European Union Leadership Crucial for Affordable & Responsible Antibiotic R&D

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I. Introduction

Antimicrobial resistance (AMR)[i] is a global threat, which refers to microbes becoming resistant to antimicrobial medicines developed to treat them. Every time an antibiotic medicine is used, it increases the possibility of the microbe becoming resistant. Currently, AMR causes an estimated 25,000 deaths per year in the European Union (EU) and 700,000 worldwide.[1]

AMR is a pressing threat to the world's sustainability and development efforts.[2] For some countries, the era of effective antibiotics will soon end. Much of the global overuse of antibiotics occurs in low- and middle-income countries (LMICs) where the drivers are magnified by a lack of access to effective antibiotics[3], unregulated antibiotics sales and availability, and limited regulatory enforcement of aggressive antibiotics marketing practices by pharmaceutical companies.[4] AMR has far-reaching implications for many of the United Nation's (UN) Sustainable Development Goals[5]; it could undermine global achievements in health, development, poverty reduction and economic growth sectors.[6]

Tackling the rise of AMR is high on the political agenda. The World Health Organization (WHO) issued its *Global Action Plan on AMR*; the UN convened a high-level meeting in September 2016, which resulted in a *Political Declaration on AMR*; and AMR has been recognised as a crucial international public health threat by the G7 and the G20. In Europe, the EU will soon launch its second *EU Action Plan on AMR*, including support for research and innovation.[7] Individual EU Member States, particularly the Netherlands, the United Kingdom (UK) and Germany, are leading the charge to tackle AMR.

Many factors contribute to AMR, including the lack of preventive measures to avoid infections, inappropriate and routine use of antibiotics to promote growth in food production and animals, and the lack of development of proper new antibiotics. Affordability of existing antibiotics is still a problem in many LMICs. While the 'One Health' approach must be implemented to effectively address the interrelated factors that contribute to AMR, this policy brief provides key recommendations for the EU and EU Member States to develop antibiotic research and development (R&D) initiatives that result in affordable and appropriately used novel antibiotics.

Many ongoing initiatives in antibiotic R&D exist at the global, EU and EU Member State levels; however, there is little alignment between them. Furthermore, most, if not all, of these R&D initiatives lack the necessary conditions to ensure appropriate use of newly developed antibiotics. Conditions that ensure affordable patient access despite an often substantive public contribution to R&D are also lacking.[8] Most antibiotic R&D efforts will originate in the EU and the United States (US) because they are home to leading research centres. It is therefore crucial to insert a 'social justice' perspective of equity when developing new innovation models for antibiotic R&D. This will ensure that valuable new antibiotics are also available, affordable and suitable for people in LMICs.

As a leader in antibiotics research, the EU and its Member States must lead the way in shaping truly innovative antibiotic R&D efforts to respond to this urgent global crisis.

[i] We acknowledge that the term AMR also includes non-bacterial infections; however, this policy report only addresses the issue of antibiotic resistance.

II. Need for High-quality Antibiotics, Vaccines & Diagnostics

Despite the urgent need for new antibiotics, few new classes of antibiotics have been discovered and developed since the 1980s.[9] The current R&D pipeline is not promising; most pipeline products consist of reiterations of existing classes that will become resistant soon after they arrive on the market.[10]

Truly novel, safe, effective, affordable and quality antibiotics are needed to address the WHO's priority list of antibiotic-resistant bacteria.[11] The total number of novel antibiotics reaching the market is less important than the therapeutic value of the antibiotics.[12] Investment in getting new antibiotics onto the market is important; however, R&D investment in health technologies that prevent clinical failure from occurring, as well as the reduction of antibiotic use, is also critical. Most importantly, new and improved rapid point-of-care diagnostics to reduce unnecessary antibiotic use, along with novel vaccines to prevent infections and lower demand for antibiotics, are also urgently needed.[13] In the US, for example, almost 67 percent of the 40 million people who are prescribed antibiotics for respiratory issues are given them unnecessarily.[14]

The best way to ensure that R&D investments meet global priorities is to develop prospective 'target product profiles' (TPPs) to guide priority setting in global R&D investments for new antibiotics, diagnostics and vaccines[ii].[15] The UK's Review on Antimicrobial Resistance by the O'Neill Commission explained that this is "the most effective way to ensure that R&D is directed towards areas that pose the greatest risk for the future."[16] It is crucial, however, during the development of TPPs that all needs are properly reflected so developed products are suitable to conditions in LMICs. For this purpose, global coordination through, for example, the WHO in cooperation with its Member States, is crucial for developing these TPPs.[17]

III. Delinkage for Access, Conservation & Needs-driven Innovation

In addition to the scientific challenges of developing new antibiotics, there are two reasons the current patent-driven business model for developing medicines is inappropriate. First, short treatment courses and relatively low prices for antibiotics make it a commercially unattractive market. Unsurprisingly, most large pharmaceutical companies have pulled out of antibiotic R&D.[18] Second, a mismatch exists between this business model and limiting use to combat resistance.[19] Under a patent-driven model, companies push for high antibiotic use to recover R&D costs during their monopoly protection periods.

> "Due to resistance, three things are simultaneously necessary for antibiotics: access, stewardship and innovation. Access alone would drive resistance; stewardship alone would hinder access and delay innovation; innovation alone is wasteful unless we make plans to preserve antibiotics and get them to the people who need them most. Antibiotic delinkage proposals are the best way to achieve all three of these aims simultaneously."
>
> Kevin Outterson, Law Professor, Boston University, and Executive Director, CARB-X

To effectively deal with these failures, consensus exists that an entirely new business model to finance antibiotic R&D—one that 'delinks' the price and volumes of antibiotic sales from the costs of R&D—is needed. This would replace the traditional patent-based R&D incentive model and would be imperative for eliminating the financial

[ii] Throughout the remainder of this report, when we refer to new antibiotics, we also mean new vaccines and diagnostics.

incentive to oversell and market new antibiotics. Under a 'delinkage model', different mechanisms, used individually or in combination, can be used to finance R&D. This may include direct funding, subsidies, and incentives based upon prize (cash) rewards.[20]

A delinkage model to finance the development of new antibiotics can—and should—be shaped to:
1. drive innovation towards the development of high-quality antibiotics (needs-driven innovation);
2. ensure affordable and equitable access (equitable access); and
3. guarantee appropriate use (conservation).

Without such conditions, delinkage proves to be nothing more than another direct subsidy pouring money in a broken innovation model.

In the following section, we further explore how these three elements can be secured in an alternative incentive model for antibiotic R&D.

IV. Key Elements of Antibiotic Delinkage R&D Proposals

Needs-driven Innovation

Any new antibiotic R&D incentive should be shaped to drive R&D investment towards global priority R&D needs. These include high-quality antibiotics, vaccines and diagnostics, defined by the WHO in TPPs, that address the specific needs of LMICs. A recent study by the London School of Economics found that, at the international, EU and national levels, there are currently more than 60 ongoing initiatives funding R&D into antibiotics, vaccines and/or diagnostics.[21] There is a worrying lack of coordination and information sharing between these initiatives, which leads to the duplication of research (including clinical trials) and inefficient public spending. Right now, for example, there are three small prize awards for new diagnostics in this area, including awards from the UK and the EU, but no coordination between these initiatives.[22]

R&D incentives that embrace the principle of delinkage can be shaped to respond to the urgent need for prioritisation by replacing the traditional reward of market exclusivities (such as patents or market/data exclusivity) with a monetary reward for the R&D efforts involved. This could include, for example, only granting rewards for R&D efforts if the outcome corresponds to the predefined targets of the TPP, or is demonstrably superior. Smaller grants could be rewarded for new antibiotics of lesser priority.[23]

At the same time, the amount of the offered reward for each stage in the development cycle should be designed to sufficiently attract all relevant R&D actors, including small- and medium-sized enterprises (SME) in the pharmaceutical and biotechnology sectors. Such targeted early-stage rewards can be smaller than late-stage rewards.[24] Rewards could also be tiered by providing a minimum reward for initial introduction and additional rewards if the new antibiotic proves effective. Moreover, the amount of the reward for reaching a milestone, or bringing a new antibiotic to market, should be adjusted based on the financial public support (e.g., grants, subsidies, tax credits) that the compound may have received earlier in the development process.[25]

Equitable Access

Today, more people still die from lack of access to effective antibiotics than from AMR. By 2050, over 90 percent of the estimated 10 million annual AMR-related deaths are expected to occur in LMICs.[26] Paradoxically, these countries still require improved access to antibiotics and, in most

cases, are least able to finance stewardship efforts due to weak health systems and resource limitations.[27] Ensuring universal appropriate access to effective antibiotics is not only a critical part of realising the right to health; it is necessary for mobilising effective collective action against the development and spread of AMR.[28] Appropriate access to antibiotics raises and exacerbates a number of ethical challenges surrounding individual liberty to protect one's health and global distributive justice, as well as our responsibility for the well-being of future generations.[29]

Since affordability of existing antibiotics is still an issue in LMICs, particularly when treating resistant infections[30], new R&D initiatives must enable affordable access to resulting new antibiotics, vaccines and diagnostics for everyone in need despite their ability to pay.

To ensure affordable access down the line, public R&D investments in developing new antibiotics need conditions that require pro-public health management of research results, including intellectual property (IP) rights. First, as a precondition for granting funding, data and reports should be made publicly available at a defined point in time to facilitate follow-on research and early identification of potential follow-on research targets. In addition, any resulting IP should be licensed to generic manufacturers on a conditional, non-exclusive basis.[31] The non-exclusive nature of the licence would rule out monopoly pricing of new antibiotics by enabling generic competition from the moment of market introduction.

Public ownership of IP through, for example, a patent buy-out as a condition of the R&D reward, would enable such pro-public health management of results through managed access.[32] In that scenario, a public body would manage the IP to ensure affordable access and appropriate use. A public health authority would not be restricted by misaligned commercial incentives to sell and market a new antibiotic in the same way as a company. For this reason, a public body would be better placed to ensure sustainable access and conservation efforts. Given the need for global coordination of conservation of new antibiotics, and the high transaction costs involved if each government separately negotiates these buy-outs/licences, this management could be hosted by an international public body or secretariat. The Medicines Patent Pool is an example of an existing international public body that manages IP for HIV/AIDS treatments and, most recently, for hepatitis C and tuberculosis.[33] IP could be transferred or licensed to such a patent pool, which can manage IP rights transparently and coordinate global access and conservation.[34] In a funding model where the IP is privately owned, the grant/reward can precondition the same kind of IP management conditions on the recipient.

However, the generic model of low prices and high volume does not pair well with the need to conserve new antibiotics. Moreover, when the IP expires and the product becomes generic, the IP protection can no longer be used to leverage conservation by the companies involved. This means additional measures must be implemented to restrict and supervise generic manufacturing and ensure appropriate distribution and use.

This pro-public health management of results, including IP, must be included as an end goal early in the development process by making this a condition for receiving R&D grants in the first phases of R&D (e.g., basic research). If not, companies enjoying this upstream public funding may decide not to engage in later stage grants. In that case, they would not be bound by the IP management rules and governments would be left without leverage to require affordable access and stewardship. These requirements are so crucial that we cannot afford to trust voluntary cooperation down the line; therefore, this needs to be a binding commitment throughout the

development process of new antibiotics. R&D incentives must be sufficiently large to compensate for these IP management conditions.

However, in the context of LMICs, affordable access also means having the necessary health infrastructure in place to treat patients, especially because effective stewardship and conservation of new antibiotics fundamentally rests on a much stronger health system in developing countries. Strategies to address truly equitable antibiotic access should then also emphasise the need for action to improve health system performance.[36] The appropriate use of antibiotics and the introduction and scale-up of new diagnostics and vaccines relies heavily on strengthening health systems. To ensure technical assistance is available to guarantee real access in LMICs, public R&D grants that require affordable access should ideally include additional revenue streams for conservation and access in low-income populations.[37] For example, payments could go into the proposed Global Antimicrobial Conservation Fund for LMICs.[38]

Tiered Pricing Not Appropriate for Equitable Access

Some suggest using tiered or differential pricing as a tool to increase access in LMICs; however, tiered pricing does not reflect the true lowest potential price of medicines, nor provide the public health benefits of generic competition. It is primarily a commercial strategy that allows pharmaceutical companies to maximise their profits in all countries because prices are often determined based on the highest price a country, or a segment of a country, is prepared to pay. As a result, tiered pricing may lower the price that LMICs pay, but that price would still be considerably higher than the price reached through generic competition. Without robust pressure against companies setting differential prices by consumers through (international) pooled procurement, tiered pricing will not provide effective lower prices.[35]

Conservation

Globally, the overuse and inappropriate use of antibiotics is a key driver of antibiotic resistance.[39] Even within Europe, large differences remain between countries regarding the consumption of antibiotics.[40] Antibiotic conservation aims to preserve the effectiveness and longevity of antibiotics through the dual approach of reducing the need for antibiotics and optimising their appropriate use. We already know that, in some cases, antibiotics are used to treat infections for which they have no effect. 'Broad-spectrum' antibiotics are prescribed in place of a targeted antibiotic, and antibiotics are often used incorrectly by the patient.[41] In addition, key antibiotics are sometimes withdrawn from the market for commercial reasons, such as when the market is considered too small. This leads to sub-optimal use of antibiotics that remain on the market.[42]

Evidence-based policies that enhance the sustainable use of antibiotics, along with measures that reduce the need for antibiotic use, are needed. These measures include improved sanitation and hygiene, education on appropriate antibiotic use, strong regulation of antibiotic marketing and use, and enhanced diagnostic testing to ensure proper treatment.[43] Better surveillance and monitoring of resistance patterns and drug susceptibility of bacteria in countries is also needed to inform clinical treatment guidelines. To be truly sustainable, such solutions must be based on the principle that antibiotics are a global good and societal ownership requires transparent commitments from a broad spectrum of actors in the public, private and civil society sectors.

Under an R&D model of delinkage for antibiotics, revenues for the developer are delinked from sales volumes, so the incentive to market or promote new antibiotics is fully removed. This is an important component because the commercial incentive to maximise sales volumes conflicts with the public health goal of controlling sales to ensure appropriate use and conservation. In addition,

delinkage could be used to make companies responsible for receiving the financial reward for conservation through IP management conditions. That said, this would only be a time-bound solution for as long as the IP runs. Once the IP expires, any generic producer would be allowed to produce and sell the antibiotic. These producers would not be bound by the conditions that governed the production and sales by the recipient of the initial grant. It is therefore crucial to explore how a delinked R&D model—where results (including IP) are preferably managed by a public body—can be coupled with measures designed to control the number and quality of global producers of any resulting new antibiotic and to control sales and distribution routes through pooled procurement and reimbursement policies. This would require companies to give up sales entirely and ensure that conservation responsibilities instead rest with a public health authority. Developing and implementing such measures requires global management by public health and regulatory authorities.

In addition to making companies responsible for contributing their part, payers and public authorities bear the largest burden for ensuring appropriate use. For example, reimbursement policies could be a powerful tool to change behaviour. When the IP expires and the product becomes generic, affordability is no longer an issue because generic competition will generally keep prices affordable. It also means, however, that the IP protection can no longer be used to leverage conservation by the companies involved. In addition, for this reason, it is important to explore how national payers and regulators can find a different model to buy and distribute antibiotics and explore how reimbursement can be linked to conservation goals.[44]

As most antibiotic R&D efforts will originate in the EU and the US, the EU has an important role in establishing an innovation model that supports conservation efforts at the global level—one that avoids relying on incentives that contradict this goal. This will respect the principles of health equity and contribute to mitigating the risk posed by the transnational migration of resistant microbes. The EU not only has a key role in assisting Member States in implementing national action plans on AMR; it should also seize the opportunity to create a repository of transferable best practices to support target setting, surveillance and harmonised data reporting globally. Efforts that focus on conservation must recognise the country-wide and system-level effects that interventions will have.[45]

Importantly, conservation efforts should not restrict access to antibiotics. The EU and other regions must commit to developing and implementing technology and building capacity in LMICs to fulfil national action plans that contribute to achieving the UN's Sustainable Development Goals.[46]

V. Assessing the Mechanisms to Incentivise Antibiotic R&D: Access, Stewardship & Needs-driven Innovation

A number of 'push' and 'pull' investment mechanisms have been proposed as the way forward for antibiotic R&D; however, some are more appropriate than others to incentivise antibiotic R&D in priority areas and ensure affordable access and conservation. The following section assesses these mechanisms.

Push Mechanisms

Direct Funding / Conditional Grants

Direct funding is generally regarded as the most appropriate R&D incentive for earlier stages of antibiotic development where a high risk of failure exists. This research phase also has the greatest potential for scientific bottlenecks, so additional targeted funding is often urgently needed.

Direct grants, which lower R&D costs, attract large players, as well as SMEs and academia. In addition, conditional grants would allow for specific R&D priorities to be targeted, and for conservation and affordable access commitments to be realised if the research results in a successful new product.[47] As in the research phase, the risk is greatest for the grant provider. The relative value of this type of grant is high, compared to funding of later drug development stages.[48] The push value of the direct grant can be further enhanced by requiring open access to research results as a condition for receipt of the funding. Open access to data can lower antibiotic research costs. It can also accelerate research by early identification of potential targets for further research. This facilitates collaboration and knowledge sharing between drug developers and prevents wasteful duplication.[49]

Direct grants can be provided in different modalities: Through direct funding of companies and research institutes, or dispersing funding through a public private partnership (PPP), such as the Innovative Medicines Initiative 2 (IMI2), or a public health-driven product development partnership (PDP), such as the recently established Global Antibiotic Research and Development Partnership (GARDP)[50]. To ensure that the grant results in public health-oriented antibiotic drug development, it is crucial that the grant is subject to the conditions described above. Currently, in EU-funded projects for new antibiotics, vaccines and diagnostics, such as those under IMI2, no such conditions are attached to funding antibiotic R&D. This is unacceptable given the urgency of AMR; however, the recently established and publicly funded GARDP promises to ensure both access and conservation of resulting new products. This demonstrates the ability for access and stewardship conditions to be attached to public antibiotic R&D funding when political will exists.

Tax Incentives

Granting tax incentives to companies is another potential push mechanism to stimulate the development of new antibiotics. While they are politically stable and easy to implement,[51] tax incentives seem to offer little in setting conditions to direct R&D towards priority R&D needs and ensuring global access and conservation commitments. They, however, can be useful as a politically stable funding stream connected to other incentive mechanisms, such as prize proposals (described below).

Pull Mechanisms

IP Incentives: Longer Exclusivities / Transferable IP Rights

A pull mechanism used to incentivise biomedical innovation is the granting of additional monopoly protection through the extension of IP or related exclusivities (market/data exclusivity). Its use, however, for antibiotic R&D is inappropriate because it does not delink development costs from the price of the new product; therefore, it cannot be used to set conditions to make global access and conservation a requirement. In addition, revenues under this model are based on sales volumes, so longer protection will only add to the incentive to promote (over)use of new antibiotics to monetise the product before this protection period expires. Longer monopolies also lead to a longer period of higher prices that limit patient access, which is particularly problematic in LMICs.[52]

To overcome this risk of further incentivising antibiotic sales, transferrable IP rights have previously been used. This refers to the practice in which the company receives the right to extend its monopoly protection for another product upon successful development of a new antibiotic. However, this simply places the burden of high prices on another group of patients. Moreover, when previously used, this mechanism has been unfair and inefficient.[53] For example, the US's Generating Antibiotics Incentives Now (GAIN) Act, which offers five additional years of exclusivity for new antibiotic development, has resulted in little antibiotic innovation and increased costs for

patients. In addition, it does not address the need for affordable access to, and conservation of, new antibiotics.[54]

Reducing Regulatory Barriers: Fast Tracking / Priority Review Voucher

It is also suggested that further reducing regulatory requirements for marketing authorisation of new antibiotics (e.g., by allowing more limited clinical trials) will reduce R&D costs and incentivise antibiotic innovation. However, in the EU and the US, regulatory requirements for testing new antibiotics for patients with multi-drug-resistant pathogens have already been lowered.[55] Lowering regulatory standards may increasingly compromise safety and efficacy of resulting antibiotics, which is unacceptable.[56] Alternatively, drug developers of a new antibiotic can be granted the right to accelerate drug approval of another medicine in their portfolio, referred to as a 'priority review voucher'. Again, this raises concerns about the safety and efficacy of these other fast-tracked medicines.[57]

Inducement Milestone or Lump Sum Monetary Prizes / Market Entry Reward

Prizes, or the similar 'market entry reward', proposed in the O'Neill Report, are outcome-based pull mechanisms. They are efficient because they only reward a successful developer. They can be designed to reward mid-term milestone results, or only be paid upon market entry of a new antibiotic, or both. The larger end-prizes generally attract larger companies. This is less the case for milestone prizes at earlier stages of development that can also attract academia and SMEs.[58] Prizes allow for incentivising antibiotic innovation in priority areas, and for imposing conditions requiring global access and conservation commitments upon reward of the grant.[59] Prizes are generally regarded as most suitable for later stage research, where there is less uncertainty. As most of the risk of failure is borne by the developer, the prize must be sufficiently large to reflect this risk.

It is, however, challenging to develop TPPs to describe the end product that will trigger the prize award in such a way that they are neither too general, nor too specific. Payment of the prize/market entry reward should also be free from political risk, as companies need certainty that the grant will remain available if the political landscape changes.[60] [61] Given the political stability of taxation as a financing mechanism, it would be interesting to explore linking the financing of the prize mechanism with taxation. Despite these challenges in implementation, prizes seem the most effective pull mechanism for later stage research to promote antibiotic innovation in priority areas and to ensure global affordable access and conservation of the products that are rewarded.

VI. Need for Hybrid R&D Model that Implements Delinkage Through Conditional Grants & Prizes

Different stages in the drug development cycle require different incentives. There is consensus that to successfully drive R&D in the area of antibiotics, a hybrid model combining push and pull R&D incentives must be used.[62] In the earlier basic research phase, push incentives in the form of conditional grants seem to be most appropriate given the high level of uncertainty. The conditional nature of the grant allows for targeting specific R&D priorities and adding conservation commitments and affordable access if the research results in a successful new product. In addition, the grant can be designed to promote the use of collaborative and open innovation models to further enhance research and uptake of results. Further down the development chain, and especially in Phase III clinical trials, prizes seem the most effective pull mechanism to promote antibiotic innovation in priority areas and ensure worldwide affordable access and conservation of

rewarded products. Prizes/market entry rewards cannot stand alone, however. They do not incentivise retrospectively enough in the development phases. In addition, without a dramatically improved pipeline and investment in discovery and early stage research, there will be nothing worth 'pulling' out of the pipeline for years to come.

However, until now, the EU and its Member States have not sufficiently explored the proper use and implemention of delinkage as a pathway to affordable access and conservation through the use alternative antibiotic R&D mechanisms. The European Commission, in its multi-annual R&D funding framework, Horizon 2020, has delivered only one prize, called Better Use of Antibiotics. This €1 million prize, which was awarded in 2016, focused on ideas to develop and/or bring to market a test to quickly identify whether a patient can be treated safely without antibiotics. At the current funding level, such a prize is more a signal of recognition than an incentive that seeks to spearhead breakthrough development in an underserved area. The European Commission also fails to make affordability a mandatory condition of eligibility for the prize. Adapting the conditions to prioritise affordability as a compulsory selection criterion would send a strong signal to developers to ensure affordable access is included in the design and planning phases of their work.[iii]

Through IMI2, the European Commission also funds the 'DRIVE-AB' initiative, which examines alternative models for antibiotic innovation and responsible antibiotic use.[63] However, despite considerable public investment from the EU of more than €6.2 million over three years, concrete, innovative thinking around alternative R&D models for new antibiotics has not been demonstrated. More importantly, pharmaceutical industry involvement in the development of conditions for an alternative R&D model (for which they will be a recipient of public funding) raises concerns about conflicts of interest in the design of DRIVE-AB.

What is promising is that the not-for-profit product development partnership, GARDP, will pilot the use of alternative incentive models that delink the cost of R&D from volume-based sales and prices of antibiotics, which supports conservation of, and access to, new antibiotics.[64] Other interesting proposals on delinking antibiotic R&D through prizes/market entry rewards include the 3P Project for tuberculosis from Médicines Sans Frontières[65] and the market entry reward proposed in the O'Neill report into AMR.[66]

Generally, however, these proposals only address later stages of development; there is insufficient targeted research into how early stage push R&D incentives could be shaped to improve the antibiotics pipeline. For new antibiotics to succeed, an effective alternative model for antibiotic R&D must address the failings at all levels of the R&D ecosystem.

VII. Conclusions & Recommendations

The EU and its Member States are influential actors in antibiotic R&D. They therefore have the potential and responsibility to shape antibiotic R&D in a way that ensures equitable access to new antibiotics in the European region and globally and safeguards appropriate use to limit resistance. To do this, they must address four key challenges:

[iii] The prize was awarded by the European Commission on 6 February, 2017, but information on affordability and effectiveness of the new diagnostic was not available at the time of publication.

1. The global antibiotic R&D landscape is crowded, as reported in a recent London School of Economics report on existing initiatives.[67] This seems like a good thing, but the lack of coordination and information sharing between these initiatives is worrying. It leads to research duplication (including duplication of clinical trials) and inefficient use of public spending.
2. There is a shortage of coordinated priority setting on antibiotic R&D spending. The current pipeline demonstrates a lack of truly valuable new antibiotics, vaccines and diagnostics. Moreover, most publicly funded R&D initiatives in this area target the basic research phase, and much less funding is available for later stages of antibiotic development.[68]
3. Current publicly funded antibiotic R&D initiatives, including those by the EU and its Member States, lack effective conditions that steer antibiotic innovation towards priority areas and manage results (including IP) to ensure affordable access and conservation of funded products. In addition, the EU and Member States are not doing enough to explore alternative R&D mechanisms that use delinkage as a pathway to stimulate R&D in priority areas and meeting the dual goal of access without excess. The EU and Member States should also do more to explore how an R&D model based on delinkage can be implemented with (global) measures to control the number and quality of global producers of any resulting new antibiotic—and to control the sales and distribution routes through pooled procurement and reimbursement policies. This is unacceptable given the urgency of the threat of AMR.
4. The EU and its Member States bear a global responsibility and self-interest in ensuring global access, conservation and priority setting in LMICs. It is imperative that a social justice perspective is inserted into new innovation models for antibiotic R&D. This will ensure that resulting valuable new antibiotics are also available and suitable for people living in LMICs. Moreover, conservation efforts of new antibiotics are only effective if implemented globally. The EU and Member States should take the lead in supporting both politically and financially new and ongoing initiatives to promote global coordination in this area, including the WHO's *Global Action Plan on AMR*, and a meaningful follow-up of the UN's *Political Declaration on AMR*.

To address these challenges, the EU and Member States should:

- Support a robust and inclusive mechanism for global priority setting and coordination of antibiotic R&D which:
  - improves EU coordination of existing and new antibiotic R&D initiatives, including clinical trials; and
  - supports new and ongoing initiatives to promote global coordination of antibiotic R&D, including the WHO's *Global Action Plan on AMR*, and a meaningful follow-up of the UN's *Political Declaration on AMR.*
- Ensure R&D investments support global priorities by developing target prospective product profiles (TPPs) to guide priority setting in (global) antibiotic R&D investments. This includes using the WHO's list of global R&D priorities for resistant pathogens.
- Attach conditions to publicly funded R&D for antibiotics that help ensure global access and conservation. These conditions include:
  - making resulting data and reports publicly available at defined points in time to facilitate follow-on research and early identification of potential targets;
  - requiring pro-public health management of research results, including IP; and

  - including a clawback mechanism when the funding recipient does not meet specified conditions.

- Explore how an R&D model based on delinkage can be coupled with (global) measures to ensure conservation and stewardship by controlling the number and quality of global producers of any resulting new antibiotic and the sales and distribution routes through pooled procurement and reimbursement policies.
- Lead in exploring and implementing alternative incentive models for antibiotic R&D that embrace delinkage as a pathway to needs-driven priority setting and global access and conservation using a mix of direct conditional grants (push) and prizes/market entry rewards (pull).
- Consider the use of (European) tax policies as a mechanism to ensure sustainable funding of antibiotic R&D.
- Insert a social justice perspective when developing new innovation models for antibiotic R&D so new and valuable antibiotics are also available and suitable for people living in LMICs. In particular:
  - public R&D grants should include additional revenue streams for conservation and access in low-income populations; and
  - the EU and Member States should commit to mobilising the means to implement technology and capacity building in LMICs to support development and implementation of their individual national action plans to combat AMR.

Endnotes

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[65] The first two pillars of the 3P Project—"pull" and "push" funding—address this issue by incentivising and rewarding participation, especially among small- and medium-sized companies, through breaking down the drug development process into distinct, manageable stages. By introducing the prize (the pull mechanism) early in the pipeline, the 3P Project helps the organisations currently investing in R&D for tuberculosis medicines to see a timely return on their investment in the early phases of drug development. It also aims to stimulate a

large increase in such investments by creating a market for the prize and, thus, a market for the development of pre-clinical drug compounds where none previously existed. The 3P Project's third pillar, IP and data pooling, responds to the unique needs of tuberculosis treatment. By pooling IP through licensing and ensuring data sharing, the 3P Project allows earlier, faster and more innovative combinations to be trialled. This mechanism of funding delinks R&D financing from the end-product price, so medicines can be made available at affordable prices. More information at: https://www.msfaccess.org/spotlight-on/3p-project-new-approach-developing-better-treatments-tb

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