

## Antibiotic research and development: business as usual?

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The global burden of antibiotic resistance is tremendous and, without new anti-infective strategies, will continue to increase in the coming decades. Despite the growing need for new antibiotics, few pharmaceutical companies today retain active antibacterial drug discovery programmes. One reason is that it is scientifically challenging to discover new antibiotics that are active against the antibiotic-resistant bacteria of current clinical concern. However, the main hurdle is diminishing economic incentives. Increased global calls to minimize the overuse of antibiotics, the cost of meeting regulatory requirements and the low prices of currently marketed antibiotics are strong deterrents to antibacterial drug development programmes. New economic models that create incentives for the discovery of new antibiotics and yet reconcile these incentives with responsible antibiotic use are long overdue. DRIVE-AB is a €9.4 million public–private consortium, funded by the EU Innovative Medicines Initiative, that aims to define a standard for the responsible use of antibiotics and to develop, test and recommend new economic models to incentivize investment in producing new anti-infective agents.

**Keywords:** multidrug resistance, antimicrobial agents, drug development, economics, patient safety, clinical studies, global health policy

### Introduction

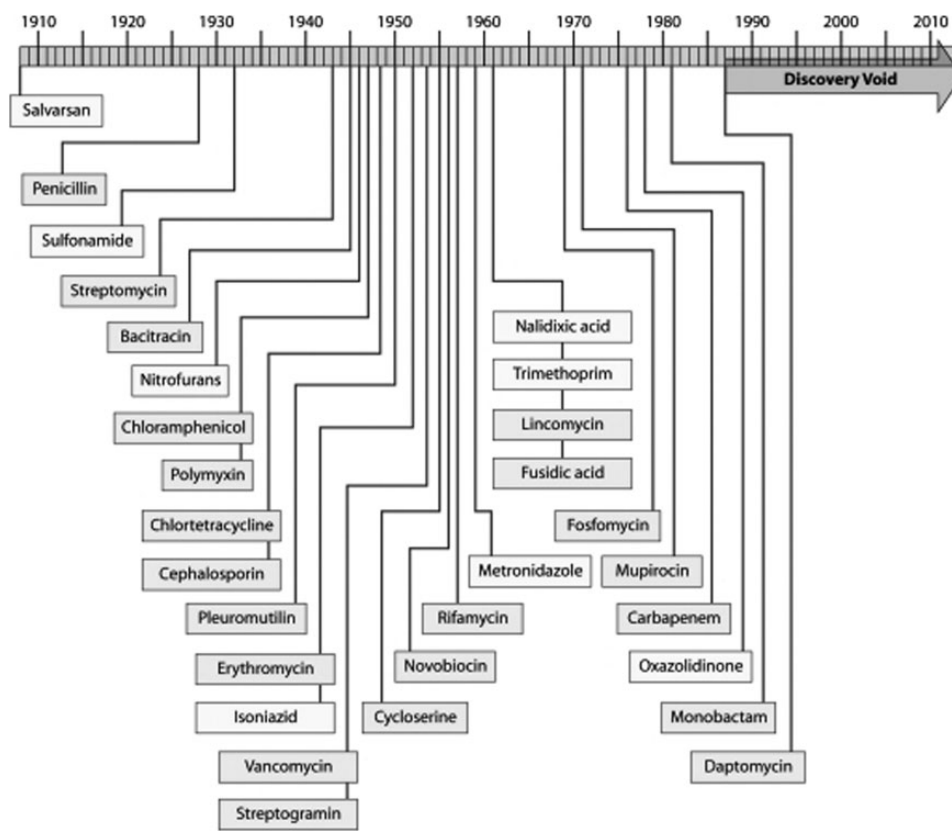
Although difficult to calculate, the worldwide burden of antibiotic resistance is high.<sup>1</sup> Despite great improvements in infection control, antibiotic stewardship and vaccine technology during the last decade, antibiotics remain a cornerstone of infectious disease therapy. Indeed, these agents are the hidden backbone of advanced medical care: surgical procedures, transplant and geriatric medicine, critical care and cancer chemotherapy all rely on their effectiveness for successful clinical outcomes.<sup>2</sup> Yet as antibiotic resistance increased across the globe, most pharmaceutical companies closed down their antibiotic research and development (R&D) units. In 1980, there were more than 25 pharmaceutical companies with active antibacterial drug discovery programmes<sup>3</sup>; today only a few of the largest companies remain active in the field. As a consequence, during the last two decades, a substantial gap in the discovery of antibacterial drugs has been created, which is responsible for the current lack of newly approved systemic antibacterial agents (Figure 1). In particular, the need for effective agents targeting MDR Gram-negative bacteria grows dire, with no agent of a new class or with a new mode of action in late clinical development.<sup>4</sup>

### Reasons for the lack of new antibiotics

There are several reasons for the dry pipeline. Scientifically, the 'low-hanging fruits' have been plucked; new breakthroughs are elusive and expensive.<sup>5</sup> Another major challenge lies in economic incentives for investment in this area, or the growing lack thereof,

compared with other therapeutic fields. Developing novel drugs for infections caused by MDR bacteria is challenging; meanwhile, the pharmaceutical industry is increasingly faced with a large number of inexpensive off-patent antibiotics, as well as tightening restrictions for placement on hospital formularies and limitations on the pricing of new antibiotics. Healthcare payers are neither accustomed nor prepared to reimburse antibiotics at prices that provide incentives to start or maintain antibacterial drug development programmes.<sup>6</sup>

Traditionally, in order to recover R&D costs and ensure financial returns, pharmaceutical companies aim to maximize the sales potential, and thus the consumption, of their products. In the case of antibiotics, however, this simple sales-based model runs counter to the public health mandate to 'steward' the consumption of these drugs in order to preserve their efficacy. Any approach to the problem of the lack of incentives for new antibiotic development must address the parallel challenge of the lack of short-term incentives for their appropriate use.<sup>7</sup> Initiatives to improve the development pipeline for new antibiotics have been proposed and some are currently being implemented on both sides of the Atlantic [e.g. the Generating Antibiotics Incentives Now (GAIN) Act in the USA, and the Innovative Medicines Initiative (IMI) in Europe].<sup>8–10</sup> Of particular note, the UK government has recently announced a financial review of economic issues surrounding antimicrobial resistance and the plan for encouraging and accelerating the discovery and development of new generations of antibiotics.<sup>11</sup> Moreover, there are many strategies to minimize the misuse of antibiotics.<sup>12,13</sup>



**Figure 1.** Illustration of the ‘discovery void’. The dates indicated are those of the reported initial discovery or patent. Figure reprinted with permission.<sup>5</sup>

**Table 1.** Partners of the DRIVE-AB Initiative

Organization	Main participant names	Type of organization	Country
BSAC	Laura Piddock	public	UK
Center for Anti-Infective Agents	Ursula Theuretzbacher	private	Austria
Chatham House	Charles Clift	private	UK
London School of Economics and Political Science	Elias Mossialos	public	UK
Norwegian Institute of Public Health	John-Arne Røttingen	public	Norway
Tel-Aviv Sourasky Medical Center	Yehuda Carmeli	public	Israel
The Radboud University Nijmegen Medical Centre	Inge Gyssens	public	Netherlands
University of Antwerp	Herman Goossens	public	Belgium
University of Geneva	Stephan Harbarth	public	Switzerland
University of Heidelberg	Timo Goeschl	public	Germany
University of Lorraine	Céline Pulcini	public	France
University of Rijeka Medical Faculty	Vera Vlahović-Palčevski	public	Croatia
University of Strathclyde	Alec Morton and Ramanan Laxminarayan	public	UK
University of Tübingen	Evelina Tacconelli	public	Germany
Uppsala University	Francesco Ciabuschi	public	Sweden
Wageningen University	Justus Wesseler	public	Netherlands
Astellas Pharma Europe Ltd	Chris Longshaw	private	UK
AstraZeneca	Judith Hackett and John Rex	private	Sweden/USA
Cubist Pharmaceuticals	Barry Eisenstein	private	USA
F. Hoffmann-La Roche Ltd	Ka Lum and Brigitte Nolet	private	Switzerland
GlaxoSmithKline R&D	David Findlay	private	UK
Pfizer Ltd	Charles Knirsch	private	USA
Sanofi-Aventis R&D	Sue Cheng	private	France

None of these initiatives, however, has linked incentives for the development of new antibiotics to the responsible use of these scarce resources; none specifically addresses the conflict traditionally inherent in these two objectives. Thus, there is an urgent need to foster a shared understanding of antibiotics as precious drugs but with a diminishing activity due to resistance, as well as to create a favourable economic environment and opportunities for the discovery of new agents. Reconciling these goals is imperative if we want to have these powerful drugs available in the future. There is also a clear awareness that such an endeavour cannot succeed if it is cultivated and championed merely by one sector of society, be it pharmaceutical companies, academia or public health.<sup>9</sup> It must find its roots among all of society's players; while these three sectors are integral, other stakeholders (patients, clinical societies, government and payers) must play an active and early role.

## The DRIVE-AB Initiative

As outlined above, alternative models that can create incentives for the R&D of novel antibiotics and yet reconcile these incentives with responsible antibiotic use are long overdue.<sup>14</sup> The IMI-funded, multistakeholder, €9.4 million DRIVE-AB (Driving Re-InVESTment in R&D and responsible AntiBiotic use) consortium, composed of 14 public and 9 private partners from 12 countries (Table 1), will produce such models in a stepwise yet interconnected process. First, it will develop an evidence-based, consensus definition for 'responsible antibiotic use', which, with its standardized quality and quantity indicators, will provide the framework for later steps. Next, data from surveillance systems and published literature will inform estimations of the present burden of antibiotic resistance from both clinical and economic perspectives across varying socioeconomic backdrops. Simulation models informed by these data as well as data from past and ongoing epidemics will estimate current and future public health needs and impact related to antibiotic resistance, in diverse socioeconomic settings. Together, these constructs will allow for valuation models that will estimate the real worth of new and existing antibiotics from the perspectives of patients, physicians, payers and society as a whole. These, in turn, will inform the creation of alternative economic strategies and reward models that will promote and sustain the development of novel antibiotics while simultaneously bolstering the appropriate consumption of existing and novel antibiotics. The most promising schemes will be presented to and tested with policy-makers and other stakeholders with attendant implementation and risk-management strategies.

What makes the DRIVE-AB project unique? As they work together over the next 3 years, the worldwide renowned expertise, motivation and diversity of the DRIVE-AB partners will be an appropriate match for the complexity and scope of the problem to be confronted. The innovative economic models will be, for the first time, extensively tested in real-time quantitative scenarios to provide reliable data for policy-making.<sup>14</sup> To facilitate the implementation of new models, DRIVE-AB will convene the first large international stakeholder platform of experts and advisory groups. This unprecedented coalition will combine experience and knowledge spanning all phases of antibiotic R&D, financing, clinical use and stewardship, in order to drive a better understanding of antibiotics as a common good. The development of models for a favourable economic environment linked to appropriate

usage and global access will finally contribute to replenished pipelines and the availability of novel antibiotics that are effective against infections caused by resistant bacteria.

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## Transparency declarations

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## References

- Huttner A, Harbarth S, Carlet J *et al.* Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum. *Antimicrob Resist Infect Control* 2013; **2**: 31.
- Yoshikawa TT. Antimicrobial resistance and aging: beginning of the end of the antibiotic era? *J Am Geriatr Soc* 2002; **50** Suppl 7: 226–9.
- Boucher HW, Talbot GH, Benjamin DK Jr *et al.* 10 × '20 Progress—development of new drugs active against Gram-negative bacilli: an update from the Infectious Diseases Society of America. *Clin Infect Dis* 2013; **56**: 1685–94.
- Huttner B, Harbarth S. Think (Gram) negative! *Crit Care* 2010; **14**: 171.
- Silver LL. Challenges of antibacterial discovery. *Clin Microbiol Rev* 2011; **24**: 71–109.
- Laxminarayan R, Powers JH. Antibacterial R&D incentives. *Nat Rev Drug Discov* 2011; **10**: 727–8.
- Laxminarayan R. Antibiotic effectiveness: balancing conservation against innovation. *Science* 2014; **345**: 1299–301.

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- 8** Kirby T. Europe to boost development of new antimicrobial drugs. *Lancet* 2012; **379**: 2229–30.
- 9** Piddock LJ. The crisis of no new antibiotics—what is the way forward? *Lancet Infect Dis* 2012; **12**: 249–53.
- 10** Brown ED. Is the GAIN Act a turning point in new antibiotic discovery? *Can J Microbiol* 2013; **59**: 153–6.
- 11** UK Government. *Prime Minister Warns of Global Threat of Antibiotic Resistance*. 2014. <https://www.gov.uk/government/news/prime-minister-warns-of-global-threat-of-antibiotic-resistance>.
- 12** Davey P, Brown E, Charani E *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013; issue **4**: CD003543.
- 13** Huttner B, Harbarth S, Nathwani D, on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP). Success stories of implementation of antimicrobial stewardship: a narrative review. *Clin Microbiol Infect* 2014; **20**: 954–62.
- 14** Mullard A. Momentum builds around new antibiotic business models. *Nat Rev Drug Discov* 2014; **13**: 711–3.