Global Principles on Incentivizing Antibiotic R&D

The COVID-19 pandemic has made it very clear that the world needs to be better prepared for global threats posed by infectious diseases. Antimicrobial resistance (AMR), if left unchecked, risks undermining the achievements of modern medicine and taking us back to a time where a simple cut could become lethal. Now, more than ever, we need to accelerate the creation of a vibrant and sustainable innovation ecosystem to support R&D for new antibiotics and other antimicrobials addressing pathogens prioritized by leading public health bodies. We call on governments to deliver new economic incentives, pragmatic antibiotic value assessments, and reimbursement reforms to enable access, that are needed to meet the needs of patients of today and tomorrow.

The Global Threat of AMR

Drug resistant infections are estimated to cause approximately 700.000 deaths each year[i]. The World Bank estimates that drug-resistant infections have the potential to cause a level of economic damage similar to that caused by the 2008 financial crisis. The predicted public health crisis of AMR has been on the agenda of politicians for years, but little action to address the fundamental market challenges has occurred.

The Current Pipeline is Insufficient

A robust, broad pipeline is needed to protect society against emerging resistance by pathogens prioritized by WHO and CDC. Unfortunately, the current pipeline is widely recognized as insufficient. For example, there are currently approximately 40 antibiotics in clinical development, of which only a handful are considered novel[ii], and only one new class of antibiotics has been launched in recent decades. Another 21 non-traditional antibacterial products[iii] and 12 antifungal agents[iv] are currently in clinical development. Because bacteria continually develop resistance to our existing antibiotics, we will always need a robust pipeline of new ones – so it is critical to have sustained investment to keep pace with growing resistance. More investment is also needed into vaccines and diagnostics to help prevent infections and support appropriate use of antibiotics. The market challenges and potential solutions for antibacterial treatments have been well-characterized by leading experts, so this paper focuses on what is needed to address the specific issues there. In addition, solutions that also encourage greater investment into other novel types of products against AMR are needed.

Antibiotics Face Unique Challenges

Given the unique challenges and dynamics of the antibiotics market, distinct measures are needed to establish an economic environment that will incentivize sufficient long-term investment into antibiotic R&D. R&D is generally challenging, with high risks of failure, despite significant investment and scientific expertise applied over many years. However, financial returns for antibiotics are low or negative, even for companies that successfully bring new products to patients.

Antibiotics need to be used appropriately to preserve their effectiveness and slow the development of resistance. As a consequence, many new antibiotics are reserved for last line use, so as to preserve clinical options for patients who fail on existing antibiotics. This unique “last line use” dynamic remains in place until another new antibiotic is introduced and it leads to almost insurmountable financial challenges for companies delivering new antibiotics and other antimicrobials to patients. As a result, companies responsible for developing one in three new antibiotics in the last decade have gone bankrupt[v] and many private and venture capital companies have exited the area. The current antibiotic pipeline is very fragile and new antibiotics may not be approved, launched, or made available to patients in many countries[*]. In addition, even when antibiotics are available in a country, reimbursement systems often discourage the use of new antibiotics largely due to cost, even when they are the most appropriate treatment choice for a patient.

Currently, the value society and healthcare systems place on antibiotics is low. With their current pricing and reimbursement systems, governments and payors are sending a clear signal that investing into R&D for new antibiotics is not a priority, despite the clear public health risks from increasing resistance.

[*] The differences between countries can be stark - for example, while 16 new antibacterial treatments have been launched in the US since 2010, only 2 have been launched in Japan, and only 2 have been approved (and only 1 launched) in Canada. 13 of the 16 have been approved by the European Medicines Agency but some have not launched or are not available in all EU countries.

Industry is taking action on AMR

The biopharmaceutical industry can play a key role in addressing AMR. In the 2016 Davos Declaration, over 100 life-sciences companies and associations committed to invest into antibiotic R&D, reduce inappropriate use of antibiotics, improve global access, and reduce environmental discharge from manufacturing.

In July 2020, 23 biopharmaceutical companies partnered with non-governmental stakeholders to respond to this urgent threat by launching a USD 1 billion AMR Action Fund with a goal of delivering up to 4 novel antibiotics by the end of the decade. The AMR Action Fund will provide much-needed support and investment for the complex and expensive later stages of development – temporarily sustaining the fragile antibiotic pipeline, which is close to collapse, and preventing promising early-stage assets supported by recent push funding from governments and others from withering on the vine. While the Fund itself will not solve the economic challenges, it will provide governments with the time to make the necessary economic policy reforms needed to build a vibrant and sustainable antibiotic pipeline.

The Proposed Way Forward

Each of the issues described can be addressed through concerted and aligned action worldwide by governments working with industry and other stakeholders. 2025 will mark ten years since the adoption of the WHO Global Action Plan (GAP) on AMR: we need to accelerate progress to address the "sustainable economic case" objective of the GAP before then. We therefore call on all countries to take steps now to deliver a clear implementation roadmap by the end of 2021, make meaningful progress in implementation by 2023, and ensure full and effective implementation by 2025 at the latest of:

1. **New economic incentives,** giving confidence to the private sector to invest in R&D at the level needed to create a robust antibiotic pipeline.
2. **Bespoke valuation of antibiotics,** assessing and recognizing the full value antibiotics deliver to society and correcting their current under-valuation, and
3. **Reimbursement reforms**, to maintain availability of antibiotics on the market and to enable patient access to the most appropriate antibiotic to treat or prevent their infection.

While the solutions to these challenges will look different in different countries – there is no "one size fits all" – this supportive policy framework is necessary to drive long-term investments in innovative antibiotics, throughout the discovery, development, and product lifecycle. In this paper, we propose a set of principles and models to establish such a framework, and we make an urgent call to Governments to drive these reforms to implementation, thereby delivering on recent G7 and G20 commitments.

Principles for Policy Changes to Foster a Sustainable Pipeline

We propose the following principles to guide policymakers in creating the framework to attract sustainable and robust investment for antibiotic R&D, based on new economic "pull" incentives:

1. Policy solutions should be implemented urgently by all countries within the G7 and beyond to ensure we are protected against emerging resistance into the future.
2. Governments have a responsibility to design and implement a package of incentives and reforms, tailored to their health care financing and delivery systems, that:
    a) attracts sustainable and robust R&D investment into new antibiotics and other antimicrobials
    b) fully recognizes the medical and societal value that antibiotics deliver
    c) ensures that patients and health care professionals (HCP) have appropriate access to new antibiotics and other antimicrobials
3. There is no one-size-fits-all solution, and all countries have a role to play.
4. To design and implement a package of incentives, governments need to:
    a) Define their key unmet medical needs, to inform their selection criteria for new incentives. For example, these could focus on new, innovative products that address the priority pathogens identified by the WHO and/or CDC.
    b) Clearly define how these new antibiotics will be:
        - Purchased, reimbursed and/or incentivized via other payment mechanisms that reduce the proportion of manufacturer revenue needed to be derived from sales volumes.
        - Valued to reflect the broad medical and societal benefits they provide; and

- Accessible and used appropriately by HCPs, based on up-to-date clinical guidance, patient-centered stewardship, and supportive reimbursement systems.

c) Ensure predictable and sustainable funding of novel incentive mechanisms for the long-term.

5. Foster successful innovation in a competitive market environment.
6. Globally, the total impact of these incentive packages must be sufficient to attract vibrant and sustainable investment in R&D by delivering a sufficient rate of return, and flexible enough to account for different health care financing mechanisms to reinvigorate the antibiotic R&D ecosystem.

What Could These Models Look Like?

There is broad alignment across academia, policymakers, and industry, on the promising models that could deliver to the above set of principles. Crucially, these models only reward successful development of high-value new antibiotics and may provide a source of revenue not derived from sales volumes, helping to align incentives with efforts to promote appropriate use of antibiotics. In all these models, the private sector continues to take on the significant investment and risk of failure in developing a novel antibiotic.

New economic incentives

Key for success will be the establishment of new economic incentives which reward successful innovation at a level sufficient to attract further R&D. These "pull" incentives could be delivered in a single payment or through annual subscription payments, in both cases triggered by the product's regulatory approval and launch. Companies receiving payments would agree how they would supply and support their product in each country as part of the incentive system.

Both types are being explored in different geographies and they are not mutually exclusive. Examples of **single payment** incentives include market entry rewards (MER), in the form of a defined payment upon market approval, or a transferable exclusivity extension (TEE), which rewards a company with a transferable exclusivity voucher that can be used for any other product in its portfolio or sold to another company. **Subscription models,** sometimes referred to as the "Netflix model", have received increasing attention as a promising method to enable timely and appropriate access for patients, provide budget predictability, and provide a predictable and sustainable return on investment for the innovator company. Annual payments are agreed between the purchaser and the company, and the antibiotic is provided as and when needed to meet appropriate medical demand. Other novel forms of contractual agreement can also be considered.

Several studies have estimated the amount of incentives needed globally in the range of USD 1 to USD 4 billion [vi, vii, viii, ix, x] for each new antibiotic successfully launched. Some recent proposals and pilots have likewise postulated specific rewards, including of up to USD 4 billion globally – for example, the recent draft PASTEUR Act proposes awards of between USD 750 million and USD 3 billion per novel antibiotic for the US incentive alone[xi]. Similarly, the UK has noted that their pilot subscription model payment, if scaled globally, would have a value of between USD 3.5 and USD 4 billion per novel antibiotic over 10 years[xii].

Bespoke antibiotic value assessments

Stakeholders recognize that the value antibiotics deliver to patients, healthcare systems and to society is not captured today by most national value assessments. Appropriate valuation systems for novel antibiotics will be very important to quantify the new economic incentives and to signal to investors that renewed investment in antibiotic R&D will generate returns for shareholders. Countries around the world use different valuation systems – broadly based on a product's benefits assessed by health economic and clinical outcomes and product attributes – and these systems must be corrected to capture the value of antibiotics sufficiently to restore supply.

It is recognized that new antibiotics and other antimicrobials deliver unique value that goes beyond individually treated patients. For example, they help control transmission of resistance and are essential enablers of other medical procedures including surgeries, chemotherapy, and transplantation, as well as provide broader "insurance value" against resistant infections (e.g. outbreaks, increases in prevalence). Capturing this value requires changes to standard valuation models, which have been described in detail (for example by OHE[xiii] and EEPRU[xiv]). Several countries are starting to re-examine the way they assess new antibiotics, including the UK and South Korea. While these are moving in the right direction, methodological challenges remain, and more work is needed to integrate

these new value elements into pricing and reimbursement decisions.

Policymakers can help companies focus investment by upfront assigning value directly to attributes new antibiotics may have. For example, as part of proposals like the draft PASTEUR Act in the US, new antibiotics that meet certain criteria or with certain attributes – targeting priority pathogens, novelty, additional indications, formulation, etc. – would be eligible for higher payments.

Reimbursement reform to enable patients to access the antibiotics they need

Reimbursement plays a key role to enable patient access to novel antibiotics. If combined with appropriate valuations, reimbursement reform could play a role to stabilize the antibiotics market. In many countries, reimbursement reform is needed to ensure that HCPs are able to prescribe the most appropriate antibiotic for patients. For example, the proposed US DISARM Act seeks to address this issue by making a separate payment to hospitals for qualified antibiotics outside of the bundled payment amounts paid for inpatient services. Given current rates of resistance, reimbursement reforms on their own may not create the economic conditions needed to attract significant new R&D investment. They would, however, encourage companies to bring their new antibiotics to market and would create a pathway for new antibiotics to reach the patients who need them.

Call to Action and Key Considerations

Collectively, all stakeholders need to seize the political momentum to protect our societies against future outbreaks of infectious disease, including AMR, which should also be part of national and regional pandemic preparedness plans. The significant mobilization of innovation by the biopharmaceutical industry responding to COVID-19 has demonstrated what a robust private-sector ecosystem is able to achieve. The activities of the UN, G7, G20, and governments around the world are also critical for progress and long-term solutions.

We, the biopharmaceutical industry, stand ready to work with leading governments to design, pilot and implement new incentives and market reforms. We recognize that implementing a package of incentives to address the different challenges to antibiotic development and commercialization is a complex undertaking. But if we work together to implement the reforms proposed in this paper in all countries (new incentives, bespoke value assessments, and reimbursement reforms), we will be able to succeed and will see increased investment into all stages of R&D, a robust and sustainable pipeline of new antibiotics and other antimicrobials addressing highest unmet needs, and new antibiotics that are launched widely and available to the patients who need them.

We therefore call on leading governments to engage with us and deliver:

1. A clear roadmap for the development and implementation of new economic incentives and market reforms along with milestones and institutional responsibilities, by the end of 2021 at the latest.
2. Annual progress updates against the roadmap.
3. Action now to ensure meaningful progress in implementation by 2023, and full and effective implementation by 2025 at the latest, of:
    - New economic incentives to attract antibiotic R&D investment and launch.
    - Bespoke valuation system for antibiotics that recognizes the full value they provide our societies.
    - Reimbursement system that encourages access to new antibiotics by removing barriers.

---

[i] Review on AMR (2014). Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Retrieved from: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf

[ii] 2019 antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline (2020). Retrieved from: https://www.who.int/publications/i/item/2019-antibiotic-agents-in-clinical-development-an-analysis-of-the-antibiotic-clinical-development-pipeline

[iii] Nontraditional Products for Bacterial Infections in Clinical Development (2020). Retrieved from: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2017/nontraditional-products-for-bacterial-infections-in-clinical-development

[iv] J. Gintjee T., A. Donnelley M., R. Thompson G. Review: Aspiring Antifungals: Review of Current Antifungal Pipeline Developments. *J. Fungi 2020, 6, 28*. Available at: https://www.mdpi.com/2309-608X/6/1/28/pdf

[v] The antibiotic paradox: why companies can't afford to create life-saving drugs (2020). Retrieved from: https://www.nature.com/articles/d41586-020-02418-x

[vi] DRIVE AB Report - Revitalizing the antibiotic pipeline (2018). Retrieved from: http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf

[vii] O'Neill, J. (2016). Tackling Drug-Resistant infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. Retrieved from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

[viii] Boston Consulting Group (2017). Breaking through the wall: A call for concerted action on antibiotics research and development. Retrieved from: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf

[ix] Review on antimicrobial resistance. (2015) Securing new drugs for future generations: the pipeline of antibiotics. Retrieved from: https://amrreview.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf

[x] Seabury S., N. (2017). Toward A New Model For Promoting The Development Of Antimicrobial Drugs, Health Affairs Blog. Retrieved from: https://www.healthaffairs.org/do/10.1377/hblog20170518.060144/full/

[xi] Draft PASTEUR Act (30 September 2020). Retrieved from: https://amr.solutions/wp-content/uploads/2020/09/PASTEUR-Act-30-Sep-2020-draft.pdf

[xii] NICE/NHS Frequently Asked Questions: developing and testing innovative models for the evaluation and purchase of antimicrobials (2020). Retrieved from: https://amr.solutions/wp-content/uploads/2020/03/2020-04-03-NHS-England-Procurement-FAQs-FINAL.pdf

[xiii] Neri, M., Hampson, G., Henshall, C. and Towse, A., (2019). HTA and payment mechanisms for new drugs to tackle AMR. OHE Research Paper, London: Office of Health Economics. Available at: https://www.ohe.org/publications/hta-and-payment-mechanisms-new-drugs-tackle-amr#overlaycontext=publications/hta-and-payment-mechanisms-new-drugs-tackle-amr

[xiv] Rothery C., Woods B., Schmitt L., Claxton K., Palmer S., Sculpher M. 2018. FRAMEWORK FOR VALUE ASSESSMENT OF NEW ANTIMICROBIALS (2018). Available at: http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf