



Policy Position

Supporting sustainable investments in antimicrobial R&D

Vaccines and antibiotics have revolutionized infectious disease prevention and treatment, saving millions of lives worldwide. Rising levels of resistance to antimicrobials is a serious threat to public health, food safety and global security. Antimicrobial resistance (AMR) reduces the effectiveness of treatments for infectious diseases and jeopardizes health care gains to society that rely on the ability to effectively treat and prevent bacterial infections, such as organ transplantation, cancer chemotherapy, and major surgery.

Drug resistant infections are estimated to cause approximately 700,000 deaths worldwide each year. Unless action is taken, the burden of deaths from AMR could reach 10 million lives each year by 2050. On this basis, by 2050, the deaths attributable to AMR would be higher than cancer (estimated at 8.2 million)ⁱ.

The World Bank estimates that drug-resistant infections have the potential to cause a level of economic damage similar to—and likely worse than—that caused by the 2008 financial crisisⁱⁱ. In OECD countries, hospitals spend, on average, an additional USD 10,000 to 40,000 to treat a patient infected by resistant bacteriaⁱⁱⁱ. The associated impact of lost economic output due to increased mortality, prolonged sickness and reduced labor efficiency could double this figure.

The biopharmaceutical industry, including both established pharmaceutical as well as early-stage biotechnology companies, plays a key role in developing new medicines and vaccines that can help address AMR. However, they face daunting challenges.

It takes more than a decade to develop a new antibiotic or vaccine and can cost more than US\$1 billion^{iv}. The Pew Charitable Trusts evaluated that only 1 in 5 of the infectious disease drugs that enter Phase 1 clinical testing will ultimately be proven safe and effective enough to make it to the market^v, while the success rate for preclinical targets is only 4%^{vi}. However, the existing pipeline is not nearly large or diverse enough to keep up with the current pace of the emergence of resistance. Over the past two decades, there has been a significant decline in the number of large pharmaceutical companies conducting antibiotic R&D^{vii}. At the time this document was written, only four of the top 50 pharmaceutical companies have antibiotics in clinical development^{viii}. Within the last two years, five large pharmaceutical and many biotechnology companies have exited this space due to the scientific, regulatory, and economic challenges posed by antibiotic discovery and development:

- **Scientific challenges:** Bacteria are resilient and constantly evolving. It is increasingly difficult to develop medicines that balance the ability to treat infections (effectiveness) with the risk of serious side effects in humans (safety and tolerability). Furthermore, the antibiotics currently on the market represent the “low hanging fruit” in terms of their targets. The next generation of antibiotics will need to exploit yet – undiscovered targets.
- **Regulatory challenges:** While there have been some recent improvements in regulatory guidance and harmonization to facilitate development of novel antimicrobials, clinical trial enrollment and design still present important challenges for these products.
- **Economic challenges:** Novel antibiotics are generally undervalued by reimbursement systems relative to the benefits they bring society. Uptake of novel antibiotics is slow, since they are usually used sparingly to preserve effectiveness when resistant infections are relatively rare and there may be limited availability of appropriate diagnostics and surveillance data. Reimbursement systems, including hospital bundled-payment mechanisms, can discourage use of novel antibiotics, even when they are the most appropriate treatment for a patient.



Policy Position

The role of industry in the global response to AMR

Policymakers have recognized the need for new antibiotics and their role to incentivize investment into antimicrobial R&D. Box 1 below includes a selection of high-level declarations made by multilateral organizations and leading governments related to antimicrobial innovation. These declarations have so far not translated into action by governments to address the fundamental economic challenges described above. New approaches are needed to address the unique market dynamics for antibiotics.

Box 1: High-level declarations on the need for incentives for antimicrobial R&D

- G20 Leaders' Declaration: Shaping an interconnected world, Hamburg, 8 July 2017: *"Concurrently, in collaboration with relevant experts including from the OECD and the WHO, we will further examine practical market incentive options."*
- G7 Milan Health Ministers' Communiqué, 5-6 November, 2017: *"We welcome the establishment of the Global Collaboration Hub on Research and Development on AMR and note its potential to become an effective platform to align and to leverage investment for AMR R&D"*
- G20 Leaders' Communiqué Hangzhou Summit, 4-5 September 2016: *"We affirm the need to explore in an inclusive manner to fight antimicrobial resistance (...) and unlock research and development into new and existing antimicrobials from a G20 value-added perspective, and call on the WHO, FAO, OIE and OECD to collectively report back in 2017 on options to address this including the economic aspects."*
- G7 Ise-Shima Leaders' Declaration, 26-27 May 2016: *"We also commit to consider potential for new incentives to promote R&D on AMR and call on the international community to take further action."*
- UN Political Declaration on AMR, 22 September 2016: *"Recognize that the keys to tackling antimicrobial resistance are ... and resolving the lack of investment in research and development, including through the provision of incentives to innovate and improve public health outcomes, particularly in the field of antibiotics."*
- Report to the U.S President on Combating Antibiotic Resistance by the President's Council of Advisors on Science and Technology, September 2014: *"The Federal Gov't should significantly increase economic incentives for developing urgently needed antibiotics...an Antibiotic Incentive Fund to provide advanced market commitments and milestone payments to reward developers ..."*
- 2013 -2018 UK AMR Action Plan: *"There is a need to do more to address the commercial viability and market failure issues that are hampering investment in antibiotic development."*

Recognizing their role in addressing AMR, over 100 companies and associations signed the Industry Declaration on AMR at the World Economic Forum in 2016 ("the Davos Declaration"), followed by the adoption of a Roadmap in September 2017 at the UN High Level Meeting on AMR, outlining a common set of principles for global action that focuses on investing in R&D to meet public health needs, reducing the development of antimicrobial resistance, improving access to antibiotics, vaccines and diagnostics, and reducing the environmental impact of manufacturing. These companies subsequently formed the AMR Industry Alliance to drive and report progress against these commitments. In the first AMR Industry Alliance progress report published in January 2018^x, pharmaceutical companies reported the following activities:

- 22 companies collectively invested at least USD 2 billion in 2016 in AMR-relevant R&D.

Policy Position

- Over 80% of all responding companies are engaged in activities to support appropriate use. This includes activities to strengthen prevention through vaccination, surveillance, education of health care professionals and revision of promotional practices.
- Most Alliance companies have access plans including one or several of the following approaches: Tiered pricing strategies (both within and between countries), increased product registration in priority countries, non-exclusive voluntary licensing approaches and product donations.
- A group of 13 companies is leading efforts to reduce the environmental impact from antibiotics manufacturing. A common antibiotic manufacturing framework was published in January 2018 and companies and their suppliers are being encouraged to adhere to it.

A suite of incentives is needed to support sustainable investment in antimicrobial R&D

To overcome the scientific, regulatory, and economic challenges and continue industry’s investments in the global AMR response, a suite of incentives, including both push and pull incentives, is needed. These incentives should be sustainable and sufficient to stimulate R&D across the full R&D lifecycle, from discovery through development, to see an impactful long-term change on the pipeline of new products.

For example, combined together a suite of incentives could: reduce the cost of clinical development and manufacturing (tax credits); provide a guaranteed financial return early in the product life cycle when use is expected to be low to off-set the risk and expense associated with supporting an R&D program (transferable exclusivity extension or market entry rewards); and address barriers to appropriate use and strengthen the market economics (reimbursement and HTA reform).

Figure 1: Suite of incentives



Push incentives*

In the past several years, a series of push mechanisms have been created to incentivize antibacterial R&D (BARDA, IMI, GARDP, CARB-X, etc.). Push mechanisms, primarily targeting pre-clinical and early stage clinical research, help “de-risk” companies’ initial investments by pooling funds and expertise. Adapted incentives should be broad enough to stimulate novel treatments. It should include antibacterials and antifungals but also a variety of associated products with preventative indication such as vaccines, immunotherapeutics, microbiome-targeting products, phage therapies, biologics, biofilm dispersants, and more. Continued regulatory reforms can also help incentivize R&D efforts by harmonizing or converging regulatory requirements while expedited and facilitate pathways will help bring novel antimicrobials to market faster thereby reducing the cost of global development. While push mechanisms are valuable and should be



Policy Position

continued, on their own they will not be sufficient to address the AMR innovation gap. These “push” incentives subsidize R&D efforts, whether successful or not; while this helps reduce the upfront spend needed to be invested in development, it does not have a significant impact on the potential returns from the investment of company or investor funds. Without adjoined, sustainable and robust pull mechanisms that form a complementary suite of incentives, companies will continue to leave the antibacterial development space and the antimicrobial innovation gap will persist.

Box 2: Regulatory tools to support antibacterial R&D

We welcome ongoing efforts made to improve and harmonize regulatory requirements and approval pathways for novel antimicrobial products, including the ongoing development and revision of guidelines in light of emergent medical needs. Increasing adoption of regulatory pathways (such as expedited and adaptive programs) that can facilitate the development of these products should be continued globally. Finally, we are encouraged by the tripartite collaboration between PMDA, EMA, and US FDA to move towards further harmonization on clinical trials designs for evaluating antibacterial drugs. We support additional harmonization between these agencies and would propose future areas of discussion could include: feasibility of disease- or pathogen-based approvals and label indications for both antibacterials and antifungals.

Novel pull incentives^{xi}

Pull mechanisms reward successful delivery of innovation with funding that increases the return on investment and improves the predictability of the return. They incentivize pharmaceutical companies to take on the necessary risk and uncertainty that comes with the research and development of novel products to address AMR. Pull incentives are critical to maintaining a healthy investment ecosystem^{xii}.

IFPMA member companies are aligned on the need for at least one of the two following high-impact novel pull incentives to address the innovation gap:

- **Transferrable Exclusivity Extension (TEE):** Company awarded with an exclusivity voucher that can be used for any other product or sold to other companies. TEEs would be useful for stimulating R&D for both pharmaceutical and biotechnology companies by transferring the value of a product in another therapeutic area to antimicrobial agents.
- **Market Entry Rewards (MERs):** A single or series of payments given to a company that launches a product addressing a pre-identified medical need. Market entry reward would provide significant revenue early in the product lifecycle when product sales volumes are generally low.

Reimbursement and HTA reform^{xiii}

There are opportunities to incentivize antibiotic innovation and stabilize the economics of antibiotic R&D through existing systems. For example, reimbursement reform for hospital-administered antibiotics would enable appropriate access to novel antibiotics by removing barriers posed by bundled-payment mechanisms. Reimbursement reform can complement and reinforce key antimicrobial stewardship components, including the use of diagnostics, de-escalation, regimen monitoring, and surveillance. Payer reform is needed to better capture the societal value of antibiotics in Health Technology Assessments (HTA). These reforms can be undertaken in the short-term within existing systems to improve appropriate patient access and strengthen market the economics of antibiotic R&D. They form an important part of the suite of incentives needed to sustainably stimulate antimicrobial R&D.

Key principles when developing policies to incentivize antimicrobial R&D

- There is no one-size-fits-all solution
- Clear definitions for products that would earn a pull reward are needed
- Market-based drug models should be retained to allocate limited resources and reward successful innovation
- Predictable and sustainable funding is critical
- The societal value of antimicrobial medicines (antibiotics and vaccines) should be reflected in the incentive mechanism
- The impact of the incentive must be sufficient to support sustainable investment in R&D
- Reduce and partially uncouple the proportion of manufacturer revenue that is derived from antibiotic sales volume
- Align with stewardship principles that support global access

Call to Action

Collectively, we need to seize the momentum provided by the UN, G-7, G-20 and the national AMR action plans sponsored by governments around the world to move forward concrete actions on AMR. The IFPMA member companies reiterate the call to action to governments made in the 2016 Industry Declaration^{xiv}. Governments need to implement new and alternative market structures that provide more dependable and sustainable market models for antibacterials and also guarantee availability of associated products that prevent bacterial infections. We are encouraged by discussions in the UK and US that are addressing the reimbursement challenges^{xv,xvi} and pull incentives need^{xvii} with a balance towards appropriate use. However, given the fragility of the market there is an immediate need to implement these and other policy proposals. We urge governments to form a “coalition of the willing” that will pilot the economic models described in this paper. We are ready to work with countries to adapt and help implement such models.

ⁱ Review on AMR, Tackling Drug-Resistant Infections Globally: Final report and recommendations, May 2016. Available at https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

ⁱⁱ World Bank, Drug-Resistant Infections, A Threat to Our Economic Future, March 2017. Available at <http://documents.worldbank.org/curated/en/323311493396993758/final-report>

ⁱⁱⁱ OECD, Antimicrobial Resistance, Policy Insights, November 2016. Available at <https://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf>

^{iv} DRIVE-AB, Revitalizing the Antibiotic Pipeline: Stimulating innovation while driving sustainable use and global access, January 2018. Available at <http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf>

^v Kathy Talkington, David Visi, and Sarah Paulin, The World Is Running Out of Antibiotics, December 2017.

^{vi} S.M. Paul et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat. Rev. Drug Discov. 2010; 9:203-214. Available at <https://www.nature.com/articles/nrd3078>

^{vii} Kinch MS et al. An analysis of FDA-approved drugs for infectious disease: antibacterial agents. Drug Discov. Today 2014; 19(9):1283-7. Available at <https://www.ncbi.nlm.nih.gov/pubmed/25043770>

^{viii} Pew Charitable Trusts. Antibiotics currently in global clinical development, September 2017. Retrieved from <http://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development>

^{ix} AMR Industry Alliance. Tracking Progress to Address AMR, January 2018. Retrieved from https://www.amrindustryalliance.org/wp-content/uploads/2018/01/AMR_Industry_Alliance_Progress_Report_January2018.pdf

^x Push mechanisms move research forward, they help « de-risk » companies' initial investments by pooling fund and expertise.

^{xi} For a more detailed position, please refer to our paper focusing on pull incentives (Paper 2)

^{xii} AMR Industry Alliance, Write-Up on “Delivering the SDGs: Focus on Industry's Actions in the Fight Against AMR”, January 2018. Available at https://www.amrindustryalliance.org/wp-content/uploads/2017/12/Write-up_AMR_Industry_Alliance_Jan18.pdf

^{xiii} For a more detailed position, please refer to our paper focusing on the HTA and Reimbursement reform (Paper 3)

^{xiv} AMR Industry Alliance, Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance, January 2016. Available at <https://www.amrindustryalliance.org/wp-content/uploads/2017/12/AMR-Industry-Declaration.pdf>

^{xv} Sculpher, M. (2018, June). Establishing the value of new antimicrobials: proposed methods for appraisal by the National Institute for Health and Care Excellence in the UK. Presented at the BIO International Convention 2018. Retrieved from <https://www.bioindustry.org/event-listing/sector-event-listing/bio-international-convention.html>

^{xvi} Davies, S. (2017, July). Priorities for tackling antimicrobial resistance and next steps for policy. Presented at the Westminster Health Forum. Retrieved from <http://www.westminsterforumprojects.co.uk/agenda/combating-antimicrobial-resistance-2017-agenda.pdf>

^{xvii} REVAMP Act, June 2018. Retrieved from <https://www.congress.gov/bill/115th-congress/house-bill/6294/text>