The European Molecular Biology Laboratory (EMBL) is one of the world's leading research institutions, and Europe's flagship laboratory for the life sciences, publicly funded by over 25 Members States and hosted at six European sites. We strongly welcome the Commission's work and call for evidence aiming to redefine its priorities and renew its engagement with the EU Member States in this area.

EMBL's research aims to understand the basis of life, gaining a molecular understanding of organisms in the context of different environments. The new Scientific Programme 2022-26 'Molecules to Ecosystems' will expand EMBL's scope to study the molecular basis of life in the context of changing environments, transforming our understanding of life on earth and informing potential solutions for some of society's biggest challenges, such as irreversible loss of biodiversity, pollution, climate change, food security, emergent pathogens, and antimicrobial resistance (AMR). Research on the AMR is a focal point of the Infection Biology transversal theme that aims to contribute to research on the biology and mechanisms of infection, as well as on diagnostics and treatment of infectious diseases. Within this context, we would like to share key steps on how to reduce the spread of AMR, and how to better coordinate actions to tackle the threat at EU level.

We have entered a post-antibiotic age. Bacteria resistant to many, if not all, available antibiotics are found in alarming numbers throughout the world. As a result, once easily treatable bacterial infections become life-threatening again, and pose an imminent threat to public health. This threat is not looming, but is actually here. The current estimates are that 1.2 million people died in the world in 2019 because of antibacterial-resistant infections[1]. The problem goes beyond infectious diseases, shaking the entire modern medicine to its foundations: invasive surgery, transplantation, chemotherapy, premature infant care, emergency care, and care of chronically ill are some the fields that largely depend on our ability to control infections.

The broad use of antibiotics in medicine but also in food industry over the past 70 years, together with the drought in new compound development over the last 3 decades, have provided the ideal settings for the rise and spread of resistance to most frontline antibiotics, even those of "last resort". The problem is complex and needs a range of coordinated actions. First, new policies and structures that regulate antibiotic use (antibiotic stewardship) and track antibiotic resistance spread can help to contain the damage. Second, fundamental research is urgently needed if we are to find solutions to the problem: provide new strategies to understand, prevent and/or revert antimicrobial resistance (AMR), rapidly diagnose and predict AMR development, and solve current scientific bottlenecks in antibiotic discovery. Third, new economic models, where public funding and investments make it to affordable products, are urgent to ensure solutions make it to applications.

In addition to important efforts to regulate antibiotic use with EU-wide regulation, we need to comprehensively evaluate the sources of AMR development and spread. For example, it has been recently suggested that non-antibiotics and polypharmacy may drive AMR development in humans[2]. On the other hand, the spread of AMR from the environment and food chain to clinics and human pathogens is still poorly characterized. Overall, our abilities to track AMR spread across pathogens, hosts and ecosystems is at its infancy. The databases and knowhow developed during the current pandemic for genomic surveillance of pathogens[3], and the rapid increase of genomic information of

[1] Antimicrobial Resistance Collaborators; Lancet 2022 Feb 12;399(10325):629-655
[2] Maier et al.; Nature 2018 Mar 29;555(7698):623-628
[3] https://www.covid19dataportal.org/ hosted by EMBL-EBI

microbial ecosystems[4],[5], including their mobile genetic elements, can both be pivotal in making the next important steps on this front.

Regulatory measurements to monitor and contain AMR are not enough by themselves to solve the crisis. For this, we also need to fuel the market with new antibacterial therapies and strategies. The broader engagement of fundamental research on this front has produced a plethora of new ideas and lead molecules in the last few years, as well as solved many of the bottlenecks in the stale antibiotic discovery pipeline. This include the use of untapped reservoirs of microbes or chemistry to find new molecules[6],[7],[8] – with environmental microbiome sequencing efforts[9] and AI-based discovery of bioactive compounds[10],[11] promising that this avenue will only provide more lead compounds in the future; the strive for narrow-spectrum therapies, which help avoiding the collateral damage to our commensal microbiota and decrease the resistance pressure[12]; the repurposing of existing medication and the exploration of combinatorial therapies[13],[14]; the revisit of phage therapy and vaccines[15]; the numerous new systematic methods to identify the target and resistance determinants of antibiotics[16],[17],[18]; and the clever strategies of making antibiotics enter bacterial cell[19] and/or more difficult to develop resistance against[20]. Overall, we are currently at a better stage than ever for developing new antibacterial therapies, and the efforts and funding need to culminate, not stop, now. It is of paramount importance that the next generation of antibiotics and therapy regimens are designed to live longer and be less prone to AMR development. Otherwise, antimicrobial discovery would be a Sisyphean effort in a battle bound to be lost.

Finally, we need to have an open discussion on how to ensure that public money invested to refuel antibiotic discovery make it back as molecules that help the entire society. This needs policies and strategies on how lead molecules and SMEs are supported to conduct clinical trials, how low profit margins for antibiotic discovery are dealt with, and what is the role of 'big pharma' in this process, which at the moment has largely shut down antibiotic discovery departments and shifted all risk taking of early development to public funding.

We encourage the Commission and Member States to reach out and involve stakeholders early at policy level, which will save lives and resources in the long term, and EMBL senior scientists are available to discuss this topic further.

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