WORLD ECONOMIC FORUM

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System Initiative on Shaping the Future of Health and Healthcare

Antimicrobial Resistance
Tackling the Gap in R&D Resources with Pull Incentives

In collaboration with Wellcome
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Executive Summary

Aim

Fresh progress is needed by a coalition of governments, pharmaceutical companies and civil society towards the design and implementation of pull mechanisms to incentivize the development of new antibiotics.

The problem

- Resistance to existing antibiotics increases with their use. Unfortunately they are commonly overused, driving more rapid rise of antimicrobial resistance (AMR).
- As resistance renders existing treatments ineffective, we need new antibiotics.
- Low return on investment has resulted in an antibiotic pipeline that is insufficient to meet the urgent and growing public health need.
- Reimbursement for new antibiotics does not reflect the substantial public health benefits that they provide.
- New incentives are needed to address these externalities, foster the development of new antibiotics and enable the appropriate use of existing antibiotics.

The solutions

Multiple actions are needed across the antibiotic pipeline:

1. Continued public and philanthropic funding for research and development
2. A mechanism to coordinate R&D initiatives
3. A pull mechanism to incentivize private-sector investment while enabling appropriate use and equitable access
4. A long-term continuity model to maintain availability of antibiotics once they go off patent.

The first two of these are increasingly being addressed through initiatives like CARB-X, GARDP and the Global AMR R&D Coordination Hub, although more remains to be done. Progress towards the implementation of pull mechanisms remains a priority to be fulfilled.

Pull mechanisms: principles and next steps

To be effective, pull mechanisms need to meet the following criteria:

- An appropriate reward size
- An appropriate balance of risk between the private and public sectors
- Prioritization of development of antibiotics which meet public health priorities
- Enabling stewardship of new antibiotics
- Enabling availability and access to new antibiotics

To move towards the design and implementation of pilot pull mechanisms, we need:

- Commitment to cross-departmental (including health and finance) conversations in governments
- Engagement of companies with products in late-stage development that could be used in exemplar pull incentives
- Stronger definition of provisions for access and stewardship
- Defined eligibility criteria for new antibiotics to qualify for pull incentives
- Valuation methodologies for new antibiotics
- Sustainable funding mechanisms to pay for incentives
- High-level agreement on alignment and coordination of different mechanisms

Introduction

AMR is a growing threat to human health and there is a limited window of opportunity to act. An estimated 700,000 people die each year from drug-resistant infections, a number that could increase to 10 million by 2050 unless effective action is taken.

Not enough new antibiotics are in development to guarantee that we can continue to treat infections. Current market conditions will not incentivize the investment necessary to restock the antibiotic pipeline, and "push" funding that directly supports early-stage R&D is insufficient to create a functioning market for the future.

At the Forum's Annual Meeting in Davos in January 2017, leaders called for the public and private sectors to work together to develop innovative solutions that can overcome these barriers and generate a sustainable supply of new antibiotics.

Pull incentives will be a key element. They guarantee or increase the future revenue of a new antibiotic by providing reimbursement in innovative or indirect ways.

This briefing outlines why pull incentives are necessary; some of the key principles they need to fulfil; and next steps towards implementing or piloting a pull incentive. The focus here is on support for the development of new antibiotics, one of multiple interventions required to combat the rise of drug-resistant infections. In the context of AMR, the markets for diagnostics and vaccines are similarly challenged, and interventions to correct these will also require further consideration.

1. Why are antibiotics different from other pharmaceutical products?

The basic business model for most pharmaceutical products involves maximizing product sales to generate enough revenue to cover the very substantial sunk costs of historic research and development (R&D) and fund new projects that will deliver innovative new treatments.

This business model creates an alignment of incentives that delivers dependable commercial returns to industry and health benefits to society. Pharmaceutical companies aim to develop products with superior health outcomes and maximize their uptake; healthcare providers typically generate the greatest net health benefit for their patients by adopting as widely as possible superior health products.

The result is motivation and resources for pharmaceutical companies to develop new products superior to the previous generation, giving healthcare providers the tools to deliver sustained health improvements.

However, the business model breaks down for antibiotics because there are insufficient revenues to incentivize industry investment and because maximizing the use of antibiotics results in sub-optimal health outcomes due to the growth of resistance.

The resulting long-term decline in investment in antibiotic R&D has left us with an inadequate pipeline of new products to address the rise of drug resistance.

Commercial incentive for industry investment is insufficient for three primary reasons:

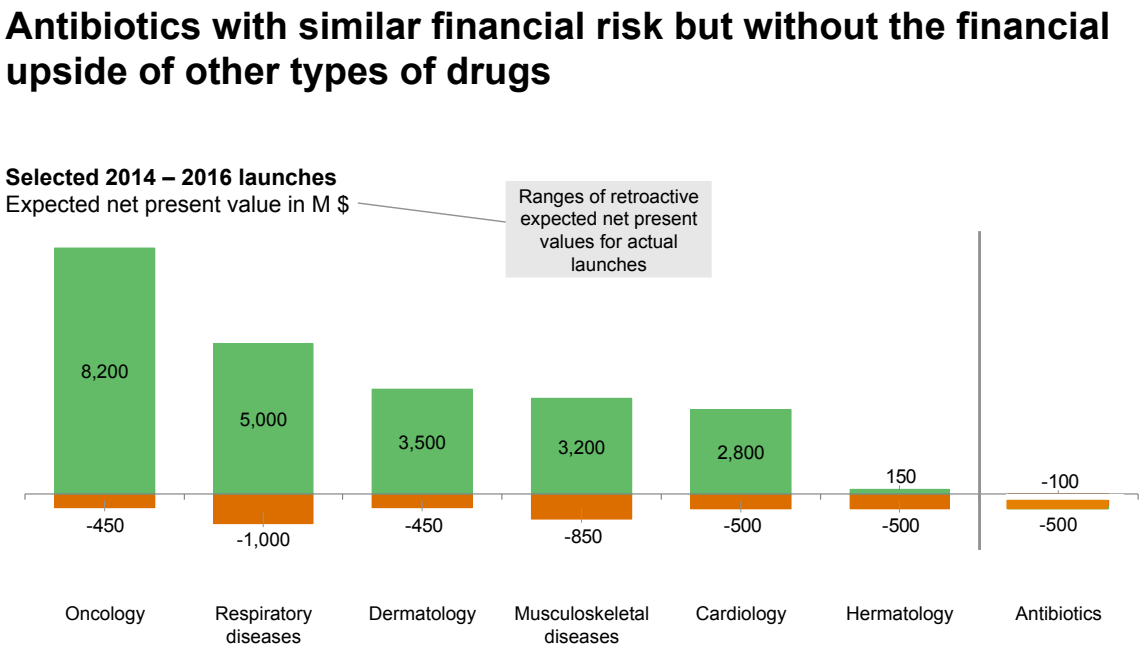
1. **The demand for new antibiotics is unpredictable**. Market economics dictate that older, cheap, off-patent antibiotics will be used wherever possible in preference to newer, more expensive products, which only offer additional benefits to a subset of patients with drug-resistant infections for whom other treatment options fail. Demand for new antibiotics is therefore reliant on the prevalence of resistant infections, which is hard to forecast.

2. **Stewardship efforts aim to minimize the inappropriate use of antibiotics** to reduce the drivers of resistance, safeguarding the efficacy of products, but also having the effect of decreasing anticipated sales revenues. From the health provider perspective, appropriate use of antibiotics is harder to achieve under a system that rewards companies for increasing uptake. We need different business models that reward and incentivize appropriate rather than maximum use, without affordability presenting barriers to access globally.

3. **Clinical trials of antibiotics are particularly complex and costly**. 65% of the cost of bringing an antibiotic to market is related to clinical trials (including risk of failure). This is because even those antibiotics intended only as back-ups must demonstrate clinical superiority to current treatments. This requires the challenging task of identifying and enrolling large numbers of people with drug-resistant infections, when such populations are typically small and dispersed.[1]

Of a total $40 billion-a-year market for antibiotics, sales of patented antibiotics only constitute about $4.7 billion (about the same as yearly sales for one top-selling cancer drug).[2] In 2015, patented antibacterials experienced a $1.1 billion decrease in sales volumes.[3] Most brand-name cancer drugs approved between 2011 and 2015 generated more than $500 million in annual sales, compared to between $24 million and $75 million on average for patented antibiotics.[4] With such meagre returns, conventional business models that work for most pharmaceutical products fail to motivate the development of new antibiotics.

Figure 1: Antibiotics with similar financial risk but without the financial upside of other types of drugs (ranges of retroactive expected net present values for actual launches)



Note: Assumptions: Varying development costs per TA ($600M–1,400M). Development costs include costs of failure. Duration of development between 6–8 years (varies across therapeutic areas).10-year revenue projections for all NMEs, COGS, and SGA based on EvaluatePharma data. Discount rate of 9%
Sources: BCG analysis; EvaluatePharma

2. What is needed now?

The pipeline of new antibiotics is insufficient to meet the threat of resistance and we cannot instantaneously restock the pipeline. Only 16 drug candidates under development target the most critical of the priority pathogens listed by the World Health Organization; almost all of them are modifications of existing antibiotic classes and address specific resistance mechanisms and, given typical development failure rates, only around five can be expected to reach market.[6,7]

We cannot delay action if we are to have new treatments ready in time to counter the threat of rising resistance rates.

3. What is the current status?

Support for antibiotic research and development can be split into two broad categories of incentives: push and pull mechanisms.

Push mechanisms share research and development costs across several parties to reduce a firm's outlays and increasing the net present value (NPV) of their antibiotic candidates, potentially creating a commercial incentive to bring new antibiotics to market.[8] They include research grants, tax incentives, public-private partnerships and data-sharing.[9]

Instead of sharing costs, **pull mechanisms** increase NPV by guaranteeing or increasing the revenue of a new antibiotic. This can be through policies that accelerate the regulatory pathway, extend market exclusivity or offer premium pricing, which are collectively termed **lego-regulatory incentives**, or via direct monetary contribution, known as **outcome-based incentives**.

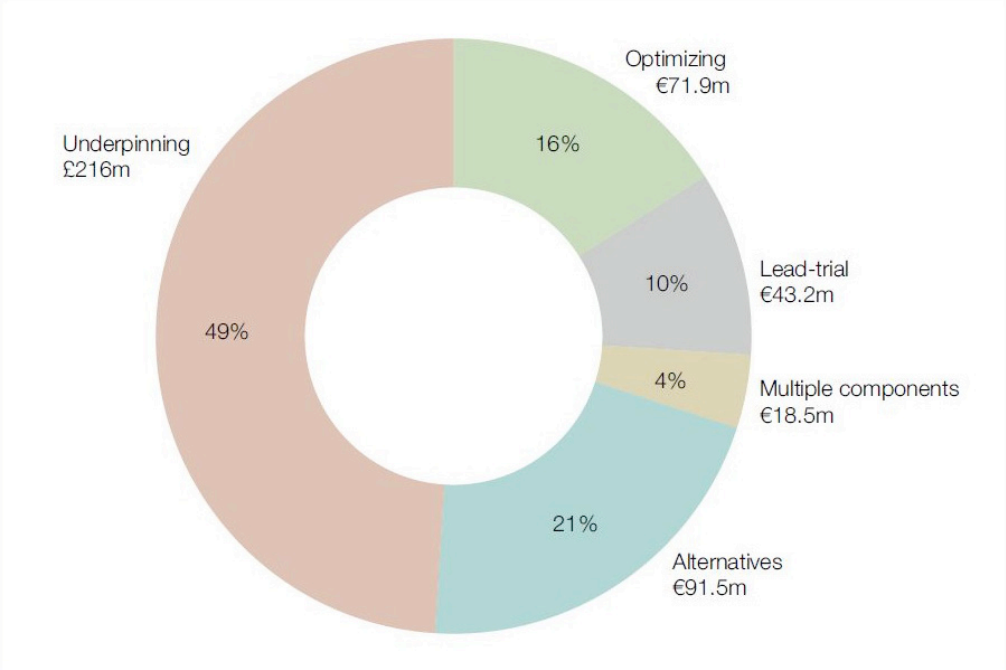
In the last couple of years, initiatives such as CARB-X, GARDP and JPI AMR have channelled extra funding into antibiotic R&D, with US contributions jumping from $260 million in 2015 to $413 million in 2016.[11] But existing programmes are exclusively push rather than pull mechanisms and, moreover, are heavily committed to basic and preclinical research as opposed to clinical development. This means that companies of all sizes are still not being sustainably incentivized to invest, and there are no drivers for taking antibiotic candidates from the early stages of research and development all the way to commercialization.[12]

Increased push funding for antibiotic development is currently providing a vital life-support mechanism for many of those products in development in the private sector. This will maintain early-stage activities in the short to medium term. It is clear, though, that a package of more fundamental market interventions – including pull incentives – is needed to sustain commercial investment in antibiotic development over the longer term.

Figure 2: Active AMR R&D initiatives based on their underlying incentives[13]

	Only push incentives	Only outcome-based pull incentives	Only lego-regulatory incentives	A hybrid of push–pull incentives
Multi-lateral	4	0	0	1
EU level	3	0	1	0
USA	1	0	1	1
UK	2	0	0	0
Total	10	0	2	2
Percent of total	71.4%	0.0%	14.3%	14.3%

Figure 3: European national-level funding of therapeutic-related antibacterial resistance projects by therapeutic sub-category (2007-2013) [14]



4. The necessity of pull mechanisms

Increasing push funding to the levels necessary to drive the development of new antibiotics all the way to market would be inefficient. Doing so would push the risks of drug development fully onto the funder. Moreover, the developer remains better placed to judge the viability of an antibiotic candidate because they retain the expertise and familiarity with their projects.

In contrast, pull incentives only compensate successful development, so firms continue to bear a fair proportion of the risk and are incentivized to maximize efficiency.[15]

Increasing push mechanism funding to levels that maintain risk-sharing does not increase NPV enough to incentivize antibiotic development. A recent modelling paper calculated an NPV of -$701 million even if public funding covers 50% of antibiotic development costs.[16]

Ultimately, while increased push funding for antibiotic development is essential to reinvigorating the antibiotic pipeline, by itself it is not adequate to sustain it. Moreover, in practical terms it cannot be scaled up indefinitely and into later stages of antibiotic development without the balance of risk borne by public and philanthropic funders becoming excessive and unsustainable.

5. Other benefits of pull mechanisms: stewardship, availability and access

The introduction of effective pull mechanisms will also offer additional opportunities to achieve important goals around improved global antibiotic stewardship, availability and access. The responsibility for delivering each of these does not rest solely with industry, which has taken some positive actions on each of these issues. But, the current pharmaceutical business model typically introduces barriers to these goals. Mechanisms used to promote antibiotic research and development also need to seize the opportunity to promote improved access and stewardship.

Currently, more deaths are due to limited and delayed access to antibiotics than to drug-resistant infections, a problem caused by health system failings as well as misaligned commercial drivers. For instance, universal access to antibiotics could avert 445,000 deaths from pneumonia in children under five each year. Pull incentives must be considered a failure if they don't enable the new drugs they fund to reach the people who need them most.

Pull incentives can enable stewardship, availability and access in two key ways.

1. They can be structured so that the reward they offer to companies is not solely based on sales volumes and prices. This removes or minimizes the incentive and imperative to maximize sales volumes of an antibiotic during its patent.
2. A pull mechanism that delivers its reward progressively can be contingent upon responsible marketing, product registration and/or pricing conditions being met.

Approaches such as patent buyouts and licencing mechanisms can potentially go further by passing the intellectual property for a new antibiotic from the private to the public or not-for-profit sector. Such models give control of the manufacture and distribution of products to public bodies and non-government entities in key territories (this may involve contracting with the private sector to take advantage of their existing capabilities in these areas).

6. Options for pursuit of pull mechanisms

There are some key principles that any pull mechanism should meet to achieve those optimal outcomes:

- An appropriate reward size that adequately incentivizes private-sector investment while not resulting in governments and/or health service providers overpaying
- An appropriate balance of risk between the private and public sectors that incentivizes efficient development and encourages private investment
- Prioritizing, through eligibility criteria or a tiered reward system, the development of antibiotics that meet the most urgent needs
- Enabling stewardship through alternative reimbursement models independent of sales volumes, reward of positive marketing practices, or transfer of intellectual property to the public sector
- Enabling availability and access by establishing manufacture and distribution of products and ensuring economic barriers to access are low

Many different forms of pull mechanisms have been proposed, and it is likely that a mix of complementary incentives will prove the long-term outcome. Lego-regulatory pull mechanisms may be integral to this for some products or in some territories but, in isolation, they are not well suited to meeting the above principles because they still rely upon market forces to deliver a return to industry and so run into issues with unpredictable demand and enabling access, stewardship and availability.

Outcomes-based pull incentives potentially offer a highly effective mechanism to guarantee a return on investment to industry and, with appropriate calculation, can provide value-for-money for health service providers. These might include market-entry rewards (which offer large lump-sum payments to the successful developers of a new product meeting certain well-defined criteria) or insurance-based systems whereby healthcare systems pay for the right to access a product rather than for each unit they use. Such models must be the priority for discussions between industry and governments.

7. Next steps

Political and industry consensus is building on the need for pull mechanisms for antibiotic development, evidenced by G20 and UN declarations and joint industry commitments.[18,19] Concurrently, academic and policy groups have been exploring options for implementation of pull mechanisms for several years, creating a strong evidence base to inform concrete actions.[20,21,22,23] Discussions now need to shift to a greater focus on the political and practical details of implementing pull incentives.

A coalition of governments and pharmaceutical companies need to make tangible, incremental progress towards the design and implementation of exemplar pull mechanisms, which will demonstrate the viability of this approach.

Before that can happen, there are several barriers to realization that must be addressed by the following:

- **Commitment by governments** to have cross-departmental conversations – particularly between ministries of health and finance – on pull mechanism options and how to pay for and guarantee rewards
- **Engagement of companies** with products in late-stage development that could be used as specific products around which exemplar pull incentives may be modelled
- **Stronger definition of provisions for access and stewardship**, and how agreements on these issues will be monitored and enforced
- **Development of eligibility criteria** for new antibiotics to qualify for pull incentives, responding to global public health needs
- **Exploration of valuation methodologies** for new antibiotics so developers are appropriately rewarded and funders do not overpay
- **Identifying sustainable funding mechanisms** to pay for the pull incentives
- **High-level agreement** on how efforts to implement pull incentives globally could be aligned and coordinated to achieve the most effective and efficient outcomes, while maintaining flexibility at the national or regional level

We are committed to supporting this necessary shift to more action-focused discussions on these topics, involving a broad range of governments, companies and civil society representatives, at the Annual Meeting 2018 and beyond. The importance of action to support antibiotic development is clear; this should be taken without further delay.

Endnotes

1. p.54, The Review on Antimicrobial Resistance 2016 – Tackling drug-resistant infections globally: final report and recommendations; p. 5, Duke-Margolis Centre for Health Policy 2017 – Value-based strategies for encouraging new development of antimicrobial drugs
2. p.6, The Review on Antimicrobial Resistance 2016 – Tackling drug-resistant infections globally: final report and recommendations
3. p.12, IMS Institute for Healthcare Informatics 2016 – Medicines use and spending in the US: A review of 2015 and outlook to 2020
4. p.4, Duke-Margolis Centre for Health Policy 2017 – Value-based strategies for encouraging new development of antimicrobial drugs
5. p.14, Boston Consulting Group 2017 – Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development
6. World Health Organization 2017 – Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics
7. p.33, World Health Organization 2017 – Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis
8. Net present value is an estimate of the commercial value of a new drug calculated by subtracting the cost of getting the drug to market from the projected future returns from that drug, adjusted to today's dollars (i.e. future revenues are discounted because of the time value of money). Product developers use net present value to evaluate market opportunities.
9. p.73, Renwick et al 2016a
10. p.73, Renwick et al 2016a
11. p.1, Renwick et al 2016b –Targeting innovation in antibiotic drug discovery and development: The need for a One Health – One Europe – One World Framework
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13. and development: progress, challenges and next steps", The Journal of Antibiotics
14. p.8, Simpkin et al 2017
15. p.23, Renwick et al 2016b
16. p.75, Renwick et al 2016a
17. Towse et al 2017 – "Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation", Health Policy
18. Laxminarayan et al 2016 – "Access to effective antimicrobials: a worldwide challenge", The Lancet
19. p.7 – Berlin Declaration of the G20 Health Ministers, May 19-20 2017; p.9 G20 Leaders' Declaration: Shaping an interconnected world, Hamburg, 8 July 2017; p.23, AMR Framework for Action Supported by the IACG, August 2017.
20. Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance (AMR); Industry Roadmap for Progress on Combating Antimicrobial Resistance – September 2016; BEAM Alliance Position Paper: Key Actions to Reinvigorate Investment and R&D in the antibacterial field now; Recommendations of the JPMA on the G7 Health Ministers' Meeting (Outline)
21. The Review on Antimicrobial Resistance 2015 – Securing New Drugs for Future Generations; The Review on Antimicrobial Resistance 2016 – Tackling Drug-Resistant Infections Globally: Final Report and Recommendations https://amr-review.org/Publications.html
22. Boston Consulting Group 2017 – Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development
23. Duke-Margolis Centre for Health Policy 2017 – Value-based strategies for encouraging new development of antimicrobial drugs