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REVIEWS

Special Issue: Antimicrobial Resistance and Novel Therapeutics

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Research, Innovation, and Policy: An Alliance Combating Antimicrobial Resistance

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The surge in antimicrobial resistance (AMR) has created a crisis that has become top priority for public health and global policy. Researchers, developers, innovators, funders, and policymakers need to curb AMR's rising trend by acting synergistically, boosting investment in developing solutions. This science–policy interface is now taking shape.

In 1945 AMR was recognized by a scientist, Alexander Fleming, who warned that misuse of antibiotics could result in selection for resistant bacteria. More than 70 years later, in 2016, it was recognized by world leaders in a Political Declaration of the United Nations General Assembly. Unfortunately, this boost in recognition was driven by a surge of resistance, turning AMR into a major health threat. In their declaration, heads of state and government acknowledged that, due to antibiotic resistance, many achievements of the 20th century are being gravely challenged, and that AMR is projected to cause millions of deaths worldwide, with massive social, economic, and global public health repercussions. The leaders committed to develop multisectoral national action plans, programmes, and policy initiatives, building on the 2015 WHO global action plan on AMR[i].

Tackling AMR to prevent and control infections in humans and animals is thus a major challenge for our society. This is being addressed via global, regional, and national policy initiatives, giving rise to national and European AMR action plans. These policy documents recognize that actions to be taken should include boosting research, development, and innovation, since they are crucial to generate novel solutions and tools, and to address knowledge gaps. But, substantial progress can only be made if policy has a positive effect on the work of researchers and innovators, if, in turn, their work can strengthen policy making [1], and when research and practice are linked through implementation research, especially in low- and middle-income countries (LMICs) [2].

During the last decade AMR policy led to a series of profound changes in the research landscape, resulting in increased coordination. In order to consolidate the fragmented national research activities, the European Union, guided by its first AMR Action plan launched in 2011[ii], supported the establishment of a Joint Programming Initiative on AMR (JPIAMR)[iii]. This expanding initiative currently brings together 27 countries around the globe, allowing them to align their national research efforts and fund transnational research projects. Aided by a scientific advisory board, stakeholders and a public consultation, JPIAMR developed a Strategic Research Agenda (SRA) setting out the research needs required to combat AMR across the full One Health spectrum. This provides scientists and stakeholders a means to inform policy makers and guide research-funding decisions. In addition, the partnering of national public funders in collaboration with the European Commission has increased opportunities for scientists to establish transnational research projects, adding to EU-funded collaborative research projects.

AMR research and development is also boosted by linking up public and private partners. As another result of the first European Action plan in 2012, the New Drugs for Bad Bugs (ND4BB) programme was launched by the Innovative Medicines Initiative. In this programme the European Commission and its industry partners in the European Federation of Pharmaceutical industries and Associations join forces, providing substantial funding to boost the pipeline of new antimicrobial agents. ND4BB has narrowed the gap between academic and industrial researchers and improved the value chain of product development [3]. In addition, the development and delivery of antibiotic treatments is explored by the Global Antibiotic Research & Development Partnership (GARDP)[iv]. This not-for-profit initiative was established in May 2016 as an element of the WHO global action plan on AMR.

Nevertheless, product development to combat AMR is severely under pressure. New medicines that might enter the market are expected to be used sparsely to prevent resistance development, while diagnostic tools to guide treatment and prescription are generally more expensive than antimicrobials. There is a need to develop novel or alternative solutions. It is therefore important to harness the innovative potential of small and medium-sized enterprises (SMEs). Initiatives that address this need include CARB-X that provides guidance and support to companies in an effort to deliver new treatments and life-saving products into clinical trials[v]. Another example is the IMI Accelerator that aims to partner SMEs with large pharmaceutical companies to enable progression of promising assets or technologies to key milestones, creating value, and sharing risk. Recognizing that product development in this area carries a high risk, the European Commission and the European Investment Bank joined forces to launch InnovFin Infectious Diseases[vi]. This finance facility provides loans to innovative players active in

developing vaccines, medicines, medical and diagnostic devices, or novel research infrastructures for combating infectious diseases. Taken together, such initiatives aim to support the value chain by moving assets from preclinical through clinical development.

AMR is an important agenda item for G7 Health ministers who, in 2016, encouraged governments to consider the need for establishing a global clinical studies network on drug resistance that provides access to a large clinical research infrastructure for the design, coordination, and conducting of clinical trials and studies[vii]. In Europe, the COMBACTE projects lay the foundation for such a network aimed at designing and implementing more efficient clinical trials. The Transatlantic task force on AMR (TATFAR), in which policy makers at both sides of the Atlantic collaborate, facilitated partnerships between US NIH-funded clinical trials and the COMBACTE network, underlining the global potential of the G7 policy aim. Horizon 2020 funds the development of a business plan for an advanced Europe-wide clinical research network. Such a network can potentially reduce the cost and time of clinical trials in infectious diseases, be an attractive partner for industrial partners, and bring more new products to patients.

It is undisputed that the societal value of new technologies addressing AMR is high, whereas the return on investment for the discovery and development of new preventions and treatments is often low or uncertain. This requires the establishment of incentives to boost the development of such products. It is generally accepted that a mixture of push and pull incentives is needed. Scientists working in the public and private sector collaborated in the IMI-funded DRIVE-AB research project to develop recommendations for new economic models that would provide the pharmaceutical industry with an incentive to invest while reconciling this with the need to use new antibiotics wisely. This provided a basis for policy makers in TATFAR to analyse pull incentives identified in DRIVE-AB [4]. Promoting increased investments into push and pull incentives for AMR R&D is now one of the main objectives of the new international R&D Collaboration Hub which was established in May, 2018, in response to the 2017 call by G20 leaders to maximize the impact of existing and new antimicrobial basic and clinical research initiatives as well as product development[viii].

Tackling AMR that moves across all borders requires a truly global response, as stressed by the United Nations Inter Agency Coordination Group [5]. Via the European & Developing Countries Clinical Trials Partnership[ix] European and sub-Saharan countries, and the EU support collaborative clinical research to prevent or treat infectious diseases in sub-Saharan Africa. Research benefitting LMICs can also be boosted by combining funds of national research funders with those of development agencies, as in the latest JPIAMR call that will support transnational research developing diagnostic and surveillance tools for AMR in LMIC settings.

The wide scope of AMR research is a logical consequence of the One Health approach. Studying the multiple aspects of this health threat, and developing solutions to tackle it, requires the involvement and interaction of scientists from many different disciplines. Mapping research provides an overview of the scale of funding, research capacity and scope, and can identify gaps. JPIAMR performed such a study [6]. This highlighted the variation of public funding between countries and across priority topics as identified in their SRA. Furthermore, it stressed the need for increased and new investment in AMR research. Following the Kobe Communiqué of the G7 Health Ministers that asks for leverage mechanisms to coordinate R&D activities, including the mapping and analysis of investments in areas such as AMR[vii], JPIAMR is presently undertaking an even more extensive mapping exercise. This thorough mapping of research projects and research performers will not only benefit funders and policymakers, but will also provide a valuable resource for scientists to identify projects of their interest and to search for potential collaborators driven by the globalization of research and the need for a multisectoral approach.

Scientific studies are very valuable to guide and support policies aimed at combating AMR. In an effort to acquire such scientific input, JPIAMR issues calls for networks in which researchers are identifying key questions to address, or analysing potential solutions. The resulting white papers, prospective views, guidelines, roadmaps, or reviews provide valuable resources to inform a range of stakeholders, and has already delivered a roadmap for antimicrobial susceptibility testing systems [7,8]. Building on this, JPIAMR currently establishes a Virtual Research Institute (JPIAMR-VRI) which aims to further strengthen contacts between the research community, funding agencies, and policymakers[x]. This global virtual network will connect researchers, facilities, and infrastructures to each other and establishes a platform to support an unprecedented level of knowledge exchange, research coordination, sharing of resources, databases, and research results. It will increase capacity, reduce duplication of effort, and expedite progress towards reducing the global burden of AMR. By connecting leaders and experts with industry, public health, and policy makers it aims to facilitate the analysis of knowledge gaps, implement breakthrough

collaborative research, and increase the visibility of the research performed. Furthermore, it will build a virtual 'corridor' facilitating the production of scientific evidence for developing policy and guidelines.

Data collected and analysed by EU-funded research projects have already been shown to be central to shaping policies that reduced the use of antimicrobials [9]. The new European One Health Action plan against AMR[xi] now provides a framework for more extensive actions, to further strengthen the alliance between research innovation and policy in Europe and beyond.

Resources

[i]https://digitallibrary.un.org/record/842813/files/A_71_L-2-EN.pdf
[ii]http://ec.europa.eu/health/amr/sites/amr/files/communication_amr_2011_748_en.pdf
[iii]www.jpiamr.eu/
[iv]www.gardp.org/
[v]https://carb-x.org/
[vi]www.eib.org/en/products/blending/innovfin/products/infectious-diseases.htm
[vii]www.mhlw.go.jp/seisakunitsuite/bunya/hokabunya/kokusai/g7kobe/KobeCommunique_en.pdf
[viii]www.g20.org/en/g20/previous-summits
[ix]www.edctp.org/
[x]www.jpiamr.eu/activities/jpiamr-virtual-research-institute/
[xi]https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

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References

1. Woolhouse, M. and Farrar, J. (2014) An intergovernmental panel on antimicrobial resistance. *Nature* 509, 555–557
2. Theobald, S. *et al.* (2018) Implementation research: new imperatives and opportunities in global health. *Lancet* 392, 2214–2228
3. Rex, J.H. (2014) ND4BB: addressing the antimicrobial resistance crisis. *Nat. Rev. Microbiol.* 12, 231–232
4. Årdal, C. *et al.* (2017) Pull incentives for antibacterial drug development: an analysis by the Trans-Atlantic Task Force on Antimicrobial Resistance. *Clin. Infect. Dis.* 65, 1378–1382
5. Rochford, C. *et al.* (2018) Global governance of antimicrobial resistance. *Lancet* 391, 1976–1978
6. Kelly, R. *et al.* (2015) Public funding for research on antibacterial resistance in the JPIAMR countries, the European Commission, and related European Union agencies: a systemic observational analysis. *Lancet Infect. Dis.* 16, 431–440
7. Editorial (2018) Progress on antibiotic resistance. *Nature* 562, 307
8. van Belkum, A. *et al.* (2018) Developmental roadmap for antimicrobial susceptibility testing systems. *Nat. Rev. Microbiol.* Published online October 17, 2018. http://dx.doi.org/10.1038/s41579-018-0098-9
9. Goossens, H. (2017) Shout about the European Union's success. *Nature* 542, 273

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Spotlight

The Scourge of Antibiotic-resistant Infections in Cystic Fibrosis

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Bacterial infections are the primary cause of respiratory decline and mortality in cystic fibrosis (CF) patients. In a recent study, Diaz Caballero and colleagues [1] (*PLoS Pathog*. 2018;14:e1007453) catalogued the molecular adaptation of a decade-long *Burkholderia multivorans* infection in a Canadian CF patient, which evolved to become resistant towards multiple classes of antibiotics.

CF is the most common heritable fatal disease in people of European descent. CF pathogenesis is most prominent in the airways, where accumulation of thick, tenacious mucus promotes a vicious cycle of excessive inflammation and infection. Chronic and recurrent infections are a major driver of disease in CF, leading to rapidly declining lung function, and in 80–95% of cases, respiratory failure and death [2]. Airway infections with members of the bacterial genus *Burkholderia* are especially feared because of their pathogenicity (e.g., cepacia syndrome, melioidosis), their impressive ability to intrinsically evade many antibiotics, their propensity for chronic persistence and associated airway decline, and, in the case of *Burkholderia cepacia* complex (Bcc) species, their transmissibility between CF patients [3]. Perhaps the most pressing concern is acquired antimicrobial resistance (AMR), a phenomenon whereby bacteria evolve within their host to evade being targeted by antibiotics, rendering once-potent drugs ineffective. In a recent study, published in *PLoS Pathogens*, Diaz Caballero and colleagues [1] monitored the evolution of the common CF pathogen, the Bcc species *Burkholderia multivorans*, over a 10-year period, during which time the infection became chronically adapted to the airways of a Canadian CF patient and was unable to be eradicated using aggressive and long-term antibiotic therapies.

Whole-genome sequencing (WGS) and RNA sequencing are high-resolution techniques that have yielded invaluable mechanistic insights into *Burkholderia* diversification and adaptation in chronically infected airways [4–9]. In this vein, Diaz Caballero *et al*. [1] used WGS to catalogue genome-wide variation among 111 *B. multivorans* isolates collected from CF airways during three phases of infection over a 10-year period. They performed repeated deep sampling at a single time point between 6 and 7 years after initial diagnosis to identify fine-scale variation and distinct lineages in the CF