

# INNOVATION IN ANTIBIOTICS

## ANALYSIS AND PROPOSALS OF SALUD POR DERECHO

### EXCLUSIVITY VOUCHERS: A PROPOSAL THAT FAILS TO ADDRESS AN INCREASINGLY URGENT PROBLEM

The European Pharmaceutical Strategy will define the actions of the European Commission (EC), having a major impact on issues of crucial importance and those related to pharmaceutical legislation or supplies of medicines for the coming years in the EU area and in the EU-27. A process that began with the conclusions of the Dutch presidency in June 2016 to strengthen the pharmaceutical system, which highlighted the need to review current European incentive policies. To this an unprecedented global health crisis was added, which the regional body faced for the first time. These developments define a context, but also mark a roadmap, as well as an opportunity to ensure that the public policies put in place address the gaps in a space where both research into new antibiotics and access are crucial.

Antibiotic resistance is a serious public health problem, responsible for 1.27 million associated deaths in 2019 alone (1). In the European context, there is evidence of an growing trend between 2016 and 2020, with a health impact comparable to that of influenza, tuberculosis and HIV/AIDS combined (2).

To tackle this growing “silent pandemic” a combination of strategies is needed, among which access to innovative antibiotics presents an issue which is becoming of increasing concern. Faced with a lack of commercial interest from the pharmaceutical industry in R&D for antibiotics that, while cornerstones of healthcare systems, may not have a large market, the EC has developed a proposal for transferable exclusivity vouchers (TEVs) as part of its review of the European Union (EU) Pharmaceutical Legislation. The development of new and effective antibiotics is an pressing need in which the public sector plays a key role in creating and coordinating the market, through upfront investments and ensuring stable and sufficiently high procurement and reimbursement processes to sustain development. However, granting TEVs, through which companies can ultimately extend monopolies on other more profitable products, will amount to losing public sector control over the final cost of antibiotics and a very ineffective measure in terms of the fair and necessary incentives that the innovative antibiotic ecosystem needs (3,4), as has already been denounced by European civil society (5).

To address a project as complex as the lack of innovative antibiotics, it is unlikely that a single incentive based on the traditional market logic will solve the present challenge (4). It is also controversial to insist on the use of the extension of exclusivity when there is no evidence that this is a measure that in

itself incentivises R&D in other therapeutic areas (6). The approach to this complex problem must be a combination of measures implemented in an end-to-end approach, taking into account certain features in terms of ensuring global access from the early stages of R&D and effective governance from the public sector, with a holistic and coordinated perspective of the whole innovation ecosystem.

## RECOMMENDATIONS

### **1.- Coordination and financing in R&D for priority pathogens. Financing for GARDP and CARB-X global initiatives**

The main barrier is the lack of large-scale stable funding, combined with other factors such as the lack of coordination and collaboration. Small and medium-sized biotech companies, as well as academic centres, are doing the vast majority of antibiotic R&D in the face of the demise of large companies in recent years (7, 8). Faced with the lack of sustainable funding for research in its initial and translational stages (9), these companies have difficulty progressing through the different clinical phases, as well as lacking prior experience in the marketing of new antibiotics. What's more, a sufficiently coordinated approach to cover priority bacteria on a global level is still lacking, with national interests taking precedence and leading to a fragmented R&D effort (10).

For this reason it is necessary to fund and strengthen support for "operative coordinators" such as CARB-X and GARDP, enlarging their donor base, and where Spain could play a key role. These actors have played a key role in recent years (11), where we have seen a positive effect on the pre-clinical chain, which is becoming more focused, more innovative and continues to be nurtured (7,12,13). GARDP (Global Antibiotic Research and Development Partnership), a not-for-profit R&D collaboration, is of particular importance in its role as a systems integrator, acting, among other things, in the commercialisation and market access phase, both in high, middle and low-income countries. It is therefore well positioned to address global public health needs, ensure return on public money while ensuring issues of global equitable access and strengthening global R&D infrastructure (11).

This is an ecosystem in which there is no viable market for antibiotics, so it is an optimal opportunity to implement alternative models for innovation that do not necessarily have to be secretive and are increasingly based on open approaches to R&D set around WHO-determined priorities, where the research agenda can remain in the public space (14). This, in turn, generates value when it comes to determining immediate financing needs, the best R&D options, and health priorities.

### **2.- Pull funding and reimbursement mechanisms independent of price and sales volume of the final product, safeguarding overall rational use, access and affordability.**

In the face of a market-based model that has failed to introduce a new class of effective antibiotics in the last 34 years, public leadership is needed to test alternative models of innovation. This leadership may materialize in two ways. On the one hand, by promoting networks of independent clinical trials and with the aim of improving the transparency of the cost of R&D and lowering the cost of new antibiotics (10).

On the other hand, instead of pull type incentives such as TEVs which do not take into account the nature of the research chain, other options should be explored, such as the introduction of milestone prizes adapted to the entire clinical chain (10,15). All public funding at all stages of R&D should include conditionalities regarding global access to antibiotics.

Similarly, there are interesting experiences with innovative reimbursement pricing models that imple-

ment the decoupling of sales volume from revenue expectations, for example the recent experience in the UK and Sweden (3,16), where an agreed fixed price has been established in exchange for ensuring the availability of antibiotics for the required time period, reducing the incentive to reward sales volume.

### **3.- To promote alternative models to intellectual property in the medium and long term, intervening at very early stages of R&D.**

Finally, it is important to remember that there are other complementary solutions away from the traditional market model, such as the European Medicines Infrastructure for pharmaceutical R&D in the public interest, proposed in a study by the European Parliament (17), the public procurement of patents for new antibiotics (18) combined with partnerships with intellectual property rights (IPR) pools, or alternative models to IPR that have proven successful in other technological fields.

## **REFERENCES**

1. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2022;399(10325): 629–655. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
2. ECDC. 35 000 annual deaths from antimicrobial resistance in the EU/EEA. 2022; <https://www.ecdc.europa.eu/en/news-events/eaad-2022-launch>
3. Årdal C, Lacotte Y, Ploy MC. Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2020;71(8): 1994. <https://doi.org/10.1093/CID/CIAA153>
4. Årdal C, Røttingen JA, Opalska A, Van Hengel AJ, Larsen J. Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance. *Clinical Infectious Diseases*. 2017;65(8): 1378–1382. <https://doi.org/10.1093/CID/CIX526>
5. Civil Society Open Letter to the Council of the European Union Concerning Transferable Exclusivity Vouchers for Antimicrobials. 2022; [https://saludporderecho.org/wp-content/uploads/2023/05/AMR\\_Letter\\_EU-TEVs\\_EN\\_05Dec2022.pdf](https://saludporderecho.org/wp-content/uploads/2023/05/AMR_Letter_EU-TEVs_EN_05Dec2022.pdf)
6. Hu Y, Eynikel D, Boulet P, Krikorian G. Supplementary protection certificates and their impact on access to medicines in Europe: Case studies of sofosbuvir, trastuzumab and imatinib. *Journal of Pharmaceutical Policy and Practice*. 2020;13(1): 1–12. <https://doi.org/10.1186/S40545-019-0198-6/TABLES/3>
7. World Health Organization. 2021 antibacterial agents in clinical and preclinical development: an overview and analysis. 2022; <https://www.who.int/publications/i/item/9789240047655>
8. The Pew Charitable Trusts. Antibiotics Currently in Global Clinical Development. <https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development>
9. Kelly R, Zoubiane G, Walsh D, Ward R, Goossens H. Public funding for research on antibacterial resistance in the JPIAMR countries, the European Commission, and related European Union agencies: a systematic observational analysis. *The Lancet. Infectious Diseases*. 2016;16(4): 431. [https://doi.org/10.1016/S1473-3099\(15\)00350-3](https://doi.org/10.1016/S1473-3099(15)00350-3)
10. Aagaard H, Malpani R, Zorzet A. Ensuring sustainable access to effective antibiotics for everyone, everywhere – How to address the global crisis in antibiotic Research and Development. *ReAct - Action on Antibiotic Resistance*. 2021; <https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf>
11. Piddock LJV, Paccaud JP, O'brien S, Childs M, Malpani R, Balasegaram M. A Nonprofit Drug Development Model Is Part of the Antimicrobial Resistance (AMR) Solution. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2022;74(10): 1866. <https://doi.org/10.1093/CID/CIAB887>
12. Årdal C, Lacotte Y, Ploy MC. EU-JAMRAI | Policy brief: Improving access to essential antibiotics. 2021; <https://eu-jamrai>

13. Årdal C, Findlay D, Laxminarayan R, Outtersson K, Rex JH. Revitalizing the antibiotic pipeline. Stimulating innovation while driving sustainable use and global access. DRIVE-AB. <http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf>
14. Todd MH, Klug DM, Idiris FIM, Blaskovich MAT, von Delft F, Dowson CG, et al. There is no market for new antibiotics: this allows an open approach to research and development. Wellcome Open Research. 2021;6. <https://doi.org/10.12688/WE-LLCOMEOPENRES.16847.1>
15. Baraldi E, Lindahl O, Savic M, Findlay D, Årdal C. Antibiotic Pipeline Coordinators. The Journal of law, medicine & ethics. 2018;46(1\_suppl): 25–31. <https://doi.org/10.1177/1073110518782912>
16. Gotham D, Moja L, van der Heijden M, Paulin S, Smith I, Beyer P. Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. Health Policy. 2021;125(3): 296–306. <https://doi.org/10.1016/J.HEALTHPOL.2020.11.015>
17. Florio M, Pancotti C, Prochazka DA. European pharmaceutical research and development: Could public infrastructure overcome market failures? European Parliament. Scientific Foresight Unit. European Parliament. 2021; [https://www.europarl.europa.eu/stoa/en/document/EPRS\\_STU\(2021\)697197](https://www.europarl.europa.eu/stoa/en/document/EPRS_STU(2021)697197)
18. Mossialos E, Morel CM, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. Policies and incentives for promoting innovation in antibiotic research. <https://apps.who.int/iris/bitstream/handle/10665/326376/9789289042130-eng.pdf>