

Public investments in R&D for new antibiotics: A call for smart and bold leadership

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Antimicrobial resistance (AMR) continues to be one of the most pressing issues in contemporary health policy. While stewardship is essential to ensure that the emergence of resistance to existing antibiotics is not picking up pace, action is needed to better incentivize R&D for new antibiotics. The recent Austrian Presidency of the European Council addressed the issue and was putting particular focus on the role of public financing and ways to steer the existing funds more effectively. Next to better coordination of existing efforts, policy-makers need to become more vocal about actions needed to ensure that innovations are reaching patients.

The rise in multi-resistant strains – including bacteria, viruses, and fungi – puts major healthcare advances, achieved in the course of the past decades, in serious jeopardy. In 2013, the World Economic Forum's *Global Risks Report* (1) has identified antimicrobial resistance (AMR) as a global threat beyond the ability of a single nation or organization to tackle effectively and estimated that drug-resistant bacteria accounts for some 25,000 deaths annually in the European Union alone and over 700,000 globally (2). Estimates predict that this number could rise to an astounding 10 million deaths per year by 2050. Adding to this human tragedy, it results in an overall cost of about €1.5 billion in the European Union every year, combining both incurred healthcare costs and expenses associated with the productivity loss.

Expert clinicians and advocates have campaigned to raise awareness of this looming danger for some time. In recent years, politicians and policy-makers from all around the globe have rightfully recognized the threat as a global health crisis. The issue was a prime item at the G20 health ministers' summit during the 2017 German G20 presidency. Their Berlin Declaration calls for urgent action and lays out a framework for possible next steps (3). Proposed steps include strong inter-agency collaboration, thorough monitoring and stewardship to prevent over- and misuse of antibiotics, and fostering national and integrated regional action plans based on a One Health approach that sets out to acknowledge the interrelation of

the health of humans, animals and ecosystems by covering multiple relevant working areas, and food safety in particular. Moreover, it calls for the creation of incentive mechanisms for R&D targeting actual need and getting delinked from high price and volume considerations. The Declaration further underlines the work of initiatives such as the Global Antibiotic Research and Development Partnership (GARDP), a non-profit partnership of the WHO and the Drugs for Neglected Disease Initiative (DNDi).

While the Berlin Declaration is indeed a much needed step in the right direction, tackling growing resistance towards antibiotic agents requires continued leadership from health policy decision-makers that is bold and dedicated to long-term commitment. What is further needed is a call for coordinated action among stakeholders on the national, regional, and international level for a joint strategy and full alignment of all funds financing the development of new antibiotics and other measures to tackle growing resistance.

Paucity of effective innovation: R&D incentives revisited

There is a growing discontent among politicians and policy-makers with how medical areas are prioritized in research and how innovation is being rewarded in current pharmaceutical system (4). In their latest report on antimicrobial agents in clinical development (5), the WHO shows that despite

the efforts in recent years, including financing models to incentivize the pharmaceutical industry to conduct research, paucity of breakthrough medicines and truly innovative products targeted at combating AMR prevails. Next to an intellectual property regime that creates monopolies that grant lasting market exclusivity for suppliers, there are other causes as to why impediments to access and effective follow-up innovation prevail.

AMR is often cited as a textbook example for why the current model of rewarding health innovation is not delivering to the benefit of patients, as it remains mostly profit- and/or volume-driven. Currently companies tend to secure return on investment by either setting high prices or by selling large volumes – or in many cases by doing both at the same time. In the case of antibiotics, both alternatives can prove detrimental – whereas high prices can impede access to needed treatments, the incentive to sell large volumes has the potential to lead to inappropriate use (6). As most antibiotic classes have lost market exclusivity by now, profit prospects for new antibiotics are fairly bleak and despite the considerable budget impact AMR has on healthcare expenses, the amount of patients actually suffering from a multi-resistant infection is comparably low, making the development of new antibiotics a fairly tough business case for companies (7). New antibiotics are further considered a last-resort tool for cases in which older compounds have already met resistance and are no longer effective. This way, the emergence of resistance towards new products should be kept at a low pace. However, this adds further hurdles to antibiotic development, as the prospective market for producers is thus diminished. In addition, drug-resistant infections often require combinations rather than single drugs and the inclusion of diagnostics. A holistic approach considering entire treatments rather than focusing on individual medicines as sole solution is needed for effectively countering AMR. Finally, research is a lengthy process requiring long-term commitment. The discovery of new antibiotics has become much more complex and consuming. The industry has become less and less interested in engaging in such long-term endeavours, mostly due to their shareholders' expectations of accelerating financial returns (8).

With their declaration, the G20 ministers commissioned the OECD to prepare a report that should give concise proposals to tackle AMR by means of incentivizing effective R&D (6). Following a One Health Approach, the report was drafted jointly with WHO, FAO and OIE. The report echoed the call for the creation of national plans of action aligned with international strategies and effective monitoring and surveillance, including consideration for food and animal health. With regards to reactivating the R&D pipeline for new antibiotics, a three-

pronged approach was proposed with an increase of public funding for basic research supporting academic institutions and SMEs, the creation of a global collaboration platform that could use the results of the previously funded projects, and an exploration of innovative incentive schemes that go beyond the traditional sales-driven model. Particularly the third step could be well complemented by Target Product Profiles that illustrate government priorities and are aligned with existing initiatives and strategies. This has already been successfully used as the base of the Global Antibiotic Research and Development Partnership's (GARDP) work (9). With the declaration sending vigorous call for action, the report provides a solid frame of effective policy tools available for decision-makers.

Before getting started, however, a mapping of the landscape of existing funds and the relevant players needs to be conducted. A comprehensive mapping to gain an overview of the acting stakeholders and their networks, as well as the resources used both nationally and internationally should include information on research goals (what is being funded?), levels of funding (how much is being promoted?), channels (who promotes?), and use of results (what happens to the results?). There are very large differences between countries and institutions in terms of institutional responsibilities or objectives; however there are also common findings – for example, that there is little structured exchange of objectives and little guidance on laying down medical need and developing mechanisms for prioritization accordingly.

This task has already been conducted for antibiotic research, in particular by the European Observatory and mandated through the Dutch government during their Council Presidency in 2016 (2). According to the report, there are a total of 58 active initiatives that aim at fostering antibiotic R&D with an additional nine initiatives indirectly involved and a further seven in the making. Most initiatives provide financial push incentives and are focused on basic research and early discovery phases. Agents engaged in these ventures are often universities and small companies, which do not have the resources to advance their results into further stages. They are often left with no choice but to sell off their results to larger companies that are mostly profit-driven or abandon projects altogether, bearing the risk of leaving promising interim results untapped for potential follow-up projects. Both the United States and Europe have invested significant amounts and resources and their efforts are expected to be further strengthened in the coming years. While there is an overall positive trend detectable and gradual success in tackling AMR conceivable, some major pitfalls prevail: the low level of coordination between funds and initiatives, their lack of alignment with national and global strategies and the missing orientation towards concrete outcomes. Moreover, there is

little to no conditionality tied to funding in relation to patient access once market entry has been achieved.

The lack of coordination of research efforts, particularly among those facilities closely tied to public funding stands out as a main hurdle to effectively steer research towards a medical needs-based approach delinked from sales. While the pharmaceutical industry surely has their share in the shortcoming of research in particular medical areas, the public needs to become aware of their own flaws and has to start altering regulation that allows or even incentivizes adverse market behaviour. The focus of the controversy surrounding the pharmaceutical sector, and pricing in particular, should shift from a sole consideration of market failures to include shortcomings in policy and how to revise them. In addition, approaching the problem should be done in a holistic fashion by putting the entire product cycle of pharmaceutical development into perspective – starting with basic research and ending with the determination of a price for reimbursement.

Tackling shortcomings in policy: Austria's case

Introducing such a holistic discussion, taking all the above mentioned into account, has been the intention of the Austrian EU Health Council Presidency in the second half of 2018 as tackling both market and policy failures was named as a prime working area. Complementing the experiences of previous presidencies that have highlighted pharmaceutical policy mainly from a pricing perspective, particularly the Dutch and the Italian, the idea was to bring research and the early development stages into focus. In doing this, Austria has demonstrated their commitment to the June 2016 European Council Conclusions on strengthening the balance in the pharmaceutical systems that had called for “a fair share of the return on [public] investment (...) [to] be used for further innovative research in the public health interest” (10). To assess the current situation and come up with concrete policy proposals to tackle the prevailing shortcomings, the European Observatory was commissioned to write a policy brief titled “Ensuring access to medicines: How to stimulate innovation to meet patients' needs” (11).

Despite its relevance for health policy, research is traditionally the responsibility of science policy, with limited opportunities for health policy-makers to contribute, leading to a high degree of fragmentation and prevailing silos. By facilitating exchange between experts and decision-makers from both policy areas, we wanted to trigger an initial encounter that could later turn into a vibrant and recurring platform of exchange. This platform was established during the Austrian presidency by means of a conference titled “Matching Health Needs and Pharmaceutical Research” on 25

September, 2018. The invitees included government decision-makers from both the healthcare and the research sector, alongside experts, representatives from funds supporting pharmaceutical research, relevant civil society actors, and industry representatives. Keynotes were delivered by Manica Balesagaram, Director of GARDP, presenting GARDP as best practice for incentivizing needs-based research prioritization, and Mariana Balasegaram, professor at the University College London (UCL) and best-selling author, who researches on the role of the public in enabling innovation.

The idea of a mission-based approach to deliver on innovation in the health sector is central to Professor Mazzucato's policy advice. Missions should be ambitious and spark public engagement through their relevance for people's everyday lives, they should have a clear direction and time-bound and measurable targets, they should be realistic, they should promote multisectoral cooperation, and not preempt any outcomes at the start but rather allow for multiple and bottom-up solutions (12). A mission-based approach will also be applied to the upcoming European Commission's ninth Framework Programme for Research and Innovation, Horizon Europe. While this may prove a great chance for public policy-makers to gain momentum in taking stronger leadership in European research programming, it is a missed opportunity that the development of new antibiotics has not been picked as the mission for innovation in healthcare by the Commission.

In addition to applying a mission-based approach to the development of research programmes, Mazzucato has also called for de-linking incentives from prices and volume. This could be done through research grants, subsidies, tax benefits or other (financial and non-financial) rewards upon achieving certain predefined targets, such as marketing of a compound addressing an area or disease with high medical need. Conditionality on public support for pharmaceutical R&D, particularly in terms of achieving actual and affordable access for the benefit of patients, reinvestment for further and follow-up innovation, sharing and pooling knowledge, as well as transparency on expenses and prices stands as another crucial principle of Mazzucato's proposal (8).

The assessment of the European Observatory report under Dutch mandate (2), outlined above, was firmly echoed by many attendees of the conference. In order to improve the needs orientation of public research, health policy-makers must take a more active role in setting the research goals. A public sector with clear priorities and a long-term vision can better track public interest in public-private partnerships. Coordinated research and development strategies are important not only at the national, but also at a multilateral level. This requires strong leadership and sound governance frameworks to manage public and private investment. In addition, an internationally

harmonized procedure for identifying needs and priorities should be developed. Since priorities can also change during the process, corresponding feedback loops are required, which represent interim results and allow for adjustments.

A call for action for decision-makers

A very promising initiative is the Global AMR R&D Hub, launched in May, 2018. Its aim is to better coordinate existing efforts and get together governments, international organizations and key funds, such as the Wellcome Trust and the Bill and Melinda Gates Foundation (13). The initiative is supported by the German Government and tied to the 2017 Berlin Declaration. There are strong indicators that the urgency of action needed – illustrated through the AMR crisis – could help facilitate a change of mindset when we think of how medical innovation is brought about and how it can be rewarded in a way that does not impede follow-up innovation and/or patient access.

Research and development is complex and requires a long-term approach and willingness to provide funding. Efforts need to go beyond traditional push mechanisms, including grants and tax breaks. Financing schemes need to appeal to the communities engaged in basic research, mostly SMEs and academia, in an effort to support them pushing their projects further in the development process. Target Product Profiles could be used as a tool to strengthen the public health system's role in creating market demand for the medical needs identified and prioritized. They could be linked to concrete rewards as a means of pull financing, targeted at providing sufficient financial incentives to engage in R&D in areas traditionally neglected in the current sales- and volumes-driven system. For this, the pooling of (financial and operational) resources is essential. This, in turn, requires strong partnerships between public health authorities, public and private investors, academia,

industry and contracting authorities. Moreover, deliverables shall be clearly defined and measurable, hence traceable. In addition, there is a need to improve exchange between the actors, as well as a commitment to overall transparency and the willingness to share trial data and other necessary means to advance promising research). ■

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References

- World Economic Forum: Global Risks 2013. Eighth Edition. http://www3.weforum.org/docs/WEF_GlobalRisks_Report_2013.pdf
- Renwick M., Simpkin V., Mossialos E.: Targeting innovation in antibiotic drug discovery and development: The need for a One Health – One Europe – One World Framework. Observatory Studies Series No. 45. WHO, Regional Office for Europe. 2016
- G20 Germany 2017: Berlin declaration of G20 health ministers. https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G20-Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf
- Ploumen, L.; Schippers, E.: Better life through medicine—let's leave no one behind. *Lancet* 2017; 389:339-341.
- World Health Organization: Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. 2017
- OECD, WHO, FAO, OIE: Tackling antimicrobial resistance Ensuring sustainable R&D. 2017. <http://www.oecd.org/g20/summits/hamburg/Tackling-Antimicrobial-Resistance-Ensuring-Sustainable-RD.pdf>
- Outterson, K.: Innovative ways to pay for new antibiotics will help fight superbugs. STAT; April 11, 2018. <https://www.statnews.com/2018/04/11/innovation-new-antibiotics-fight-superbugs/>
- The People's Prescription: Reimagining health innovation to deliver public value, IIPP Policy Report. UCL Institute for Innovation and Public Purpose (IIPP); 2018. <https://www.ucl.ac.uk/bartlett/public-purpose/wp2018-10>
- Balasegaram M., Beyer P., Paccaud J.: A not-for-profit antibiotic developer – the Global Antibiotic Research and Development Partnership. *AMR Control* 2018: 85-88.
- Council of the European Union: Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States. June 17, 2016. <https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/>
- Panteli, D., Edwards S: Ensuring access to medicines: How to stimulate innovation to meet patients' need? Policy Brief 29. WHO, Regional Office for Europe; 2018. http://www.euro.who.int/_data/assets/pdf_file/0009/379701/PB29_AUSTRIA_web_13082018.pdf
- Mazzucato M.: Mission-Oriented Research & Innovation in the European Union. A problem solving approach to fuel innovation-led growth. European Commission; 2018. https://ec.europa.eu/info/sites/info/files/mazzucato_report_2018.pdf
- Global Antimicrobial Resistance R&D Hub Launched At Health Assembly. IP Watch; May 22, 2018. <http://www.ip-watch.org/2018/05/22/global-antimicrobial-resistance-rd-hub-launched-health-assembly/>