't know (2)	This does not solve the inherent problem with antibacterial R&D, i.e., that the development costs outweigh the revenues. Bonds must be repaid with interest, and this incentive does not generate additional revenues.

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	investors.		
Fund-related mechanism	**Antibiotic government bond**: A government-issued bond meant to raise funds specifically for investment into antibiotic R&D. Governments would pay out proceeds as either grants or non-dilutive capital to developers. Bonds could be partially or fully repaid through future earnings.	Not able (3) **Weakly (5)** Moderately (4) Strongly (0) Don't know (2)	It would be cheaper for governments to directly finance R&D grants (no need to pay interest) than issue government debt. Also, this does not change the business model – antibiotics will remain an unattractive business case and future earnings should remain small to moderate. Lastly, governments do not typically issue earmarked bonds.
Fund-related mechanism	**The Fast Track Option**: A variant of the Priority Review Voucher, this incentive gives companies the option to purchase an expedited regulatory review for a drug of their choice. The funds raised as a result can be pooled to support antibacterial R&D.	**Not able (6)** **Weakly (6)** Moderately (1) Strongly (1) Don't know (0)	This mechanism expedites market entry based upon ability to pay rather than medical need, which is an undesirable outcome. The value of the Fast Track Option would be greatly diminished if many manufacturers purchased it, as the regulatory agency would not necessarily have the capacity to fulfil its commitments. Also, this does not change the business model – antibiotics will remain an unattractive business case and future earnings should remain small to moderate.
Fund-related mechanism	**Big science joint fund and infrastructure**: Modelled after big science projects like the Large Hadron Particle Collider at CERN or the International Space Station, two or more countries finance a common antibiotic R&D platform/infrastructure consisting of equipment, facilities and labour as well as ongoing operating costs. This platform can be used both by "member" and "non-member" countries to run specific projects, whose running costs are covered by the specific countries taking the initiative for each project. Any revenues generated from the R&D could be divided as per the agreement between countries.	Not able (0) Weakly (3)* **Moderately (7)** Strongly (4) Don't know (0) *All from industry	This collaborative model is one that is already implemented virtually through Europe's Innovative Medicines Initiative and the Joint Programming Initiative on AMR (particularly through the forthcoming Virtual Research Institute). The value of having a physical centre is uncertain. The two examples given (CERN and ISS) must share one location. Yet for antibiotics the drivers of early-phase discovery and development have been SMEs. We estimate that there are more than 200 SMEs focusing on antibacterial R&D. It is impractical for them to be consolidated in one location, and there would be concerns regarding anti-competitiveness and management of intellectual property. (We do support multinational collaborative funding but include this as a financing option.)
Fund-related mechanism	**Publicly financed venture capital**: A mechanism where one or more	Not able (0) **Weakly (6)** **Moderately (6)**	This mechanism is already in place through the European Investment Bank's InnovFin programme, which provides attractive

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	governments would establish an antibiotic venture capital fund. Investments would be made mainly on commercial terms but also be based on clinical need and for the purpose of supporting early-phase start-ups. Exit occurs by selling individual shares, or by transferring entire portfolios to other investment funds. Initially the fund would need public funding, but private capital could be invited to participate from an early stage. Later on, exits and gains from previous investments could possibly make the fund self-sustaining and profitable.	Strongly (2) Don't know (0)	financing tools to companies working within the infectious disease space. InnovFin financing tools cover a wide range of loans, guarantees and equity-type funding. Yet SMEs criticize InnovFin because investments in antibiotics are considered too risky and insufficiently profitable. That is, this mechanism does not change the business model – antibiotics will remain an unattractive business case and future earnings should remain small to moderate.
Grant-related mechanisms	**Incubator/accelerator services**: Incubators typically provide business mentoring, financial advice, office space and other services to start-ups. Accelerators assist small companies to achieve rapid growth (for example, securing venture capital or achieving specific milestones), also through mentoring and other services. Incubators tend to be government-funded and also earn income from office rents. Accelerators typically expect equity in the company. An antibiotic-related incubator or accelerator can focus not only on antibiotics but also on diagnostics, preventive measures and all other supplementary and complementary technologies.	Not able (0) **Weakly (7)** **Moderately (7)** Strongly (0) Don't know (0)	Although this mechanism was deemed to have merit for supporting SMEs, it was determined not to be enough of an incentive to shift investment patterns. However, it may be a beneficial enhancement to another innovation incentive. Indeed, this has subsequently been combined with grants and strong portfolio management through the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X).
Grant-related	**Public R&D procurer**: A	Not able (2)*	The experts were split over the merit of this

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
mechanisms	"central public body", either a national state or a transnational organization, procures specified R&D activities from a range of actors via open, competitive tenders. The R&D delivery contract specifies the deadlines for the various R&D stages and milestones covered by the agreement, with rigorous requirements on quality, reliability and safety. Ownership of the R&D results is retained by the central public body commissioning the R&D activities, including patents.	Weakly (3)* Moderately (1) **Strongly (7)** Don't know (1) *All from industry	idea, with industry universally against the mechanism. The rationale is that the process of tendering to perform R&D is not the business model of the pharmaceutical industry (big or small). Industry wants to invest in areas matching its product portfolio and risk profile, with the opportunity to reap the rewards of these investments. Companies are not interested in simply being paid on a fee-for-development basis where they do not own the intellectual property. One can argue that a similar (but more flexible) model is that of the Global Antibiotic Development Partnership (GARDP). GARDP does not tender out development activities but actively collaborates and finances companies working within its specified scope. This approach has been taken within the Pipeline Coordinator model.
Monopoly protections	**Exclusivities**: Data exclusivity protects the clinical trial data, preventing other organizations from seeking regulatory approval of a product using the same clinical trial data as the originating organization for a specified period of time (from 5 to 8 years for new chemical entities and up to 12 years for biological products). Since it is unethical to perform redundant clinical trials on patients, in countries where data exclusivity has been granted this gives a company an automatic, temporary monopoly on the medicine. Market exclusivity gives a company exclusive marketing rights for a particular medicine for a set period of time. It is used to incentivize R&D in areas that otherwise may not be pursued, such as	Not able (1) **Weakly (9)** Moderately (4) Strongly (0) Don't know (0)	Five additional years of market exclusivity have already been given through the US GAIN Act. This gives qualifying antibiotics ten years of exclusivity in the US from FDA regulatory approval. Since there is typically a decade of patent protection available at US regulatory approval, this exclusivity runs in parallel. However, even if the exclusivity period extends the monopoly period where the innovator can charge high prices, it does little to improve the market attractiveness. That is, newer antibiotics will still need to be conserved, translating into minimal sales. Exclusivities are only able to change the market dynamics if the antibiotic achieves greater consumption, which may be undesirable.

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	paediatric medicines or medicines for rare diseases. It can be made conditional on meeting conservation targets.		
Monopoly protections	**Transferable exclusivity voucher**: This would grant a legal right to extend the monopoly time period (through exclusivities) of any other patented drug, in exchange for the successful regulatory approval of a specified antibiotic. The voucher would be transferable or saleable. For example, if a company developed "Antibiotic A" it could receive an exclusivity voucher that can prolong the monopoly period of its own "Blockbuster Oncology Drug" or sell the voucher to the patent holder of this drug.	Not able (1) Weakly (2) **Moderately (5)** Strongly (4) Don't know (2)	Although this mechanism would highly incentivize antibacterial innovation, the cost is estimated to be too high relative to the gains. A company would pay for the exclusivity voucher only if it expected to profit from it (i.e., cover the costs of the antibacterial R&D and return a profit margin). Since in most European countries the government is the healthcare provider, this profit would be at the expense of the government, i.e., it may be cheaper for the government to pay an alternative reward, like a Market Entry Reward. In non-government-provided healthcare systems, this incentive has ethical ramifications since it would prolong high prices of important medicines, which in some countries would have a disproportionate impact on the un- or underinsured. Since the voucher is designed as a one-time transaction, it would be difficult to rescind the voucher in cases where either the antibiotic was removed from the market, or sustainable use and equitability availability guidelines were disregarded.
Prizes	**Lump sum diminishing payments** As with a Market Entry Reward, developers would receive a series of annual delinked payments at the time of marketing approval for a new antibiotic meeting a specific target product profile (TPP). In exchange, the developer would agree to a per unit price cap on the antibiotic. Over time, the per unit price cap would be increased and the annual delinked payment decreased. The aim is that by the end of the exclusivity period, the unit price is high and prescription volumes may	Not able (1) Weakly (3) **Moderately (5)** Strongly (2) Don't know (3)	Market Entry Rewards are meant to incentivize the commercialization of important new antibiotics with anticipated low consumption. This variation increases the price towards generic transition to encourage generic manufacturers. Yet generic manufacturers will be incentivized to over-sell the antibiotic, which is undesirable from a sustainable use perspective.

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	remain relatively low. Therefore, there will be an incentive for generic manufacturers to enter the market.		
Prizes	**Priority review vouchers**: A priority review voucher is awarded upon marketing authorization for a specific novel antibiotic. The voucher creates a transferable/saleable right to have a regulatory agency evaluate the approval of a non-related drug in a more expedited period.	Not able (1) **Weakly (9)** Moderately (3) Strongly (1) Don't know (0)	Priority Review Vouchers (PRVs) are already in place in the US for neglected tropical diseases, rare paediatric diseases and "medical countermeasures" for terrorism. The market value of the PRVs varies. One has been sold for $67.5 million (€55.7 million) and another for $350 million (€289 million). This mechanism is too unpredictable and probably too small to stimulate antibacterial innovation. Developers will need to know the anticipated value of the PRV at least five years in advance to make the net present value calculations required for an investment decision. Additionally strides are being made by regulatory agencies to hasten the review process, which may limit the value of the PRV.
Prizes	**Traditional prizes**: Monetary prizes can take a number of different forms, with variations on when the payment is received, how many payments are received, how many recipients may win the prize, and who may control the resulting intellectual property.	Not able (1) Weakly (2) **Moderately (8)** Strongly (3) Don't know (0)	Prizes have successfully stimulated innovation in other industries, and the Longitude Prize has done this for antibiotic-related diagnostics. A Market Entry Reward is a type of prize, and the experts agreed that it is better to focus on this particular prize form. There was considerable debate regarding the viability of Milestone Prizes, a mechanism favoured by SMEs. Concerns include the potential for gaming the prize (i.e., important trials that are difficult to predefine might not be performed), and that potentially important antibiotics are not incentivized to actually reach the market, which is the desired public health outcome. It was anticipated that if the Market Entry Reward was perceived as attractive, this would facilitate greater interest from larger companies to purchase assets from smaller ones (which is, in essence, a Milestone Prize). However, milestone payments may provide useful supplementary financing for grant funders.
Regulatory mechanisms	**Limited Population Antibacterial Drug (LPAD) Approval Mechanism**: Where an urgent unmet clinical need exists, an antibiotic's safety and	Not able (0) **Weakly (8)** Moderately (5) Strongly (0) Don't know (0)	LPAD has already been implemented in the US and is recognized to be an important factor for facilitating antibacterial innovation. LPAD allows for smaller and therefore less expensive clinical trials, but this in itself is not enough to change the

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	effectiveness can be tested in smaller, more rapid, and less expensive clinical trials. Successful trials give the antibiotic a narrow indication for use in small, well-defined populations of patients for whom the drug's benefits have been shown to outweigh their risks.		market – revenues from the sales of these antibiotics are likely to remain small and therefore it will continue to be an unattractive business case.
Regulatory mechanisms	**Regulatory harmonization**: Regulatory harmonization occurs when countries agree to standardize their documentation requirements and processes for pharmaceutical marketing authorization. This allows a company to seek regulatory approval in many countries more expediently. For example, Europe has implemented a centralized procedure for applying for marketing authorization in all EEA countries.	Not able (1) **Weakly (9)** Moderately (3) Strongly (0) Don't know (0)	Although regulatory harmonization is an important initiative to more rapidly launch products across many markets, this does not solve the inherent problem with antibiotics, i.e., that revenues from their sales are likely to remain small globally, and therefore it will continue to be an unattractive business case.
Revenue guarantees or assurances	**Advance market commitment**: An Advance Market Commitment (AMC) is a legally enforceable commitment by a government or a private/international organization to purchase a specified quantity of a drug or a vaccine that meets certain criteria pre-specified by the purchasers at a predetermined price. There are two approaches to an AMC: the "winner takes all" approach or the "multiple winners" approach.	Not able (0) Weakly (1) **Moderately (12)** Strongly (0) Don't know (0)	Whereas an AMC has the potential to fix the unattractive business case, it does so tied to purchasing commitments. This means that either the price per unit has to be extremely high or excessive quantities will be produced. In countries with strong stewardship and low resistance patterns, sales may be very limited, leading to potentially higher prices than seen in other therapeutic areas. Alternatively, larger quantities can be produced and stored, but this leads to waste, including costs for responsible destruction. The Market Entry Reward was deemed a stronger incentive since it is not tied to units.
Revenue guarantees or assurances	**Call option for antibiotics (COA)**: Governments (and/or private	Not able (2) **Weakly (6)** Moderately (2)	COA seems to be designed to resolve the problem of high-priced medicines, but antibiotics to date are not highly priced

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	actors/philanthropic organizations) offer to buy rights to purchase drugs at fixed unit prices, during earlier stages of development. This enables developers to obtain R&D financing, and governments to ensure that antibiotics are priced predictably once they come to market.	Strongly (2) Don't know (1)	because they have to compete with effective generic antibiotics. COA does not resolve the main problem with the antibiotic business model – revenues from the sales of these antibiotics are likely to remain small. Pre-negotiated lower prices will not solve this problem. Funding for R&D is welcome, but it will not make the market more attractive. Additionally, it is unclear how this incentive would transfer between companies if the IP is sold or out-licensed, which occurs commonly.
Revenue guarantees or assurances	**Global purchaser and distributor for antibiotics**: This model calls for the creation of a global purchaser for antibiotics in line with the GAVI/UNICEF model for vaccines or the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). Health systems would then purchase some or all antibiotics needed from this entity. It may be restricted to only those antibiotics that are considered as medical last resorts.	Not able (2) **Weakly (5)** Moderately (3)* Strongly (3)* Don't know (0) * Only academic and policy experts	Whereas GAVI and GFATM definitely improve access to important commodities, there is little to no evidence that they have stimulated greater innovation within their respective mandates. Rather, CEPI is seen to be emerging as the organization that is propelling greater vaccine innovations. Therefore, in order for this model to stimulate innovation, it would need to be paired with an innovation incentive like a Market Entry Reward. GAVI and GFATM are financed through development aid funds, which tend to be budgets that are more flexible and not tied to long-term financing commitments. General antibiotic innovation falls outside the classification for official development assistance (ODA) since antibiotics are global public goods, not targeted only at low- and middle-income countries. Therefore, the funding of this organization would come from budgets already funding national systems such as healthcare and education. Additionally, despite being funded by development aid, there is always a great deal of uncertainty that GAVI and GFATM will successfully meet their financing replenishment goals. This mechanism combines the costs of paying out Market Entry Rewards with the creation and maintenance of a new, multinational organization responsible for distributing novel, critical antibiotics. This new structure, if limited to antibiotics receiving Market Entry Rewards, would control and distribute about ten antibiotics every decade. This is a considerable administrative investment for so few medicines. Countries with effective

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
			antibiotic stewardship programmes in place would be unlikely to understand the benefit of the extra organizational structure. Therefore, it is unclear that countries are interested in a sole distributor for novel antibiotics. Since the mechanism must be paired with another innovation incentive, the experts felt that Market Entry Rewards must be tested first to determine their effectiveness for stimulating antibiotic innovation.
Revenue guarantees or assurances	**Patent buy-out**: A government (or coalition) purchases the national patent rights to an antibiotic once the antibiotic has received national marketing authorization. Then the actual antibiotics are sold by the government, which may or may not outsource the production. Governments may choose this option for particularly important molecules that are not yet needed.	Not able (2) Weakly (3) **Moderately (5)** Strongly (1) Don't know (2)	This model was excluded for many of the same reasons as stated in the Global Purchaser and Distributor model. Governments are typically not in the business of owning and producing medicines, which requires unique competencies. It is unlikely that a novel antibiotic is brought to market that is not needed by any patient globally. In such a case there is considerable uncertainty whether it will ever be needed. Pharmaceutical companies are often cautious about selling their intellectual property given the uncertainty that it may be valuable across more than one therapeutic area (although SMEs may be more willing). This could require higher payouts than a standard Market Entry Reward. This is a type of Market Entry Reward that still must be tested first to determine if it appropriately stimulates innovation.
Risk-sharing mechanisms	**Cost-sharing for clinical trials**: Governments would share the cost of clinical trials with pharmaceutical companies, perhaps with conditions on responsible use and/or price. Financing could be determined on a matching basis. Alternatively, governments could commit to support the trial in public hospitals and clinics. Governments may choose this option for particularly important molecules or indications.	Not able (0) Weakly (5) **Moderately (6)** Strongly (2) Don't know (0)	This is the BARDA and CARB-X model today. Both partially finance clinical trials and are considered successful models. This model was deemed an important incentive and was merged into Grants.
Risk-sharing mechanisms	**Risk-sharing loans**: Governments (or publicly	**Not able (3) Weakly (3)**	This is the European Investment Bank's InnovFin scheme. While these loans are a

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	funded institutions) provide loans for high-risk projects within a specified profile at lower-than-market interest rates. If the contractual project milestones are achieved, the loans are expected to be paid in full. If not, portions or the entire loan are written off. These risk-sharing loans are meant to attract co-investment from other investors by reducing the risk profile.	**Moderately (3)** Strongly (2) Don't know (2)	welcome addition to reducing the costs of R&D and reducing the risk, the scheme does not solve an inherent problem with antibiotics, i.e., that revenues from their sales are likely to remain small globally, and therefore it will continue to be an unattractive business case.
Risk-sharing mechanisms	**Liability protection**: A programme that would fairly and efficiently compensate individuals harmed by certain antibiotics that were properly manufactured. This type of liability protection has been applied to childhood vaccines in the US under the Vaccine Injury Compensation Program. This is especially relevant in cases where there are only few patients with the resistant pathogen (i.e., very small clinical populations) and it is therefore practically impossible to perform a full clinical trial.	**Not able (7)** Weakly (4) Moderately (0) Strongly (0) Don't know (2)	Liability protection does not solve an inherent problem with antibiotics, i.e., that their development costs outweigh the revenues. Additionally it is in the public interest to maintain a strong focus on developing antibiotics that are safe for human consumption.
Tax reduction mechanisms	**Regulatory fee exemptions**: A developer receives an exemption from the regulatory fees when applying for marketing authorization of a specified antibiotic.	**Not able (8)** Weakly (3) Moderately (1) Strongly (1) Don't know (0)	Regulatory fees are a relatively small portion of the overall R&D costs. While this is helpful, the impact is too small to stimulate greater innovation.
Tax reduction mechanisms	**Tax credits and deferrals:** A tax credit is a tax incentive which allows certain taxpayers to subtract the amount of the credit from the total they owe the state. A variation is to allow the tax credit to be	Not able (2) Weakly (3) **Moderately (5)** Strongly (1) Don't know (2)	General R&D tax credits and deferrals are widely implemented today, e.g., the UK's Patent Box and the Research & Experimentation Tax Credits in the US. They are not targeted specifically at antibacterial R&D. Experts questioned the benefit of additional tax relief. This is also strongly biased towards companies with taxable income, which is often not the case with

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	transferrable to a future year. Tax deferral refers to instances where a taxpayer can delay paying taxes to some future period.		SMEs. Therefore, this would primarily only benefit large companies.
Tax reduction mechanisms	**Fully refundable R&D tax credit**: Under a fully refundable tax credit, companies report their annual investment in R&D towards specified antibiotics, and the tax credit that the company would have received if it had taxable income is instead paid out in cash.	Not able (0) Weakly (3) **Moderately (5)** Strongly (3) Don't know (2)	Tax incentives are a less transparent method of government funding and need to be fairly automatic and easy to understand in order for tax authorities to implement them correctly. It is unlikely that the tax authorities would have the necessary competence to assess if the R&D is actually related to unmet public health needs. The potential for gaming the system is too great.
Collaboration mechanisms	**Collaboration platforms:** Collaboration platforms facilitate collaboration during drug discovery and development. They may assist with testing and optimizing molecules that are still in the earlier stages of drug discovery but have the potential to become future drug candidates. Platforms can be open (so anyone can contribute) or closed (so that only invited individuals can contribute). Open platforms may place the knowledge and collaboration in the public domain so that anyone else can freely utilize or further develop it. If collaboration is targeting late-stage development, exemptions to anti-trust laws may be required. Another variation is to allow the collaboration to be performed through regular gatherings where knowledge is shared.	Not able (1) Weakly (1) **Moderately (9)** Strongly (2) Don't know (0)	JPIAMR's Virtual Research Institute and IMI's ENABLE are examples of collaboration platforms, already implemented (or in the process of being implemented), specifically for antibiotics. Collaboration platforms tend to work best at pre-competitive stages (basic science and early discovery) before intellectual property is applicable. This mechanism has been further combined with Grants since it is dependent upon grant financing.
Collaboration mechanisms	**Joint, multilateral, non-pooled financing and coordination of R&D targets:** A group of willing countries would form a	Not able (1) Weakly (3) **Moderately (6)** Strongly (1) Don't know (2)	The group considered this an interesting financing and potential governance mechanism. However, there are already substantial financing and organizations in place that work across priorities. For

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	non-binding coalition to finance antibiotic R&D priorities. Countries would select one or more priorities in which they commit to finance R&D. Smaller countries may choose to consolidate their financing. Commitments and "ownership" would be pledged publicly for accountability. Countries could then internally determine the best route of financing the R&D for the targets they have selected, e.g., some countries may pair with industry. There is no pooled funding.		example, CARB-X works across all priority pathogens. JPIAMR works across not only antibiotic innovation but also other important aspects of antimicrobial resistance.
Collaboration mechanisms	**InnoCentive**: An online marketplace where organizations with specific innovation needs post challenges along with an appropriate award. The award is paid to the solver who best meets the solution requirements.	Not able (4) **Weakly (7)** Moderately (2) Strongly (0) Don't know (0)	While this is helpful, the impact is too small to stimulate greater innovation.
Collaboration mechanisms	**Patent pools:** These enable the collective acquisition and management of intellectual property for use by third parties for a fee. Patent holders from the public or private sector may contribute patents to the pool. Subsequently, a developer wanting to use the patent to develop a new product can seek a licence from the pool against the payment of royalties to produce the medicines. This allows for incremental innovation. Patent pools also increase access to patented technologies by allowing a producer to produce	**Not able (4)** Weakly (3) **Moderately (4)*** Strongly (0) Don't know (2) * Only academics and policy experts	Patent pools function well for technologies comprised of multiple patented components, e.g. mobile phones. In pharmaceuticals, they could be effective for combination therapies. Although antibiotics are often given in combination, it is the physician who determines the combination and they are delivered separately. Patent pools are an important tool for ensuring access to already developed antibiotics, but they do not assist in bringing a novel product to market.

Type	Name and description	Ability to stimulate innovation	Rationale for exclusion
	and sell for specified geographies in exchange for a royalty to the patent holder.		

Appendix C: The Antibiotic R&D Pipeline Simulator

Introduction

This section presents the basic functioning and results of the antibiotic R&D pipeline simulator created within DRIVE-AB's Work Package 2, Task 9, and employed for large-scale simulation comprising 90,000 runs. These results cover the effects of intervention mechanisms investigated by DRIVE-AB on the global antibiotic R&D pipeline, under specific circumstances (such as input data parameters and assumptions on developers' behaviour). These results are intended to support policy decisions about these intervention mechanisms, but do not concern details of their implementation. Since the simulator is a software tool that is being continuously developed and upgraded, in terms of both parameters and functions, upcoming papers may present slightly different results based on newer versions of the simulator.

In general, the simulator models the innovation process inherent in the global antibiotics industry, and has been designed to explore intervention mechanisms aimed to stimulate the development of antibiotics. The simulator reflects the key financial decision-making process of pharmaceutical companies in the various steps leading to bringing new molecules to market. It reflects recent trends in the antibiotic industry, with discovery and early-stage-development occuring primarily in small "biotech" firms (SMEs), often supported by venture capitalists, their projects later acquired by larger pharmaceutical companies (Big Pharma) which bring the product to market.

A policy intervention is modelled as a change to one or more properties of the simulated antibiotic pipeline (e.g., companies' properties, revenues and costs, length of phases). The intervention(s) will have an impact on the emergent behaviour and trigger other changes as several elements in the simulation are interrelated. This section covers the effects of two prototypical interventions: grants and market entry rewards. We consider two variations of market entry rewards: fully delinked (FD) and partially delinked (PD). An FD reward entails a payment provided instead of a project's market sales. Conversely, a PD reward entails a payment provided in addition to a project's market sales. FD rewards thus replace unit sales, while PD rewards supplement them.

In brief, our results show that:

1. A fully delinked reward doubles the likelihood of market approval[xiii] at $800 million (€680 million). It starts having an effect at $600 million (€495 million) and reaches a plateau at around $1,500–1,750 million (€1,443 million).
2. A partially delinked reward doubles the likelihood of market approval at $600 million.It starts having an effect at $200 million (€170 million) and reaches a plateau at around $1,200 million (€1.02 million).
3. Grants alone increase the final likelihood of market approval by only about 0.2%.
4. Grants alone increase the likelihood of entry into the various R&D phases as follows: 3.5% increase for entries into Phase I; 2.5% for Phase II; and 1% for Phase III.
5. The additive effect of grants combined with market entry rewards is to increase the likelihood of market approval by 0.2–0.4%, up to reward sizes of $1,500 million (€1,236 million).
6. The impact of a market entry reward on antibiotics with total net global revenues over $1,500 million is negligible. The above results thus only apply to antibiotics with total net global revenues at or below $1,500 million.

[xiii] This likelihood is the percentage of projects starting the preclinical stage that are eventually approved for market sales.

7. Increasing market revenues by 50% over $1,500 million increases the market approval likelihood from 2.3% to 2.9%; while a 100% increase to $3,000 million (€2,474 million) increases market approvals from 2.3% to 3.1%.

Methods

We have constructed a Monte Carlo simulation that explores the likelihood of antibiotics reaching market under different initial conditions (technical probability of success; development costs; development times; expected revenues; requirements of venture capitalists, partners and acquirers) and under different policy interventions (push and pull). In order to reach market approval, antibiotics need to successfully navigate the heavily regulated phases of pharmaceutical R&D comprising preclinical, Phase I, Phase II, Phase III and approval.

In our simulation, the likelihood of an antibiotic reaching market approval (i.e., successfully completing the approval stage) is determined by (1) the risk of technical failure (due to e.g. toxicity) at the various phases, and (2) the financial decisions made by developers, venture capitalists, partners and acquirers at each phase and associated decision-point. Antibiotic projects enter the simulation in the preclinical stage at an artificially derived rate which we term "entry rate" (see below for details). The technical success of an antibiotic in each phase is assumed to be purely probabilistic, so that transitioning from any phase to another is an independent event.

The developer's and financier's decision on whether to continue funding an antibiotic project is assumed to be based solely on its expected net P=present value (eNPV). The eNPV is a widely applied decision-making approach used to evaluate the profitability of major investments. It is common practice among large pharmaceutical companies, and has previously been used to model decision-making in pharmaceutical organizations (see e.g. Blau et al., 2004; Okhravi et al., 2017). The simulator calculates eNPV as:

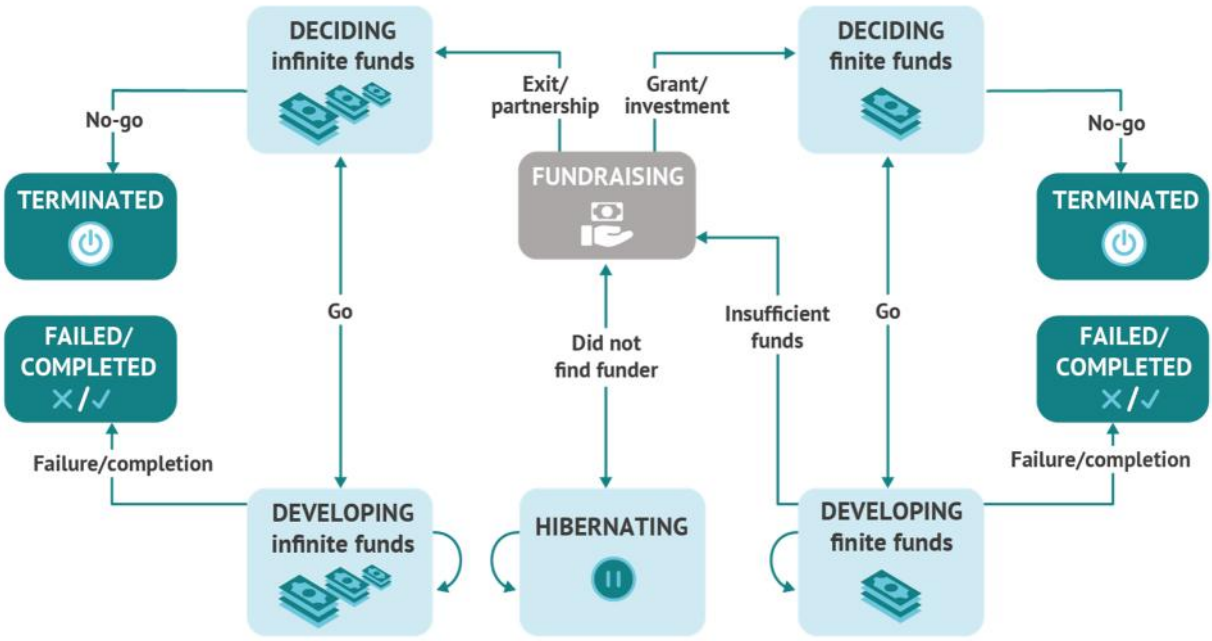
$$\mathrm{eNPV}(\mathrm{i},\mathrm{n}) = \mathrm{P}(\mathrm{n}) \sum_{\mathrm{t}=0}^{\mathrm{n}} \frac{\mathrm{C}(\mathrm{t})}{(1+\mathrm{i})^{\mathrm{t}}}$$

where i is the discount rate (cost of capital) of the evaluator, n is the final month of cashflow (in our simulation, usually patent expiry), P(n) the probability of reaching the final month, and C(t) the cashflow at time step (month) t.

We assume that projects are evaluated on the basis of their eNPV only before transitioning to a new phase, referred to as a "decision-point". The project is pursued if eNPV is ≥ than the threshold of the actor investing in the project, otherwise it is TERMINATED.

While all projects enter the simulation at the preclinical stage, they leave the simulation as TERMINATED, FAILED or COMPLETED (by reaching market entry, i.e. successfully leaving the approval stage). Each simulation step represents one month. A project in the simulation can be in any of the seven different states outlined, along with allowed transitions shown in Figure 16. In the simulation, any project populating the pipeline can, at any moment in time, only ever be in a single state, and every simulation step entails a single event. A project either transitions to another state or remains in the same state.

Figure 16: Project states and transitions between states



As illustrated in Figure 16, in the first step of the simulation all projects start in a FUNDRAISING state because they are assumed to enter the preclinical stage through an SME developer assumed to lack "infinite" funds for R&D. The simulation allows exits to or partnerships with large companies, assumed to have "infinite" funds, only after the preclinical stage. Securing funds for a project can be achieved through four options: grants, venture capital (VC) investments, partnerships and exits. First, a project will receive any grant it is eligible for. If the project receives a grant it will transition to DECIDING, since it now has some funds to initiate development. If the project does not receive a grant (because it is not eligible, or it did indeed not receive a grant in that phase) the project then pursues one of the remaining three options (VC investments, partnerships and exits). Which of these three alternatives is pursued during the time step is randomly selected.

If, after FUNDRAISING, the project does not have sufficient funds to perform the next step (i.e. one month's worth of development), it transitions into HIBERNATING. To proxy the fact that securing funding is a difficult and time-consuming activity, we force the project to wait before trying a new round of FUNDRAISING – i.e. it is forced to remain in "hibernation" for periods of increasing length equal to a power of two months after each attempt.

If the project secures a VC investment we assume that it has the capital necessary to complete the coming R&D phase in full. Thus it transitions to DECIDING "without infinite funds". If the project secures a partnership or an exit with a major company, we assume it will receive the capital necessary to develop the project to completion. In this case it transitions to DECIDING "with infinite funds".

At the DECIDING state, the eNPV of the project is calculated from the perspective of a hypothetical actor representing the composite of all actors involved in the project at that point. This composite can consist of: (a) only the initial developer (an SME), (b) the initial developer and VC investors, (c) the initial developer and a partner (large company), (d) the initial developer, some VC investors and a

partner (large company), or (e) only the new owner (large company) after an exit. If the calculated eNPV is at or above the threshold of the composite actor, then the project transitions into DEVELOPING, but if not, the project is TERMINATED.

The project will remain in DEVELOPING as long as it has the necessary funds and has not yet reached a decision-point. The project always has the necessary funds if it has experienced an exit or a partnership. Projects with the necessary funds reaching a decision-point transition to DECIDING, while projects without the necessary funds (i.e. because they have spent their available grants and/or their received investments) transition to FUNDRAISING.

Input data

We undertook a triangular distribution of data on antibiotic development times, costs and probabilities based on Sertkaya et al. (2014). While these authors consider a set of numerous indications, we employ a single widely distributed typology and therefore combine their distributions into a single set of distributions. More specifically, for any given parameter we construct a triangular distribution where the lowest point of the distribution is the lowest point of the triangular distribution for that parameter reported by Sertkaya et al. (2014), the mode as the mean of that distribution and the maximum point as the highest point from their distribution.

Data on expected net revenues (i.e. sales minus costs of sold goods) were also derived from Sertkaya et al. (2014) by considering the point estimate in the triangular distribution as the average values of market size and market share for all different indications. These values were then corrected for inflation into 2017 US dollars (by a 6% increase). From here we used empirical data to define the expected revenues of year 1 after approval and stretching to year 10 (included), and assumed that linear interpolation is representative for every year in-between. We assume that sales of year 10 after approval remain constant until patent expiry (if not already expired). Peak-year sales thus necessarily occur at year 10, if not earlier (owing to patent expiry caused by delayed development).

The market simulated to define a project's specific expected net revenues is the global market. This in turn includes high-income countries (HICs) with approximately 90% of global buying power. Even if low- and middle-income countries (LMICs) account for the remaining 10% of buying power, the profit potential perceived by pharmaceutical firms is generally insignificant, since the costs for licences, registration and logistics are comparatively large. Therefore, the net contribution of LMICs to the revenues of novel antibiotics is negligible and hence so is its impact on the simulation. Moreover, to estimate the global market from the US-based data in Sertkaya et al. (2014), we doubled the market size (reflecting the fact that the US accounts for about 50% of the global HIC market), but simultaneously we halved yearly market shares, since a global market is considerably more difficult and slower to penetrate than only the US market.

While we triangularly distribute the expected net revenues for years 1 and 10 using the mode-mean, max-max strategy, we made two further adjustments to the data from Sertkaya et al. (2014): (1) we forced the lowest point of the distribution to 0, to proxy the fact that some antibiotics may completely lack a market at the moment of approval; and (2) we lowered the peak year net revenues (i.e., at year 10) to $800 million (€680 million) after expert discussions with EFPIA partners in DRIVE-AB.

In summary, our input data were vetted and accordingly modified during discussions with an expert panel comprised of representatives from Big Pharma, public health and academia. The expert panel included members of the DRIVE-AB consortium. The full set of input data is reported in Table 13.

Table 13: The list of parameters and values used as input data in the simulation

Parameter	**Value(s)**
Number of simulation runs	90,000
Time horizon	30 years (360 months)
Preclinical entries per month	0.5–10
Big Pharma threshold ($ million)	50/100/200/ 500
Big Pharma discount rate	8%–13%
VC threshold ($ million)	0
VC discount rate	5%–30%
VC investment stages targeted	Preclinical, Phase I, Phase II, Phase III
PEW rojects	Included in initial state
Grants (% of costs)	0%–100%
Grants stages targeted	Preclinical, Phase I, Phase II, Phase III
Preclinical prob (%)	17.5–35.2–69
Preclinical duration	52–66–72 months
Preclinical cost ($ million)	14.25–21.10–29
Phase I success prob (%)	25–33–83.7
Phase I duration	9–10.5–21.6 months
Phase I cost ($ million)	13.1–24–37.96
Phase II success prob (%)	34–50–74
Phase II duration	9–13.33–30 months
Phase II cost ($ million)	12.95–4.55–46.36
Phase III success prob (%)	31.4–67–78.6
Phase III duration	10–21.8–47 months
Phase III cost ($ million)	27.99–62.6–168.4
Approval prob (%)	83–85–99
Approval duration	6–9–12.5 months

Approval cost ($ million)	55.5–88.35–127.91
Net revenues at market entry ($ million)	0–22.4–67.2 yearly
Net revenues after peak sale year ($ million)	0–489.5– 800 yearly
Market entry reward size ($ million)	0–3,000 (spread over 5 years)
Market entry reward type	Partial delinkage/Full delinkage

Results

This analysis contributes to the discussion on how to optimize policy interventions aimed at stimulating antibiotics development. While the concept of optimality is open for debate, we define it here as the minimum public spending required to achieve a targeted likelihood of market approval per antibiotic entering the R&D system. The likelihood of market approval indicates in our model the number of antibiotics that reached market approval, divided by the total number of antibiotics that entered the simulation at the preclinical stage.

When this likelihood of market approval is calculated on a subset of antibiotics subject to particular conditions (e.g., low expected revenue), the denominator equals the number of antibiotics subject to that criteria (e.g., with revenues below a certain point), rather than all antibiotics in the simulation. Similarly, the nominator is the number of antibiotics that reached the market out of those subjected to these criteria, rather than all that reached market approval.

A sensitivity analysis comprising results from 45,000 runs indicates that a few key parameters explain a high proportion of the variance in the likelihood of market approval (see Table 14 and Supplementary Figure 1f). These parameters include (a) antibiotic characteristics such as projected **R&D costs**, **revenues** and technical **probability of success**, as well as (b) characteristics of developers and private investors such as **discount rates** and **eNPV thresholds**. In particular, while technical probability of success and projected net revenues explain a high proportion of this variance, with ranges of 8.9% and 3.5% much lower ranges are attributable to R&D costs, VC discount rates and Big Pharma eNPV threshold (see Table 14).

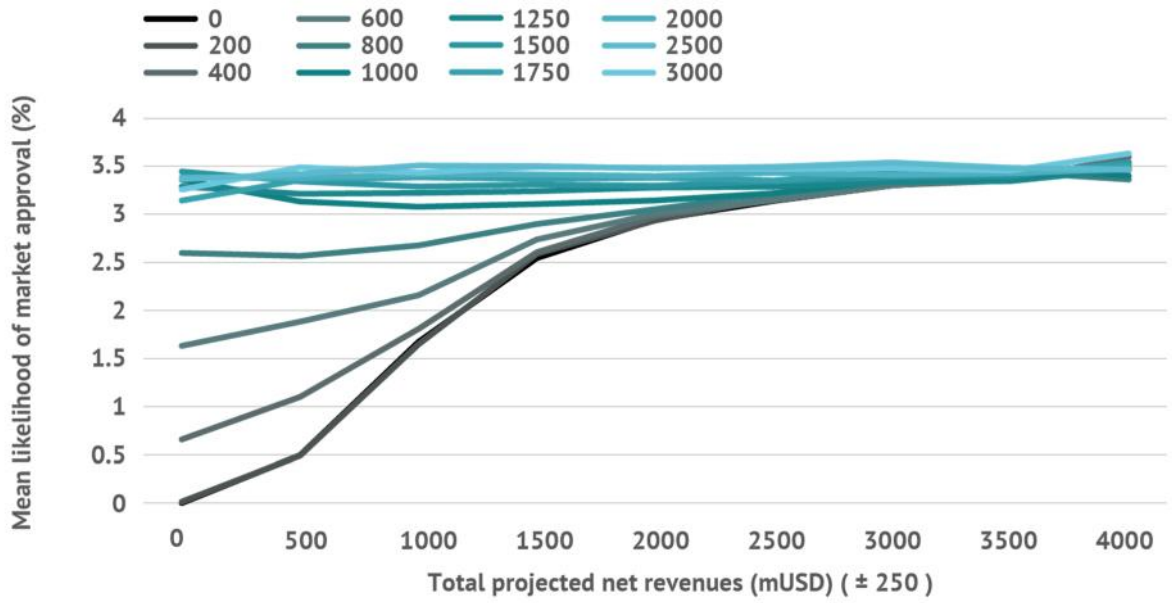
Table 14: The variance in likelihood of market approval explained by different parameters (NB: 45,000 runs)

Parameter	Input values	Range of likelihood of market approval
Probability of success	0.39–15 (%)	~ 8.9 percentage points (8.9–0%)
Global net revenues	0–4000 ($ million)	~ 3.5 percentage points (3.5–0%)
VC discount rate	8–30 (%)	~ 1.1 percentage points (3.1–2%)
Big Pharma threshold	50/100/200/500 ($ million)	~ 0.7 percentage points (3.1–2.4%)
R&D costs	190–340 ($ million)	~ 0.6 percentage points (3.1–2.5%)

Moreover, Figure 17 shows the variance of the mean likelihood of market approvals caused by total expected (or projected) net revenues alongside the offsetting effects of market entry rewards of

different sizes (from $0 to $3,000 million/€2,474 million). For more details on the sensitivity of market approvals to other parameters, see Supplementary Figures 1a–f.

Figure 17: Total projected net revenues explaining variance in mean likelihood of market approval (NB: 45,000 runs)



As Figure 17 shows, a policy intervention focused on revenue improvement (pull) ought to be able to raise market approval rates (from zero to 3.6%) by increasing the total expected market revenues (zero to $4,000 million/€3,299 million). Based on this sensitivity analysis, we identify effects related to total market revenues: (1) an increase in total net estimated market revenues by 50%, from $1,500 to $2,250 million (€1,236 to €2,060 million) globally, increases the average market approval likelihood from 2.3 % to 2.9%; and (2) an increase in total net market revenues by 100%, from $1,500 to $3,000 million (€1,236 to €2,474 million) globally, increases market approvals from 2.3 % to 3.1% (see these different values along the zero-level market entry reward plot, lowest line in Figure 17).

However, Figure 17 also confirms that antibiotics with a large market and hence high revenues do not suffer from market failure. Indeed, an important result of the simulation is that the impact of market entry rewards in terms of new market approvals is negligible for antibiotics with total global net revenues from sales of more than $1,500 million (see the convergence in Figure 17 of the lines corresponding to various levels of reward above that level), since these projects already have a satisfactory profitability according to other eNPV parameters. In other words, the market for these antibiotics is not “broken” and pull incentives such as market entry rewards are superfluous.

Thus the simulation results suggest that rewards should not be offered to products with projected global revenues above $1,500 million. When designing a reward scheme, issuing bodies could complement a target product profile (TPP) with a profitability analysis. This would help to avoid spending public money on antibiotics that would have reached the market anyway and enable the fine-tuning of reward levels to the specific financial profile of any given antibiotic.

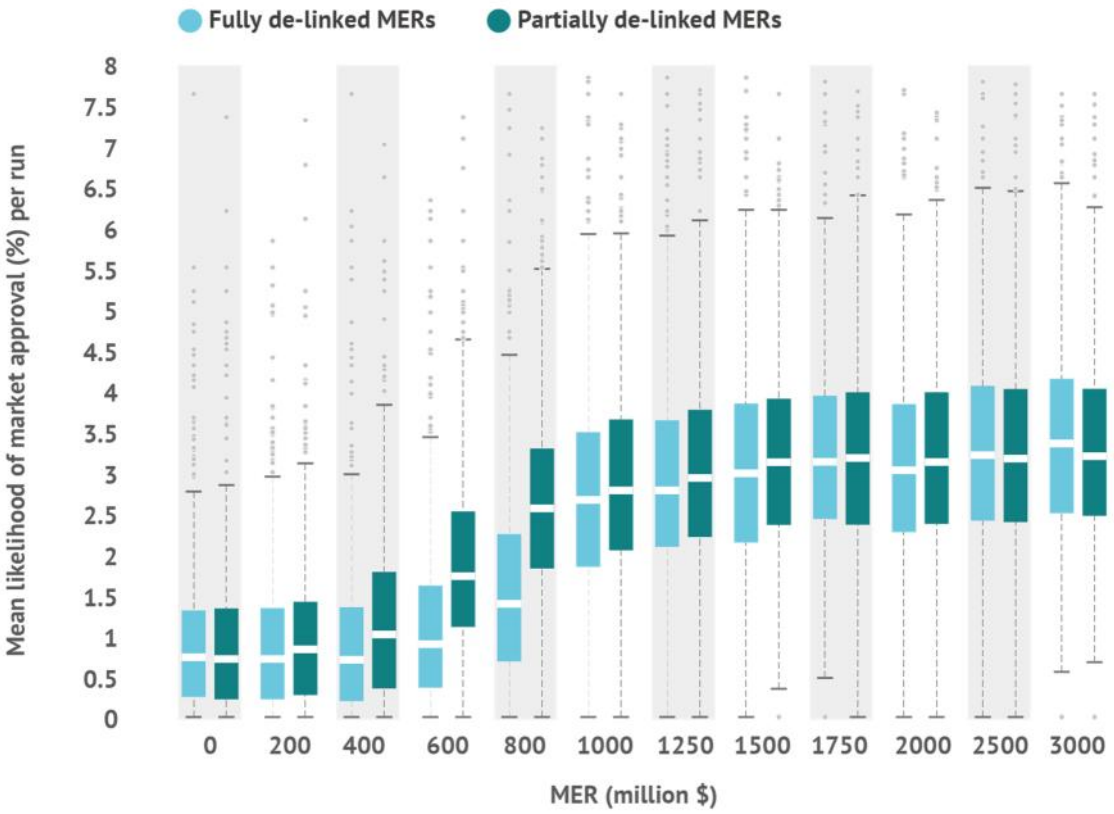
Summing up, our sensitivity analysis performed on a smaller simulation output (45,000 runs) indicates that the effects of incentives are susceptible to particular parameters – especially the

technical probability of success, the total expected revenues, and the profitability requirements of investors, as expressed by VC discount rates, and of developers, as expressed by Big Pharma eNPV thresholds (see Table 14 and Supplementary Figures 1a–f).

Therefore, we now present the results of a larger simulation experiment (90,000 runs) and the specific effects on new antibiotic approvals of various combinations of pull and push incentives based on a selection of these parameters that is realistic and that makes the effect of pull and push incentives meaningful. This scenario is as follows: large-company eNPV thresholds are between $200 and $500 million (€165 and €412 million); VC discount rates are between 18% and 30%; and, importantly, total expected market revenues per antibiotic are less than or equal to $1,500 million globally.

A fully delinked market entry reward has a clearly positive effect. Specifically, the introduction of rewards at the $800 million (€680 million) level doubles the mean likelihood of market approval – that is, the ratio between the number of antibiotics reaching market approval and the number of antibiotics entering the preclinical stage – from about 0.8% to 1.5% (see Figure 18).

Figure 18: Boxplot showing the changes in mean likelihood of market approval under different sizes of fully and partially delinked market entry rewards

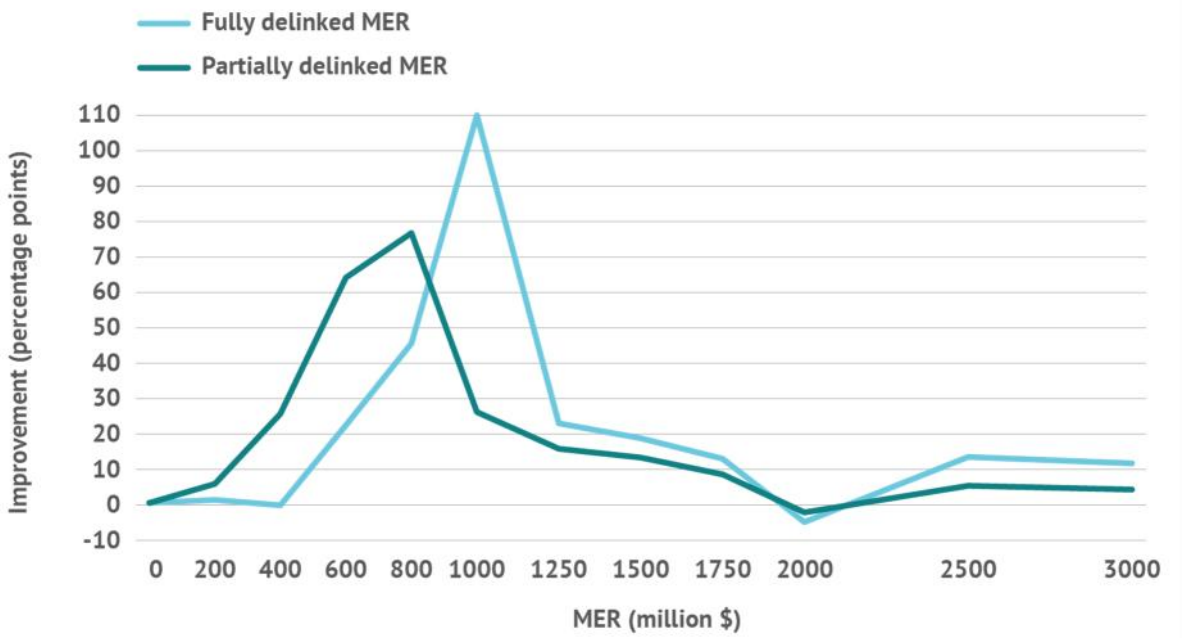


Increasing the size of the fully delinked market entry rewards increases the number of market approvals steadily up to $1,500–1,750 million (€1,236–1,443 million), reaching a plateau in the mean likelihood of market approval at around 3%. This plateau indicates that almost all antibiotics surviving the attrition rates at the various R&D stages are eventually made profitable by that size of intervention. Beyond this level the marginal return on investment in terms of additional market approvals becomes extremely low.

Figure 18 shows that a partially delinked reward starts producing effects earlier than the fully delinked reward, already at $200 million (€170 million), and at $600 million (€495 million) the number of new market approvals doubles compared with the status quo (reaching a mean likelihood of market approval of 1.7%). Market approvals then become more frequent with the increase in size of the partially delinked reward, up to a plateau of approximately 3% in the mean likelihood of market approval, which is reached at around $1,250 million (€1.030 million) (see Figure 18).

The plateau is the point at which an intervention has made nearly all antibiotics sufficiently profitable. At this point, any remaining variation in the likelihood of market approval must be explained by other parameters (e.g. technical probability of success). However, this level of public spending on a market entry reward might not be optimal, especially if the public funder prefers particular antibiotics. Moreover, the marginal improvement in market approvals varies when the value of the reward is increased. Based on Figure 18, Figure 19 shows that the optimal incremental gain is obtained at $1,000 million (€850 million) for full delinkage (with a gain from 1.5% to 2.7% in Figure 18) and at $800 million (€680 million) for partial delinkage (with a gain in new market approvals from 1.8% to 2.6% in Figure 18).

Figure 19: Improvement of likelihood of market approval by reward



The role of grants and combining push and pull interventions

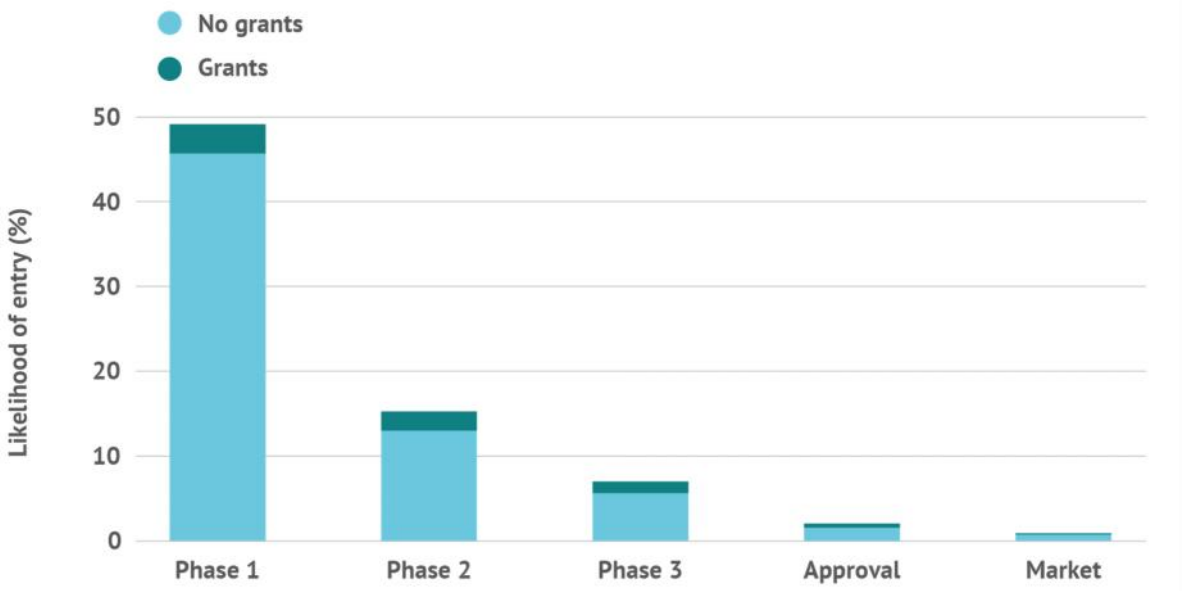
We also tested the isolated effect of grants as a push incentive, meeting between 2% and 100% of the cost of development up to Phase II. The isolated effect of grants on market approvals was less than that of market entry rewards: grants above 40% of total cost increase the mean likelihood of market approvals only from 0.76% (without any intervention) to 0.94%, that is, by 0.2%. The main reason for this is that market approvals are less sensitive to the level of total R&D costs than to the level of total expected market sales (see Supplementary Figure 1). Therefore, since grants are intended to reduce costs, they have a limited impact on the likelihood of market approval.

However, the role of grants should not be overlooked as they could have important indirect effects on market approvals: (1) in the form of early-discovery grants (not included in our simulation), grants could improve the entry rates in the preclinical phase and hence the absolute number of approvals;

(2) they could reinvigorate the pipeline by increasing the number of projects in the early stages; and (3) they could improve the effect of a market entry reward. Below, we elaborate on the second and third kind of effect of grants.

Our simulation suggest that grants improve (1) the likelihood of starting Phase I from about 46.0% (with no grants) to 49.5%, hence an increase of 3.5%; (2) the likelihood of starting Phase II from about 13.0% (no grants) to 15.5%, an increase of 2.5%; and (3) the likelihood of starting Phase III from about 6% (no grants) to 7%, an increase of 1% (see Figure 18). Calculating the relative effect, these results mean that grants allow an increase of 7.6% in the number of projects starting Phase I, of 19.2% in those starting Phase II, and of 16.7% in those starting Phase III. Thus grants contribute to a stronger antibiotic pipeline by increasing the number of projects in each of its phases. In turn, the entry rate into preclinical research depends on the rate of drug discovery, which is strongly related to another kind of grant for basic and academic research, not modelled here.

Figure 20: Likelihood of phase entry, with and without grants.



The additive effect of grants combined with a market entry reward is rather small, owing to the lower portion of overall variance in market approvals associated with R&D costs (see Table 14 above). The additive effect of grants varies between an improvement of 0.2% and 0.4% in the likelihood of market approval as a result of market entry rewards. The effect is visible in Figure 21a, where bold numbers show the various likelihoods of market approval (ranging from 0.7% to 3.5%) resulting from various combinations of grants coverage and reward sizes, both for fully and partially delinked rewards. The improvement in market approvals due to grants is the difference between the bold numbers with push/grants funding (higher up on both tables) and those with zero push/grants funding (lower down on both tables). The additive effect of grants allows a reduction in the size of a market entry reward to obtain a given level of market approvals, or provides more approvals for the same level of reward. As noted above, this additive effect is present only up to reward sizes of $1,500 million (€1,236 million), after which it disappears (see Figure 21a).

Figure 21a: Level plot linking likelihood of market approval to combinations of push and pull incentives and respective public investments (full delinkage)

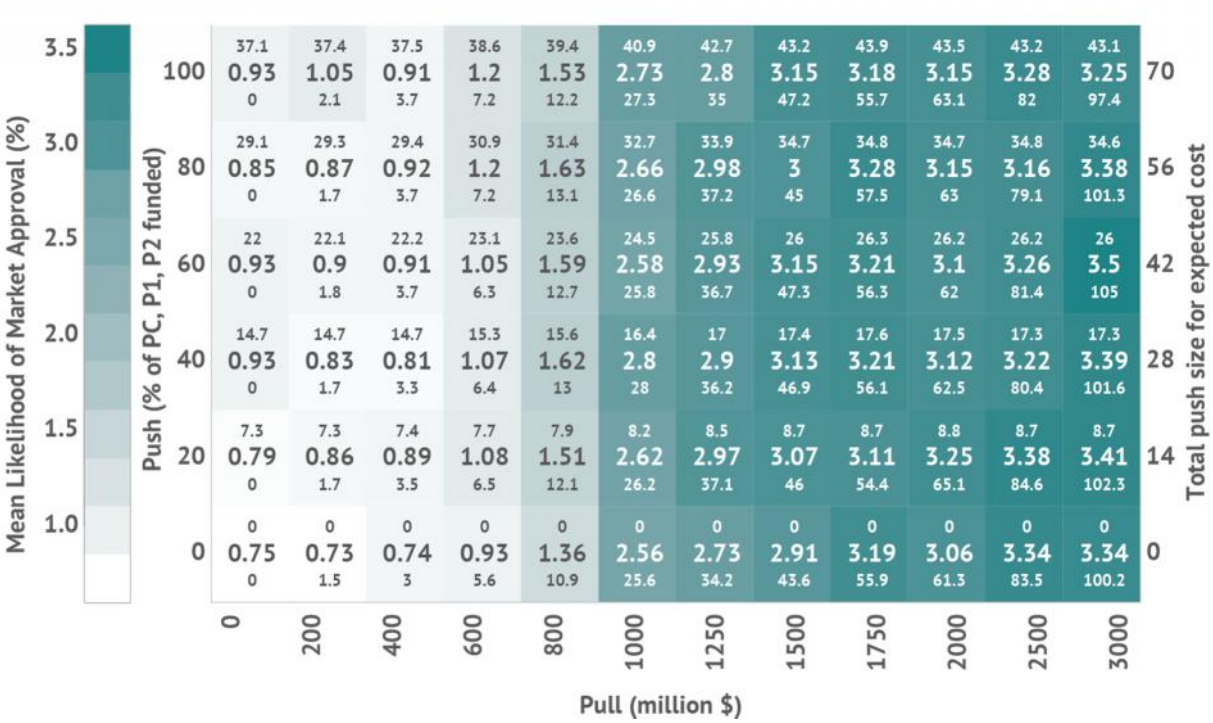
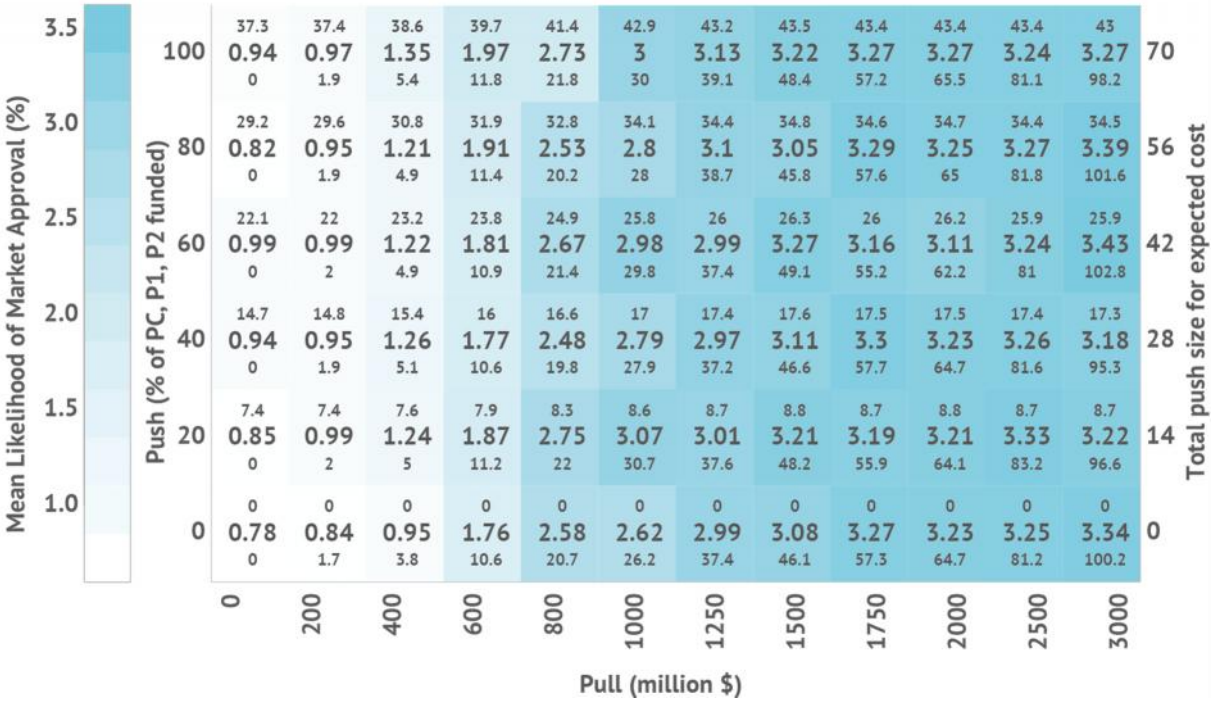


Figure 21b: Level plot linking likelihood of market approval to combinations of push and pull incentives, and respective public investments (partial delinkage).



Notes: Left vertical axis: fraction of R&D costs covered by grants.
Right vertical axis: expected cost covered by grants per receiver.
Cell's values: expected *grant* costs (higher up) and expected *reward* costs (lower down) per antibiotic entering preclinical research.

Figure 21 can also help balance between push and pull interventions, as it indicates both the likelihood of market approval obtained by various combinations of push and pull sizes (bold numbers inside every cell) and each combination's push investment (upper number in every cell) and pull investment (lower number in every cell) per antibiotic entering preclinical research. Under any intervention combination, the paying authority commits to make specific push- and pull-based payments. However, high rates of termination and failure mean that these amounts are not necessarily paid to every antibiotic entering preclinical research. We compute the pull cost as:

$$\text{pull} * \frac{|\text{approvals}|}{|\text{projects}|}$$

where *'pull'* is the market entry reward size under consideration, *'approvals'* is the number of projects subject to that particular push and pull combination that reached market approval, and *'projects'* is the number of all projects subject to that particular push and pull combination. Consequently |*approvals* | / |*projects* | is the likelihood that a project subject to this intervention combination reaches market approval.

Further, we compute the push cost as:

$$\sum_{s \in S} \text{push} * \text{EV}\big(\text{C(s)}\big) * \frac{|\text{projects_at(s)}|}{|\text{projects}|}$$

where *'push'* is the grant fraction under consideration (varying between 20% and 100%), S is the set of the phases preclinical, phase I, and phase II in which we simulate that grants are paid to developers, and $EV(C(s))$ is the expected value of the cost distribution of the phase s.

As a hypothetical example, if we want to increase the number of market-approved antibiotics by at least 50%, we can consider a number of viable combinations of push and pull incentives enabling one to improve the likelihood of market approval from about 0.76% (corresponding to no intervention) to about 1.15%. This goal is not achievable though grants alone, as shown in the first column to the left in Figures 21a and 21b. However, market entry rewards enable the 1.15% target likelihood of market approval, with or without grants, to be reached.

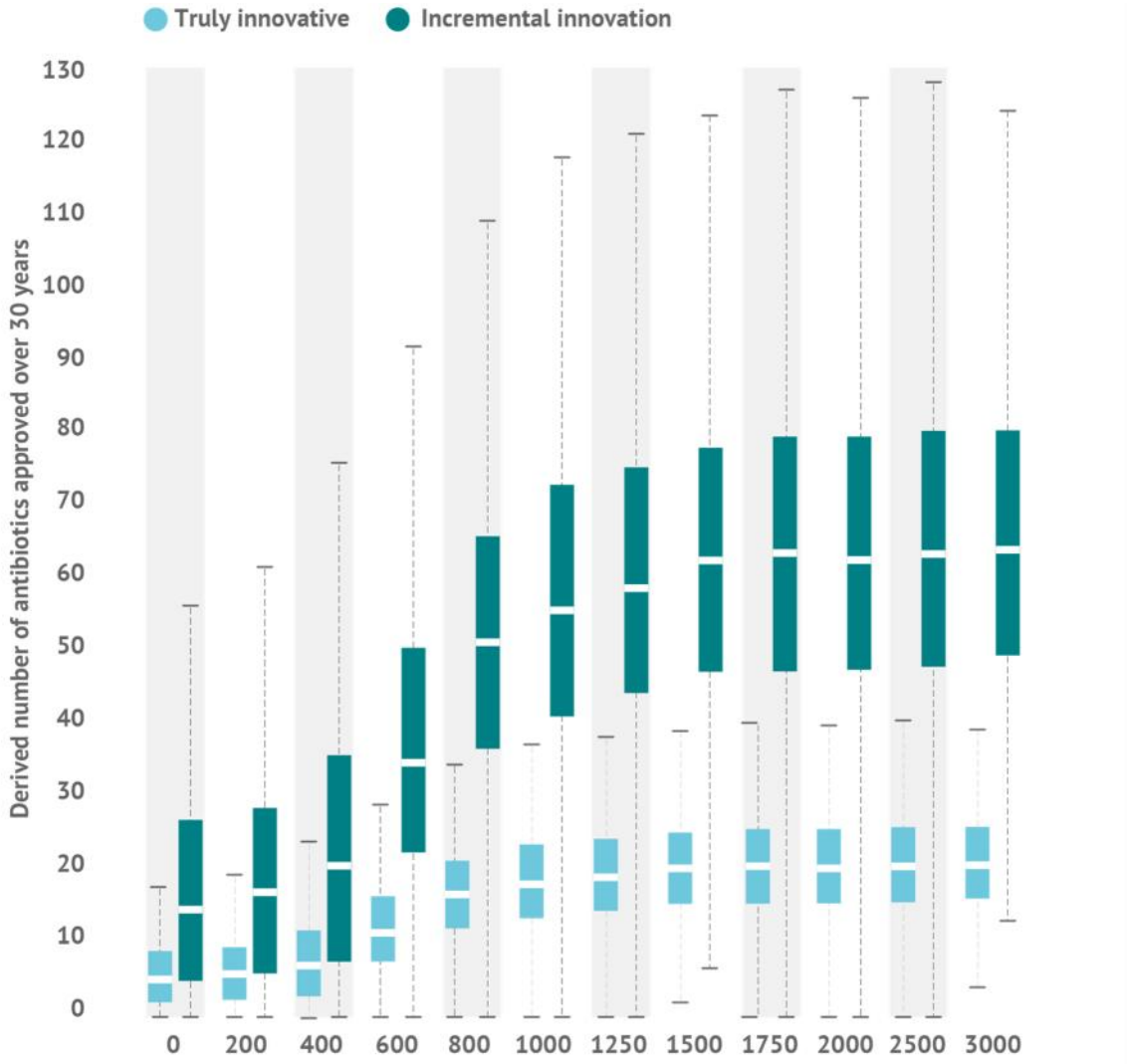
A fully delinked reward (Figure 21a) of $800 million (€680 million) reaches beyond the target likelihood *without* grants (1.36%). However, with grants covering up to 80% of R&D costs until Phase II (i.e., on average $56 million/€46.2 million per project), a reward of $600 million (€495 million) would suffice (1.2% likelihood). The expected public investment per preclinical entry would in the former case (pull only with a reward of $800 million/€680 million) be $10.9 million, while in the latter case (push and pull) it would be $38.1 million (€31.4 million). A partially delinked reward (Figure 21b) of $600 million is needed to reach the target likelihood *without* grants (1.76% likelihood). However, with grants covering just 20% of R&D costs until Phase II (i.e. on average $14 million/€11.5 million per project), a reward of $400 million (€330 million) would suffice (1.24% likelihood). The expected public investment per preclinical entry would in the former case (pull only with a reward of $600 million) be $10.6 million (€8.7 million), while in the latter (push and pull) it would be $12.6 million (€10.4 million).

Projections on absolute numbers of approved antibiotics

It has been suggested that applying a market entry reward broadly or narrowly could lead to different effects on the pipeline. We define a "narrow" reward as an incentive awarded to a type of antibiotic that is only rarely discovered, while a "broad" reward is awarded also to types of antibiotics that are less rare. Our simulation models the difference between these two kinds of rewards by introducing antibiotics into the preclinical stage at different entry rates (i.e., antibiotics that are discovered with different frequency).

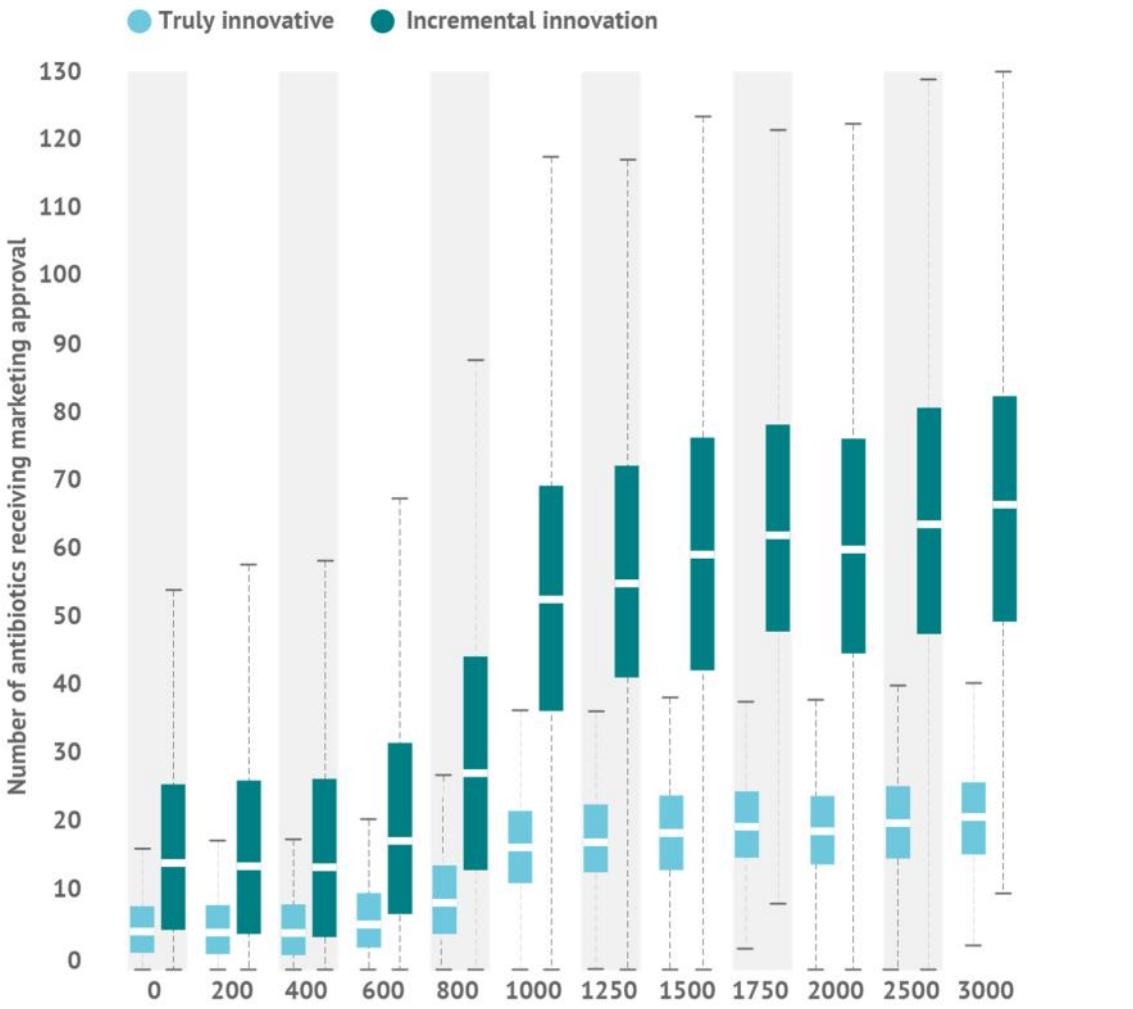
We consider the three following hypothetical types of antibiotics entering preclinical research: Type A at a rate of 0.5–3 per month, Type B at a rate of 3–8 per month and Type C at a rate of 8–10 per month. The "narrow" reward exclusively targets the rare Type A antibiotics, while the "broad" reward targets both Type A and the less rare Type B. The more common Type C antibiotics are not eligible for either kind of reward. Under the assumption of these entry rates, a partially and fully delinked reward yields the results reported in Figures 22a and 22b respectively, over a period of 30 years.

Figure 22a: Boxplot showing the total number of different type of antibiotics reaching market under different sizes of partially delinked market entry rewards



Note: Entry rates assumed in preclinical: Type A = 0.5-3/month; Type B = 3-8/month; Type C=8-10/month)

Figure 22b: Boxplot showing the total number of different type of antibiotics reaching market under different sizes of fully delinked market entry rewards



Note: Entry rates assumed in preclinical: Type A = 0.5-3/month; Type B = 3-8/month; Type C= 8-10/month)

While without any intervention (neither pull nor push), fewer than five Type A antibiotics will be market-approved during the next 30 years, this number is more than tripled to around 16 new Type A antibiotics by a "narrow" market entry reward of $800 million (€680 million) if partially delinked (Figure 22a) or $1,000 million (€800 million) if fully delinked (Figure 20b). Type A market approvals reach a plateau of about 20 new approvals in 30 years, obtained at about $1,500 million (€1,236 million) if partially delinked, or $1,750 million (€1,442) if fully delinked. Therefore, a narrow market entry reward between $1,500 million and $1,750 million makes almost all projects profitable to the extent that any further increase in reward size is irrelevant for these rarely occurring antibiotics.

With a "broad" market entry reward (targeting both Type A and Type B antibiotics), approximately 15 new Type B approvals obtained without any intervention would more than triple to more than 50 with a reward size of $800 million if partially delinked (see Figure 22a) or $1,000 million if fully delinked (see Figure 20b). A plateau of about 63 new Type B approvals is reached by partially delinked rewards at $1,500 million/€1,236 million(Figure 22a) and about 64 new approvals by fully delinked rewards at $1,750 million.

As already noted, the effect on market approvals of grants alone is not as strong as the effect of market entry rewards alone. Grants increase the mean likelihood of market approvals by about 0.2%. This means, with the entry rates of antibiotics assumed above, that grants alone would improve the number of Type A antibiotics approved in 30 years from fewer than five to almost six, and the number of Type B market approvals from about 15 to 18 (see Table 15 for details).

Table 15: The effect of narrow and broad market entry rewards, with and without grants, on absolute approvals of various antibiotic types

	Total numbers of market approvals												
	Reward size ($ million)	**0**	**200**	**400**	**600**	**800**	**1000**	**1250**	**1500**	**1750**	**2000**	**2500**	**3000**
FD market entry reward	**Type A**	**4.7**	**4.6**	**4.7**	**5.9**	**8.6**	**16.1**	**17.2**	**18.3**	**20.1**	**19.3**	**21.0**	**21.0**
	Type A + grants	**5.6**	**5.7**	**5.6**	**7.1**	**9.9**	**16.9**	**18.4**	**19.5**	**20.1**	**19.9**	**20.5**	**21.3**
	Type B	**14.9**	**14.5**	**14.7**	**18.4**	**26.9**	**50.7**	**54.1**	**57.6**	**63.2**	**60.6**	**66.1**	**66.1**
	Type B + grants	**17.5**	**17.9**	**17.6**	**22.2**	**31.2**	**53.0**	**57.7**	**61.4**	**63.3**	**62.4**	**64.5**	**67.0**
	Type C	**24.3**	**23.7**	**24.0**	**30.1**	**44.1**	**82.9**	**88.5**	**94.3**	**103.4**	**99.1**	**108.2**	**108.2**
	Type C + grants	**28.7**	**29.2**	**28.8**	**36.3**	**51.1**	**86.8**	**94.5**	**100.4**	**103.6**	**102.2**	**105.6**	**109.7**
PD market entry reward	**Type A**	**4.9**	**5.3**	**6.0**	**11.1**	**16.3**	**16.5**	**18.8**	**19.4**	**20.6**	**20.3**	**20.5**	**21.0**
	Type A + grants	**5.7**	**6.1**	**7.9**	**11.8**	**16.6**	**18.4**	**19.2**	**20.0**	**20.4**	**20.2**	**20.6**	**20.8**
	Type B	**15.4**	**16.6**	**18.8**	**34.8**	**51.1**	**51.9**	**59.2**	**61.0**	**64.7**	**64.0**	**64.4**	**66.1**
	Type B + grants	**18.0**	**19.2**	**24.9**	**36.9**	**52.1**	**58.0**	**60.2**	**62.8**	**64.2**	**63.6**	**64.7**	**65.3**
	Type C	**25.3**	**27.2**	**30.8**	**57.0**	**83.6**	**84.9**	**96.9**	**99.8**	**105.9**	**104.7**	**105.3**	**108.2**
	Type C + grants	**29.4**	**31.4**	**40.7**	**60.5**	**85.3**	**94.9**	**98.5**	**102.8**	**105.0**	**104.1**	**105.9**	**106.9**

Note: Entry rates assumed in preclinical: Type A = 0.5-3/month; Type B = 3-8/month; Type C= 8-10/month). FD = fully delinked; PD = partially delinked.

Finally, the additive effect of grants in relation to market entry rewards allows the level of rewards to obtain a given level of market approvals to be reduced, or provides more approvals for the same level of reward. For example, grants allow a partially delinked reward of $400 million (€300 million) to increase Type A approvals from six to eight and Type B from 19 to 25. Similarly, grants allow the fully delinked reward to obtain 18 Type A market approvals and 58 Type B approvals to be reduced from $1,500 million/€1,236 million to $1,250 million/€1,030 million (see Table 15).

These results illustrate that there are various combinations of grants and market entry rewards that yield the very same effect in terms of numbers of market approvals, so that public funders can explore those that match their preference in terms of pull and push investments (see also Figure 21 above). Importantly, the cost differences for different combinations of rewards and grants with the same effect might vary significantly and should therefore be further explored. Put simply, a reward dollar and a grant dollar are not substitutes.

Conclusion

Antibiotics with large markets and expected total global net revenues of $1.5 billion (€1.2 billion) or more do not suffer from a market failure, and the improvement caused by the introduction of an intervention is thus modest (see Figure 17). The evidence suggests that the small relative improvement warrants defining intervention eligibility on the basis of projected revenues. Clearly, however, other factors such as how early a product can be determined to be eligible for a market entry reward may alter the relative improvement.

As can be observed in Figure 21, under certain scenarios the same effect in terms of market approvals can be reached with various combinations of both market entry rewards and grants, even if these combinations entail different levels of public spending. However, assessing the optimal mix of rewards and grants requires further research, including also capitalization of the cost of interventions (i.e., while grants are a cost today, a reward is a cost in the future). This entails further investigating the interaction effects of grants and rewards, including also variations in the total available pool of grant funds. This would also enable a more agent-based simulation, whereby developers compete with each other for grants and other kinds of funding. More sophisticated algorithms are also needed to capture how decision-makers consider the more certain cost reductions allowed by grants as opposed to the lesser increase in antibiotic approvals allowed by rewards. The simulator does not cover grants for basic research, but since these have a strong impact on entry rates into preclinical stage, they deserve further research and possibly to be modelled within the same R&D simulation.

In general, the reliance of our simulator on eNPV formulas as the key decision rule in R&D is certainly a limitation, as it neglects other decision logics such as less formalized strategic choices taking account of portfolio effects for a developer considering several antibiotic projects, or even non-financial logics such as those entailed by corporate social responsibility. The modelling of such decision approaches requires further research. We believe that our choice of a rather broad span for all major input parameters (see Table 13) counterbalances the partial lack of detailed data and helps represent the heterogeneity of projects and developers in the antibiotic field. However, further research on how the various parameters are related to each other (e.g., R&D costs with success probabilities or market revenues) would help to create a more realistic simulation.

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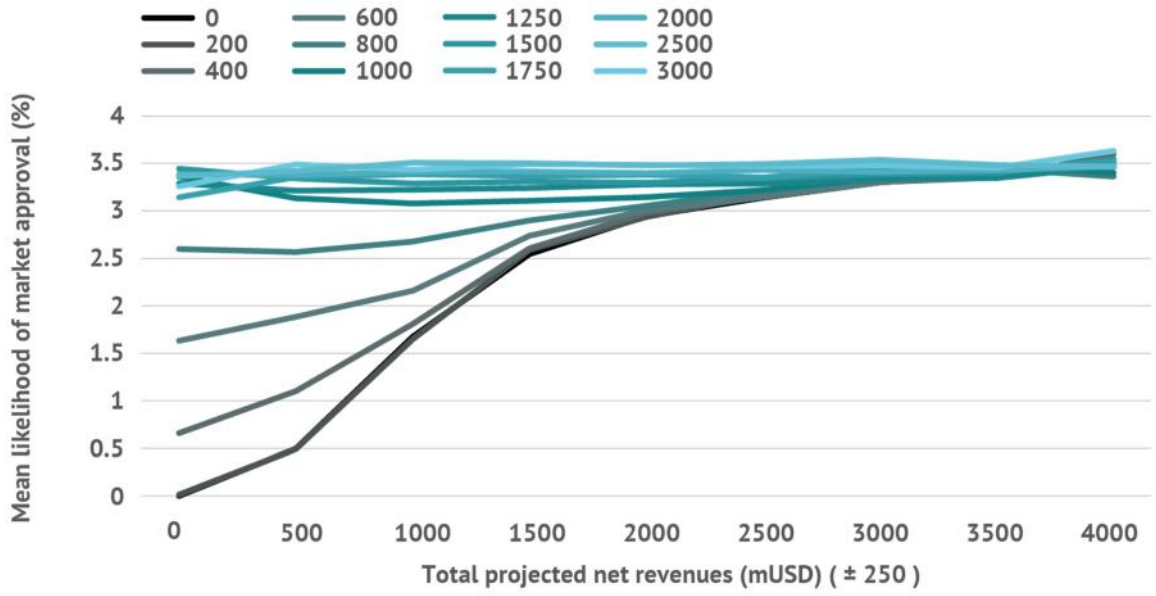
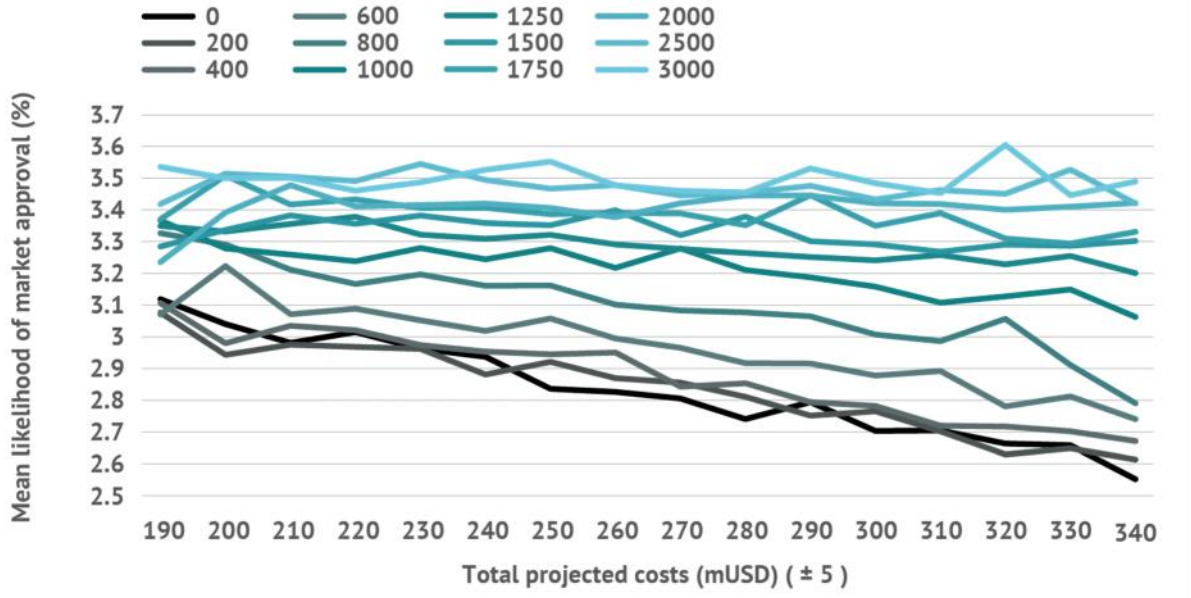
Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, Outterson K, 2014. *Analytical Framework for Examining the Value of Antibiotic Products*,Technical report, Eastern Research Group, Inc.

Supplementary Figure 1: Line plots relating the variance in likelihood of market approval under different market entry reward sizes ($0–3,000 million/€2,474 million) to different input parameters including: projected net revenues (a), total R&D costs (b), technical probability of success (c), VCs discount rates (d) and Big Pharma eNPV thresholds (e). (NB: 45,000 runs)
X axis: values of mean likelihood of market approval; Y axis: different values tested for each input parameter

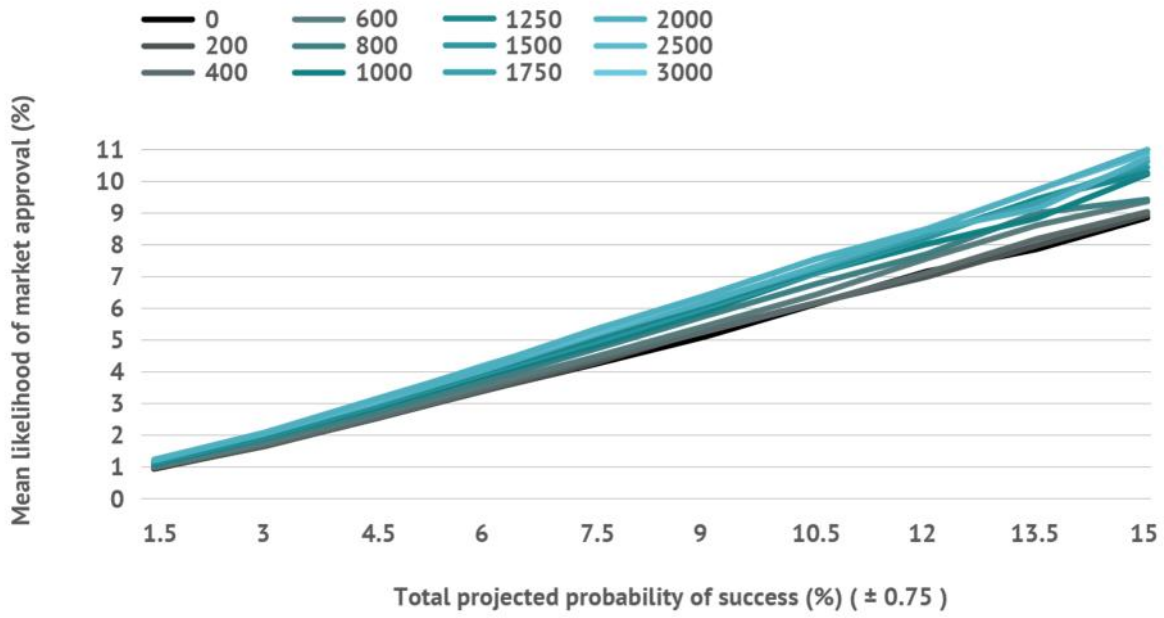
a)



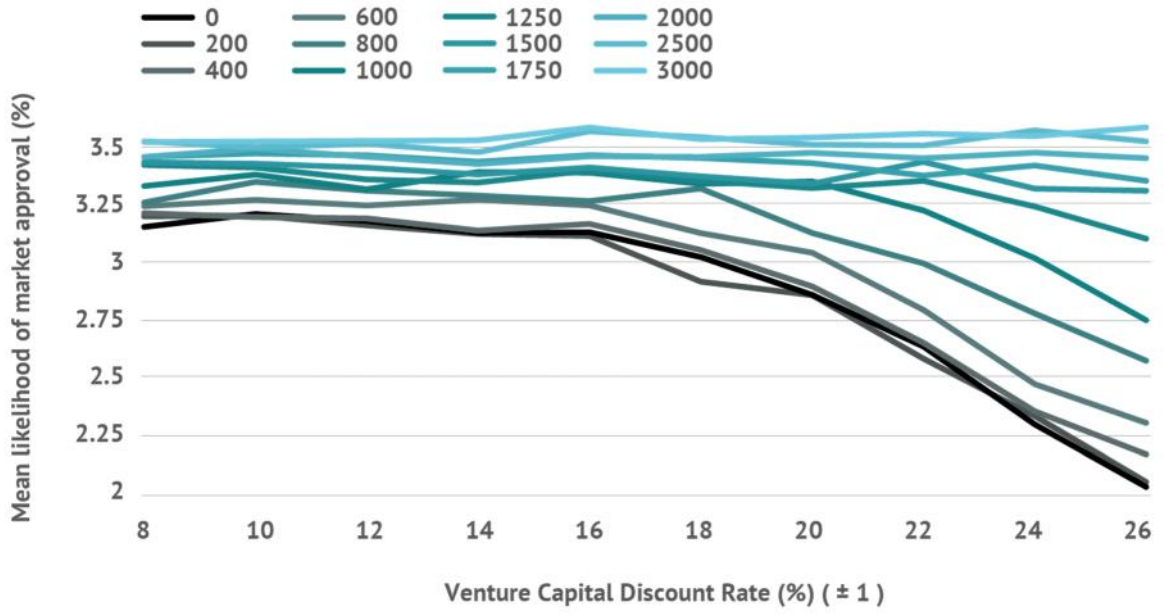
b)



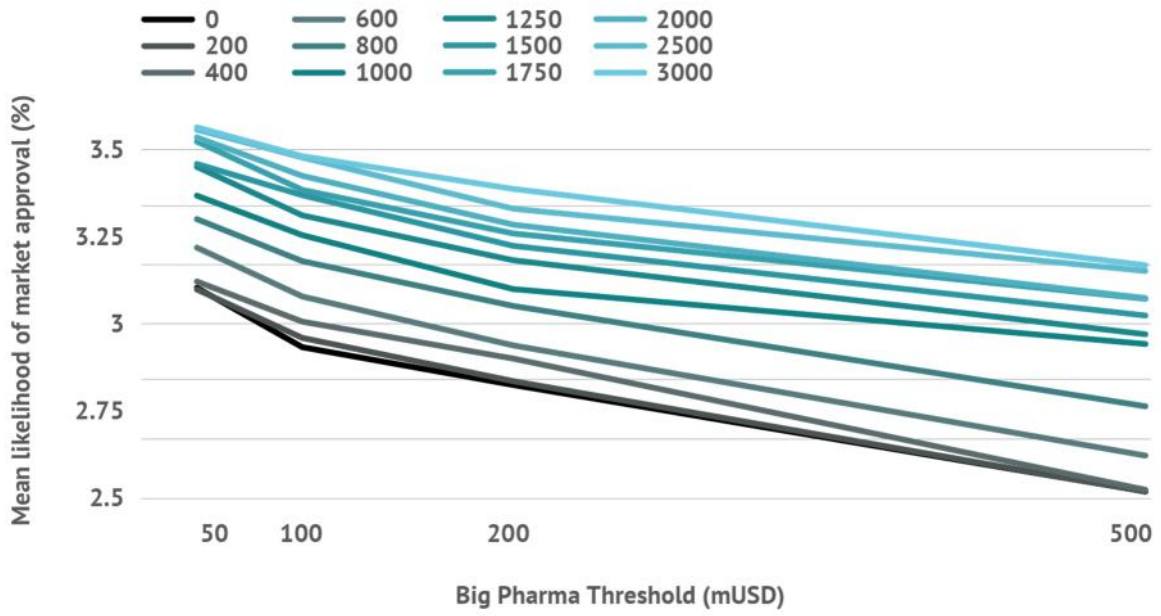
c)


0
200
400
600
800
1000
1250
1500
1750
2000
2500
3000
Mean likelihood of market approval (%)
0
1
2
3
4
5
6
7
8
9
10
11
1.5
3
4.5
6
7.5
9
10.5
12
13.5
15
Total projected probability of success (%) (± 0.75)

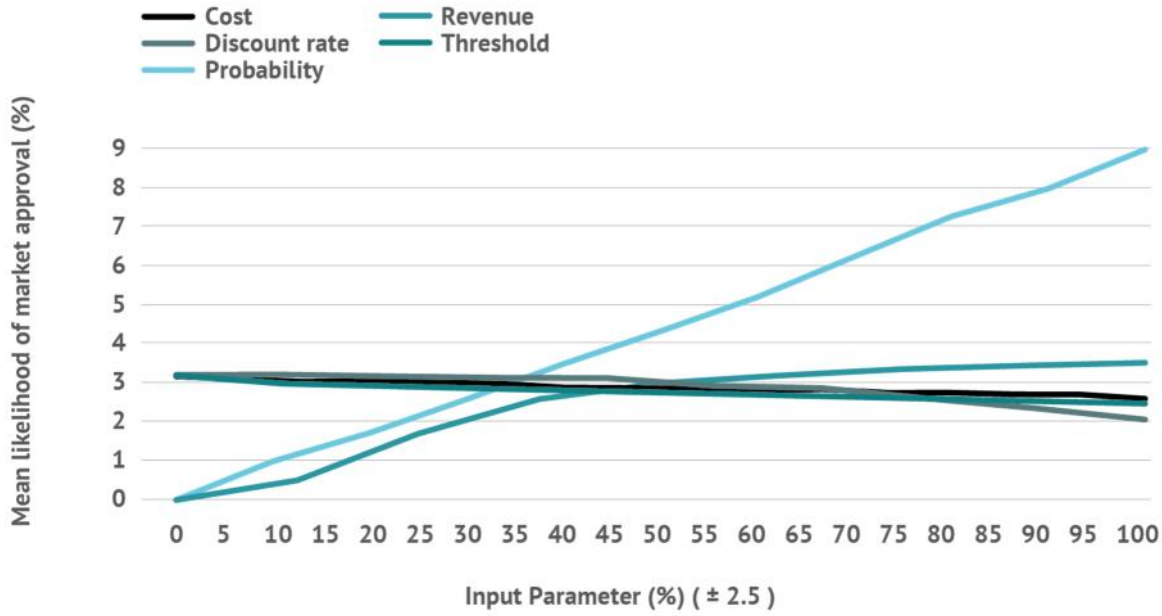
d)


0
200
400
600
800
1000
1250
1500
1750
2000
2500
3000
Mean likelihood of market approval (%)
2
2.25
2.5
2.75
3
3.25
3.5
8
10
12
14
16
18
20
22
24
26
Venture Capital Discount Rate (%) (± 1)

e)



f)



Supplementary Figure 1f: Sensitivity analysis across all parameters showing technical probability of success and projected revenues as much stronger determinant in variance of mean likelihood of market approval

Appendix D: Examples of types of antibiotic value

Enablement value

Methods: DRIVE-AB investigated the potential impact of increases in antibiotic resistance on the ten most common surgical procedures and immunosuppressing cancer chemotherapies that rely on antibiotic prophylaxis in the US. We identified meta-analyses and reviews of randomized controlled trials (RCTs) or quasi-RCTs to estimate the efficacy of antibiotic prophylaxis in preventing infections and infection-related deaths after surgical procedures and immunosuppressing cancer chemotherapy. We varied the identified effect sizes under different scenarios of reduction in the efficacy of antibiotic prophylaxis (10%, 30%, 70% and 100% reduction) and estimated the additional number of infections and infection-related deaths per year in the US for each scenario. We estimated the percentage of pathogens causing infections following these procedures that are resistant to standard prophylactic antibiotics in the US.

Increasing antibiotic resistance potentially threatens the safety and efficacy of surgical procedures and immunosuppressing chemotherapy.

The declining efficacy of existing antibiotics potentially jeopardizes outcomes in patients undergoing medical procedures. We estimate that 20–51% of pathogens causing surgical site infections and 27% of pathogens causing infections following chemotherapy are resistant to standard prophylactic antibiotics in the US. A 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 120,000 additional surgical site infections and infections following chemotherapy per year in the US (40,000–280,000 for a 10–70% reduction in efficacy), and 6,300 infection-related deaths (2,100–15,000 for a 10–70% reduction in efficacy). We estimated that each year, 13,120 infections (42%) following prostate biopsy are attributable to resistance to fluoroquinolones in the US.

Increasing antibiotic resistance potentially threatens the safety and efficacy of surgical procedures and immunosuppressing chemotherapy. More data are required to determine how antibiotic prophylaxis recommendations should be modified in the context of increasing resistance rates.

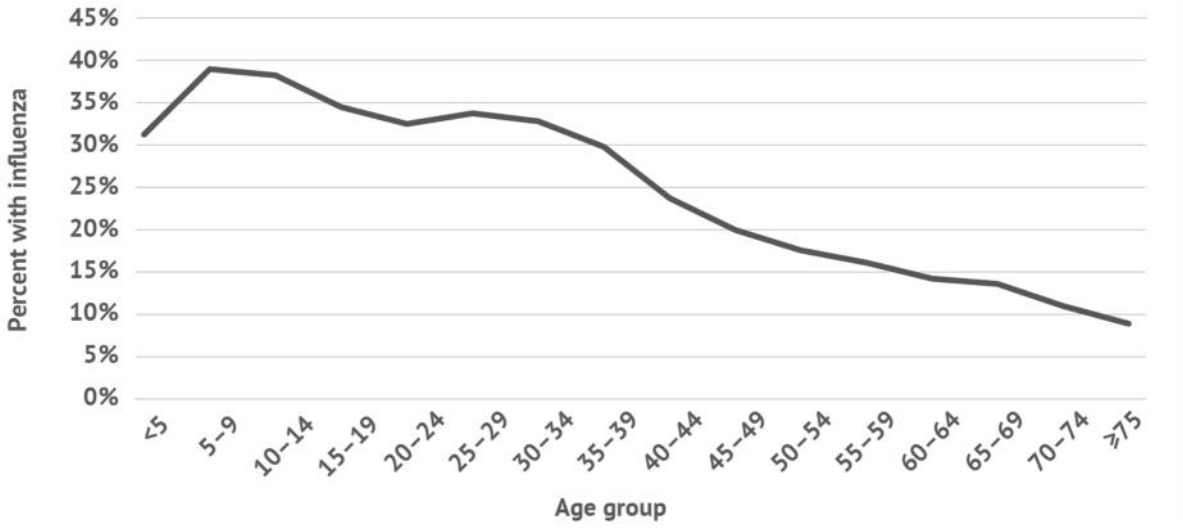
Option value

Methods: DRIVE-AB developed a valuation model of the option of withholding wide use of a novel antibiotic until an influenza pandemic is identified. We constructed hypothetical influenza pandemic scenarios that lead to secondary infections with a *Staphylococcus aureus* strain resistant to oral options other than the novel antibiotic.

An approach to estimating the value of a novel antibiotic: what is the cost of not having it at a moment of crisis?

In the past 400 years, three influenza pandemics on average have spread across the world each century, killing millions of people.[90] The 1918 (H1N1) pandemic, known as the "Spanish Flu", was by far the most devastating, infecting a third of the world's population and killing 50–100 million people.[91] More than 95% of deaths in the 1918 pandemic were complicated by a bacterial coinfection,[92] and had antibiotics been available in 1918, many of those deaths could have been avoided.[93] At the time, not many ways to treat the sick and alleviate the burden were available. Since then, experience and science have taught us more about influenza viruses and pandemics (1957, 1968 and 2009), and we have developed tools such as better infection control, vaccines, antivirals and antibiotics to prepare for and combat future pandemics.

Figure 23: **The estimated age-group-specific influenza case rates during the 1918 flu pandemic**



The emergence of multi-drug-resistant and pan-drug-resistant (PDR) untreatable infections, and the potential prospect of a post-antibiotic era, emphasize the value of protecting our investment in effective antibiotics, whether existing or in development.[94] In a world with prevalent PDR bacteria, treatment costs increase significantly, cuts and scrapes can be life-threatening and common surgical procedures and cancer chemotherapy may lead to unacceptably high rates of untreatable infections.[46,95] In the event of a significant influenza pandemic, secondary infections caused by prevalent PDR bacteria could be catastrophic. Ensuring we have effective antibiotics in the future is a public health priority, and only three new classes of antibiotics have reached the market since the 1970s.[4,6] We will need to develop new drugs to reduce the potential for a world with prevalent PDR pathogens. However, perhaps more importantly, we will need to manage these new drugs and the portfolio of drugs in our arsenal to maximize their lifetime value.

Conserving the effectiveness of antibiotics implies a value for the option to mitigate future catastrophic events. We find that the value of withholding the antibiotic can be significant unless the pandemic is mild and causes few secondary infections with the strain, or patients can be treated intravenously. The most influential parameter is the availability of intravenous (IV) therapy. In our base-case scenario, when 50% of individuals infected with the strain can be treated by IV therapy, the value of withholding wide use prior to identifying the pandemic is $1.3 billion (€1.07 billion). When only 20% can be treated by IV therapy, the value of withholding a potentially life-saving antibiotic is $3.4 billion (€2.8 bilion). However, if 80% of patients can be treated intravenously the value is $800 million (€680 million). Although the option value of withholding a novel antibiotic is

sensitive to uncertainty in the model parameters, our results show it can be significant, and further analysis on a case-by-case basis should be done to compare the value relative to immediate use.

Diversity value

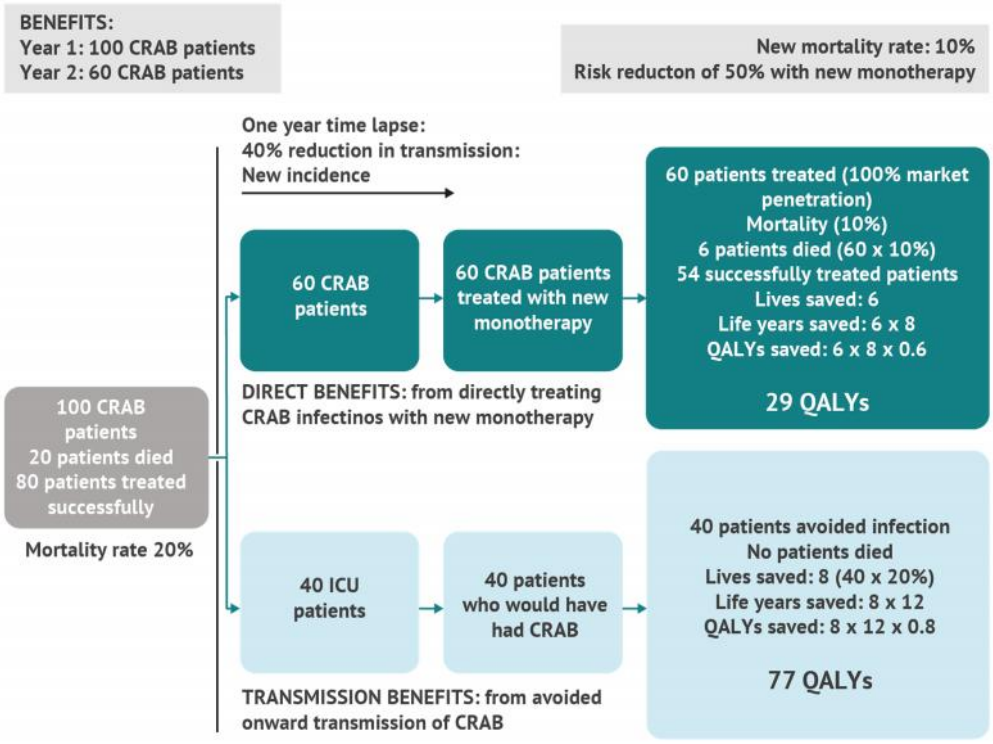
Methods: DRIVE-AB developed a framework based upon a literature review of the various dimensions of value offered by antibiotics. We then present a worked example of a cost per quality-adjusted life year (QALY) to show how it may be possible to capture these dimensions of value in a more formal manner.

To clearly demonstrate how analysis might be conducted in a way which is more specific to antibiotics and to suggest how new considerations might be built into the evaluation process, we present a worked example based on a fictional antibiotic hypothesized in 2013 by Spellberg and Rex, who conducted a cost-effectiveness analysis associated with the introduction of the new antibiotic in the United States.[96] The purpose of this analysis to sketch how an antibiotic might be assessed using the ideas in our framework.

The fictional monotherapy targets carbapenem-resistant *Acinetobacter baumannii* (CRAB), which is a resilient micro-organism with the ability to survive in the environment for long periods of time.[96] The carbapenem class of antibiotics comprises drugs that are often used as a last resort to treat multi-drug-resistant infections in hospitals, in particular intensive care units (ICUs).

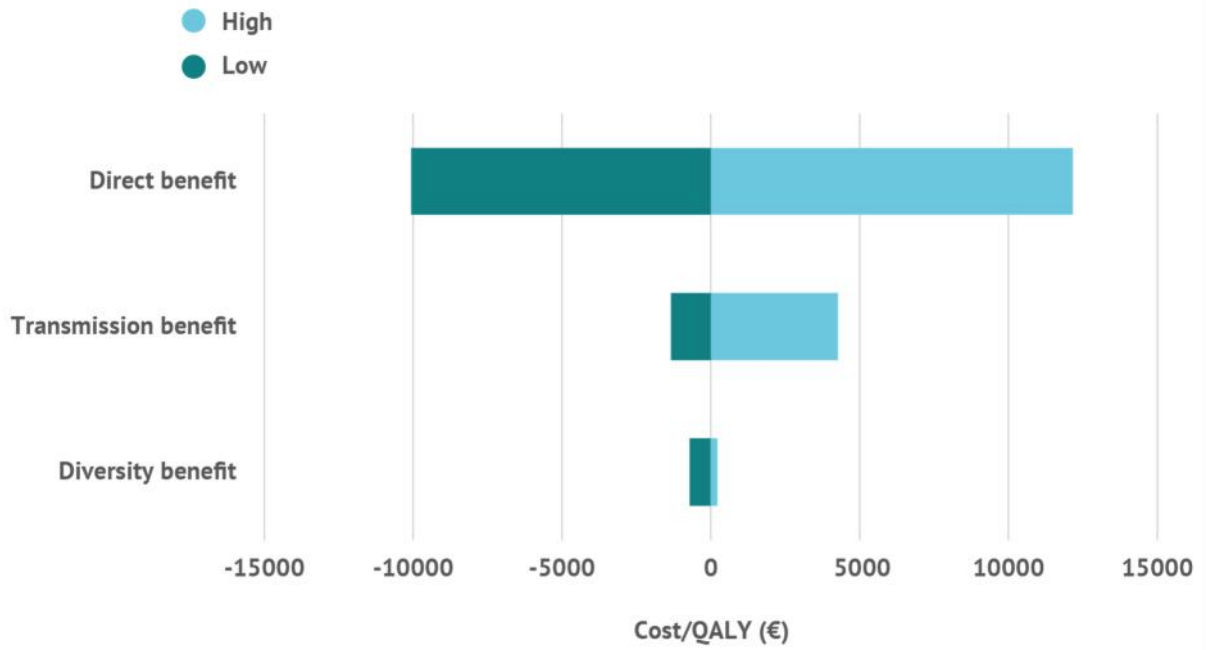
CRAB is an opportunistic pathogen, causing debilitating infections in immunosuppressed and hospitalized patients, with a mortality rate of 20%. Current treatment options for suspected CRAB infections include last-resort antibiotics such as polymyxins. This reliance on last-line antibiotics creates a selection pressure on organisms to develop resistance to these costly drugs.

Figure 24: Logic of direct and transmission benefit calculations applied to 100 patients



We used the benefit calculations (Figure 24) to calculate a cost per QALY for the monotherapy. Upper and lower bounds for all three classes of benefit (direct, transmission, diversity) were applied individually to the QALY equation in order to display the uncertainty around each benefit value displayed in Figure 25. The figure shows that the impact of uncertainty is greatest for the direct (or enabling) value, second greatest for the transmission (or insurance) value and lowest for the diversity value. In all cases, for a significant range of parameter values, the technology has a negative cost/QALY saved, reflecting that it is not cost-reducing, at the price of €25,000, which is higher than the price assumed by Spellberg and Rex. We do, however, note that even if the technology is revenue-neutral or cost-saving, the budget impact – the direct cost – of this new technology is quite large and it may be challenging for providers and payers to afford this technology. This is especially true in systems where there is divided responsibility for costs, or where there are intense short-term financial pressures.

Figure 25: Tornado diagram displaying the uncertainty of the direct, transmission and diversity benefits ($)



Health technology assessment is used widely across geographies and applied across a range of therapeutic areas to support reimbursement decision-making in a consistent, fair and transparent manner (though assessment criteria per country vary widely). It is well accepted that there are limitations in HTA methodology (e.g., caregiver value is not typically accounted for) and there are situations where standard HTA processes may need to be adapted, e.g. for orphan drug evaluations where study recruitment is considered challenging. In this report, we have aimed to demonstrate that significant value could be overlooked if antibiotics are assessed within the confines of current HTA methodology and without the consideration of the unique value attributes associated with these medicines. Further, we propose that practical solutions to include them in cost-effectiveness analyses may be feasible.

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

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