Innovation in Antibiotic Drug Discovery and Development

2U

2016

International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development

The need for a One Health – One Europe – One World Framework

A report for the 2016 Dutch Presidency of the European Union - **Executive Summary**

Matthew Renwick[1], Victoria Simpkin[1], and Elias Mossialos[1,2]

[1]LSE Health, Department of Social Policy, London School of Economics and Political Science, London, United Kingdom
[2]European Observatory on Health Systems and Policies, London, United Kingdom

Development of novel antibiotics, alternative therapies, and diagnostics tools is critical to the global fight against AMR. However, the pipeline for antibiotics and related products is limited. Since 2000, only 5 novel classes of antibiotics have been marketed. However, none of these target deadly and highly resistant gram-negative bacteria, which desperately require new antibacterial agents. The total number of submitted antibiotic patents has declined by 34.8% between 2007 and 2012.

A partial picture of the **EU/US antibiotic pipeline** shows that are at least 19 antibiotic products (including alternative therapies) in clinical development Phase I, 27 in Phase II, and 6 in Phase III (Figure 1). Despite 52 products in the pipeline, only one is a systemic antibiotic with a novel mechanism of action, and it is limited to a specific bacteria. A development timeline for these pipeline drugs is unknown.

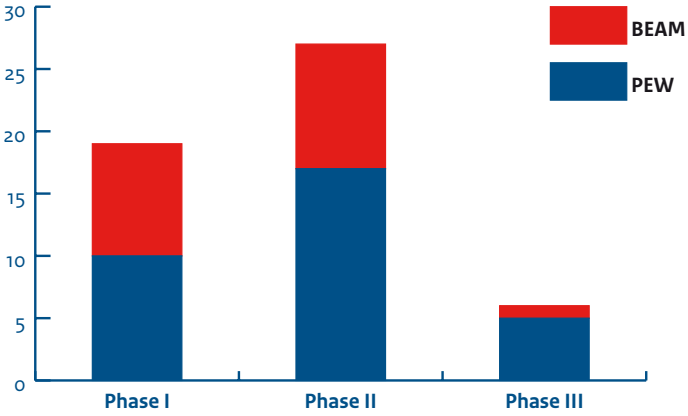

Figure 1. . Partial picture of the current development pipeline of antibiotics and related products as compiled from data provided by the PEW Charitable Trusts and the BEAM Alliance (Biopharmaceutical companies from Europe innovating in Anti-Microbial resistance research).

A partial picture of US and EU public funding of antibiotic R&D shows that Europe has invested ~€147 million annually between 2007-13 and the US has invested ~$260 million (€240 million) in 2015 (Figure 2). Having been stable since 2010, US investment in antibiotic R&D is expected to grow to $413 million (€382 million) in 2016. European and US governments do not appear to have any method of eventually recapturing these large investments should their funding result in marketable antibiotics.

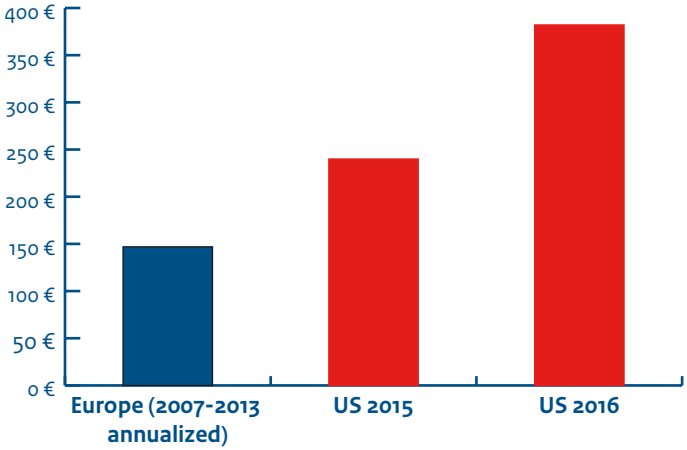

Figure 2. Estimated annual public funding of R&D of antibiotics and related products, Europe and the USA, Millions of Euros

Regarding private investment, global **venture capital in antimicrobial R&D** has declined by 28% between the two five year periods of 2004-08 ($ 1.053 million) and 2009-13 ($ 753 million). Venture capital investment in Gram-negative antimicrobials has increased by 51% during these two periods to $ 223 million, but it still comprises only 12% of total venture capital investment in antimicrobials. The amount of internal capital invested by pharmaceutical companies into their own antibiotic projects is unknown.

In response to this growing crisis, there has been a proliferation of initiatives to incentivize the antibiotic development pipeline. In total, there are **61 active R&D initiatives at global, EU, and national levels** (UK, France, Germany, Netherlands, Sweden, US, and Canada) analyzed in this report. Additionally, there are 5 initiatives that are either proposed or in preliminary stages of implementation.

Most initiatives improve the economic value of antibiotic R&D, but there is a heavy **imbalance towards the use of push incentive tools**. Of the active initiatives, 75% use only push mechanisms, 7% use only outcome-based pull mechanisms, 2% use lego-regulatory policies, and 15% only coordinate AMR action and provide no form of R&D incentive.

Hybrid push-pull approaches to incentivization are not being used at all. The top three incentives are: direct project funding, research collaborations, and research grants & fellowships *(Figure 3)*.

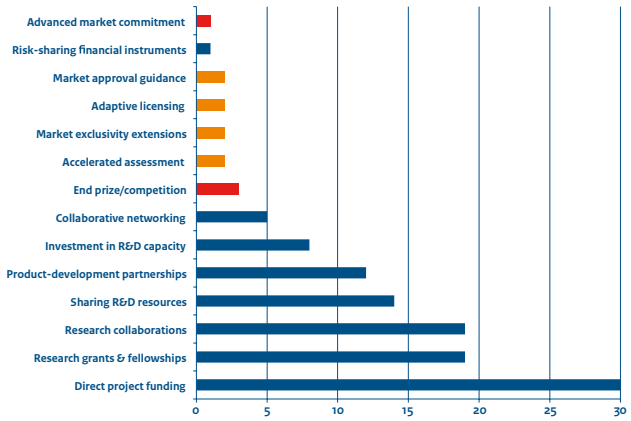

Figure 3. *Distribution of incentives used by antibiotic R&D initiatives (Blue = Push incentive; Red = Outcome-base pull incentive; Orange = lego-regulatory incentive).*

Due to this push/pull imbalance, there is an **unequal distribution of initiatives across the antibiotic value chain** that favours basic research and early drug discovery phases (Figure 4). In addition, R&D initiatives primarily assist academic institutions and large pharmaceutical companies. **SMEs are lacking support and often struggle to reach the clinical phases of development and market approval**. At the end of the antibiotic value chain, commercialization-focused pull incentives that are missing or are underutilized include: end prizes/competitions, value-based pricing and reimbursement, and taxation policies. Moreover, the EMA and FDA are using regulatory tools to facilitate antibiotic market authorization. But, there remains a **lack of harmonization and cooperation between the EMA and FDA**, as well as other drug regulatory agencies.

Finally, from a public health perspective, antibiotic stewardship and patient access goals are poorly integrated into the current set of R&D initiatives. Many initiatives have not explicitly linked their incentives to high-priority medical needs in infectious disease.

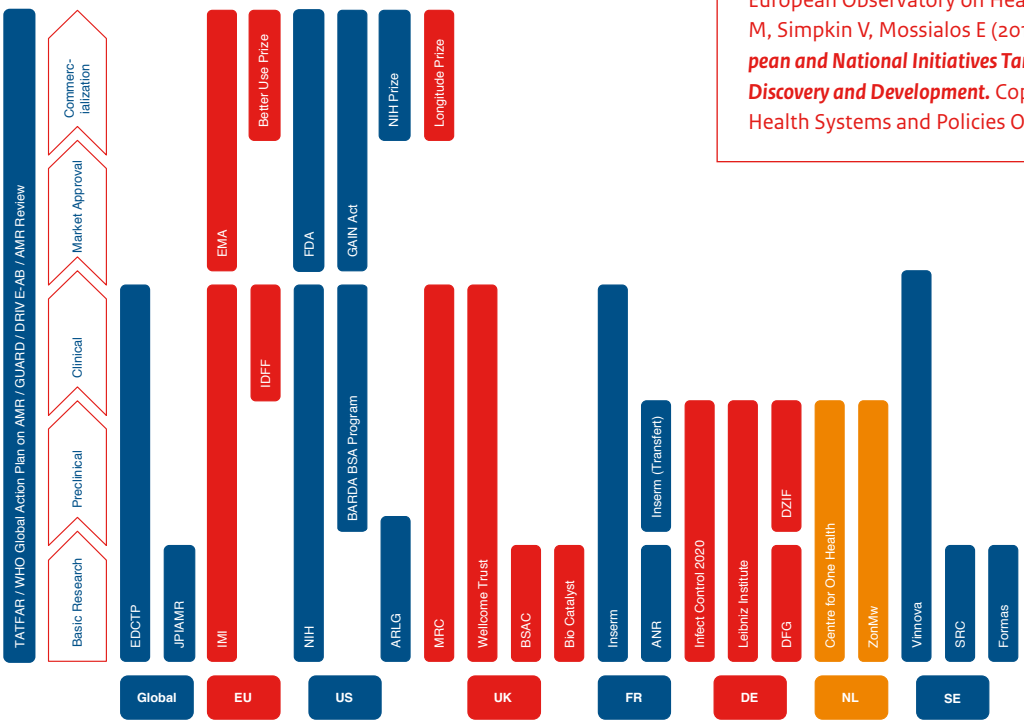

Figure 4. *Distribution of international, EU, and select European national antibiotic R&D initiatives across the antibiotic value chain.*

Given this research report's key findings, we put forth the following 14 recommendations to the policy officials attending the 2016 EU Ministerial Conference on AMR:

1. Align existing and new antibiotic R&D initiatives to function within the broader One Health approach to AMR.
2. Consolidate and coordinate existing and new European AMR and antibiotic R&D initiatives under a One Europe approach.
3. Establish a global AMR policy coordination & governing body that brings worldwide coherence under a One World approach.
4. Intensify efforts to coordinate and expand European and global antibiotic clinical trial programs under One Europe and One World agendas.
5. Ensure antibiotic incentives are explicitly attached to specific high-priority medical needs in infectious disease.
6. Launch a global AMR observatory that collects AMR and antibiotic pipeline data, shares knowledge, and disseminates best practices in AMR and antibiotic innovation.
7. Establish European and global commitment to antibiotic pull incentives.
8. Explore the role for European joint procurement of high-value antibiotics to ensure their conservation.
9. Consider the feasibility of European tax policies that encourage antibiotic R&D.
10. Incorporate methods of clawing back public investment in antibiotic R&D into incentive packages.
11. Improve antibiotic harmonization across global drug regulatory agencies and encourage joint antibiotic authorization between the EMA and FDA.
12. Address key market weaknesses by enabling SME participation and facilitating preclinical development.
13. Explore the incentive preferences of different industry players.
14. Investigate the value of different partnership models in antibiotic R&D and learn from the experiences of the US Biomedical Advanced Research and Development Authority.

This summary factsheet is based on the forthcoming publication produced by the London School of Economics in collaboration with the Dutch Ministry of Health, Welfare and Sport, and the European Observatory on Health Systems and Policies: Renwick M, Simpkin V, Mossialos E (2016). ***A Review of International, European and National Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development.*** Copenhagen, European Observatory on Health Systems and Policies Occasional Series.

EUNL2016
Ministry of Health, Welfare and Sport
www.rijksoverheid.nl
eu2016.nl