

AIM Position Paper on Antibiotic Use and Antimicrobial Resistance (AMR)

Key facts and figures

- Globally it is estimated that **only half of antibiotics** are used correctly.¹
- Resistance to antibiotics is often high and increasing. In many countries, resistance rates have more than **doubled** in the past five years.²
- Antimicrobial resistance (AMR) is responsible for an estimated **33,000 patients' deaths per year in the EU³** and **700,000 patients' deaths** throughout the world.⁴
- Globally, **10 million deaths** per year are projected between 2015 and 2050 if current infection and resistance trends are not reversed.⁵
- It is estimated that AMR costs the EU **EUR 1.5 billion per year in healthcare costs and productivity losses** and by 2050 estimated economic costs of **USD 100 trillion worldwide (EUR 84 trillion)**^{6, 7}.

Setting the scene

Wanted: innovation in antimicrobials!

The level of investment in antimicrobials is disappointing. No new antibiotic classes, the decisive criteria for those medicines' effectiveness on bacteria, were discovered since the 1980s⁸; the last antibacterial class to fight superbugs belonging to the very resistant Gram-negative bacteria was even found in the 1960s! According to the World Health Organization (WHO), the pipeline is not very promising either: the 60 products in development (50 antibiotics and 10 biologics) will most likely bring little benefit over existing treatments and very few target the most critical resistant bacteria

¹ AMR: a major European and Global challenge, European Commission Website, Accessed September 2020.
https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_factsheet.pdf

² Antibiotic resistance – facts and figures, European Center for Disease Control Website, Accessed September 2020.
<https://antibiotic.ecdc.europa.eu/sites/default/files/media/en/eaad/Documents/antibiotics-factsheet-primary-care-prescribers.pdf>

³ EU Action on Antimicrobial Resistance, European Commission, Accessed September 2020.
https://ec.europa.eu/health/amr/antimicrobial-resistance_en

⁴ <https://reports.weforum.org/global-risks-2018/anti-microbial-resistance/>

⁵ AMR: a major European and Global challenge, European Commission Website, Accessed September 2020.
https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_factsheet.pdf

⁶ EU Action on Antimicrobial Resistance, European Commission, Accessed September 2020.
https://ec.europa.eu/health/amr/antimicrobial-resistance_en

⁷ Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The Review on Antimicrobial Resistance, Chaired by Jim O'Neill. May 2016, available at: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf, p. 1.

⁸ Challenges of Antibacterial Discovery, Lynn L. Silver, Clinical Microbiology Reviews Jan 2011, 24 (1) 71-109; DOI: 10.1128/CMR.00030-10, available at: <https://cmr.asm.org/content/24/1/71>

(Gram-negative, especially carbapenem-resistant strains of *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and the Enterobacteriaceae family)⁹.

Indeed, besides scientific challenges, a reason for the lack of innovation often claimed by the pharmaceutical industry is the lack of profitability. First, antibiotics are only to be used when really necessary, as bacteria develop resistance as they are exposed to antimicrobials^{10, 11}. Second, while there are cases where a preventive treatment with antibiotics is reasonable, antibiotics are mostly curative and are usually not suited for chronic use. Lastly, intense competition in the antibiotics field drives prices down and makes antimicrobials less profitable than products against chronic diseases. This inherently limits the profit prospects for companies in the existing economic model.

Current solutions based on incentives to the pharmaceutical industry have shown their limits.

To address the profitability issue, many incentives initiatives have been implemented. Already more than 50 national and international initiatives were taken the last decade to incentivize research and development (R&D) in antibiotics. For example, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), being a multi-lateral effort, focuses on streamlining and coordinating research. It was established in 2011 and currently has 22 participating Member States. It provides international coordination to direct national funding towards research projects that fill key knowledge gaps in AMR.

The Broad Spectrum Antimicrobials project of the Biomedical Advanced Research and Development Authority's (BARDA) on the other hand, goes out from the USA. It uses innovative business models to establish public – private partnerships with industry (both large pharmaceutical companies and small and medium-size enterprises).

The New Drugs 4 Bad Bugs programme (ND4BB), a European Union initiative, is a partnership between industry, academia, and biotech companies. They look more in detail into finding solutions to the scientific, regulatory, and business challenges hampering the development of new antibiotics.

These initiatives are highly relevant and promising in and off themselves but there are some gaps in the incentive system.

First, there seems to be a lack of global coordination.

Second, the majority of these initiatives (71%) is based on early stage push mechanisms¹², meaning funding of basic research and preclinical trials on academic level. Push mechanisms are dominant because they reduce R&D costs for companies. They help as a number of companies that develop new antimicrobials are small and medium-sized companies. Pull strategies intervene at a later stage but don't help so much with products being developed in the first place.

⁹ 2019 Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

¹⁰ Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The Review on Antimicrobial Resistance, Chaired by Jim O'Neill. May 2016, available at: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf, p. 1.

¹¹ Simpkin VL, Renwick MJ, Kelly R, Mossialos E. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. *J Antibiot (Tokyo)* 2017; 70(12):1087-1096.

¹² Simpkin VL, Renwick MJ, Kelly R, Mossialos E. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. *J Antibiot (Tokyo)* 2017; 70(12):1087-1096.

Push strategies address small and medium size enterprises (SMEs). Pull strategies do not do that to the same extent. Moreover, sustainability requirements and patient access are poorly integrated into R&D incentive programmes.¹³

Many of these programmes have not yet resulted in the antibiotic we need to tackle current resistance issues. A new financing model is needed if we want meaningful progress in antimicrobials development. Furthermore, we do not want an outcome similar to that of orphan drugs - very high prices for a small number of patients mainly preserved for countries who can afford them.

Prevention and rational use as essential elements of any strategy to fight AMR: low hanging fruit!

Above all, antibiotics that are available now and future ones, have to be used in a responsible way in every sector (including the veterinary sector) so that their effectiveness can be safeguarded. Tackling AMR indeed requires a One Health Approach, involving all sectors and stakeholders. Many countries are working hard to make patients and health care workers become aware of the problem. Primary care workers are key in conveying trustful information to their patients thus contributing to ensure that antibiotics are used wisely. Public campaigns, incentives, stewardship programmes and other measures that are taken, meet with varying degrees of success. They are not sufficient. Stronger preventative measures (e.g. vaccination, hygiene, infection control practices) and rational prescribing and use are necessary, as it will take a while before new drugs will come out of the pipeline. The achievement of higher degrees of health literacy amongst the population is also a key issue to be looked at. Government, healthcare workers and citizens have to work together as it is in the interest of all of us to prevent bacteria to develop further resistance to the existent antibiotics. We all are at risk for AMR.

Our Recommendations:

- ***Prevent the misuse of antibiotics through higher levels of health literacy.***

Member States and the European Commission should organise communication campaigns in collaboration with all stakeholders (healthcare payers, doctors, NGOs, patients, etc.) to raise awareness of proper antibiotic use and of the consequences of AMR.

People should be made aware of the impact of antibiotic resistance and its origins. They should be empowered to properly use antibiotics and only when prescribed by a certified health professional. They should also be informed about the prevention of infectious diseases through key and simple measures such as washing hands, hygienic food preparation, and vaccination. In the same vein, empowering consumers to make healthy and sustainable consumption choices could contribute to fighting AMR (e.g. less meat consumption, more organic products, etc.). That empowerment should be combined with measures to make those alternatives more accessible. (see [AIM Healthy Diet Factsheet](#))

¹³ Simpkin VL, Renwick MJ, Kelly R, Mossialos E. Incentivising innovation in antibiotic drug discovery and development: progress, challenges and next steps. *J Antibiot (Tokyo)* 2017; 70(12):1087-1096.

- **Strengthen the role of primary care in tackling AMR.**

Primary care accounts for about 80 to 90% of all antibiotic prescriptions.¹⁴ Primary care doctors and other healthcare providers clearly have a key role to play in the fight against AMR. They are in direct contact with patients and are responsible for prescribing medicines. They should be trained and advised by specialists on antimicrobial prescribing. Before prescribing a treatment, they are expected to carry-out thorough clinical evaluations and to ensure that microbiological samples are taken before the treatment is started. Prescribers should also select an antimicrobial with a spectrum of activity as narrow as possible. Their advice also has an impact on patient's perceptions towards their illness and their consequent perceived need for antibiotics. They therefore have the responsibility to inform their patients on why/how to use antibiotics prudently and appropriately. In no way should that information consist in merchandising for antibiotics. It should be objective, evidence based and adapted to the level of literacy of the patient.

Up to 50% of all antibiotic use in hospitals can be inappropriate. Misuse of antibiotics in hospitals is one of the main factors driving development of antibiotic resistance. AIM backs up the European Centre for Disease Prevention and Control (ECDC) recommendations for prudent use of antibiotics in hospitals which include: "the continuous education of prescribers and specialists included in comprehensive hospital strategies, the development of evidence-based hospital antibiotic guidelines and policies, and a proper monitoring of hospital antibiotic resistance".¹⁵

- **Collect more and better data on AMR.**

Updated figures on AMR are necessary to ensure effective policy responses. Evidence is also needed on the outcomes of the actions which are being carried out. If it is useful to know whether a measure is implemented by a Member State (MS), it is even more important to know whether the actions implemented work and to which extent. AIM encourages the ECDC to improve data collection in the field.

In its "Communication to the European Parliament and the Council on the Action Plan against the rising threats of AMR"¹⁶, the Commission acknowledges the importance of proper data collection. Some of the data gathered are not comparable and other important data is missing. There is thus a clear need to improve surveillance of antibiotic-resistant infections and their impact.

The ECDC report "Antimicrobial resistance surveillance in Europe 2014" also highlights the lack of comparable data, which has made impossible the identification of clear trends in the level of AMR in the EU. Furthermore, no updated information is available on surgical site infections, which are among the most common healthcare associated infections.¹⁷

¹⁴ Antibiotic resistance – facts and figures, European Center for Disease Control Website, Accessed September 2020. <https://antibiotic.ecdc.europa.eu/sites/default/files/media/en/eaad/Documents/antibiotics-factsheet-primary-care-prescribers.pdf>

¹⁵ Antibiotic resistance – facts and figures, European Center for Disease Control Website, Accessed September 2020. <https://antibiotic.ecdc.europa.eu/sites/default/files/media/en/eaad/Documents/antibiotics-factsheet-primary-care-prescribers.pdf>

¹⁶ Communication from the Commission to the European Parliament and the Council - Action plan against the rising threats from Antimicrobial Resistance, European Commission, 2011. https://ec.europa.eu/health/amr/sites/amr/files/communication_amr_2011_748_en.pdf

¹⁷ Antimicrobial resistance surveillance in Europe 2014, European Center for Disease Control Website, Accessed September 2020. <https://data.europa.eu/euodp/data/storage/f/2016-06-29T140054/antimicrobial-resistance-europe-2014.pdf>

- **Follow the One Health approach.**

Given that resistant micro-organisms exist in humans, animals and the environment, it is vital to follow a One Health Approach in tackling AMR, looking at the link between those areas and developing policies which target the whole scope of the problem.

The European Commission Farm to Fork strategy has the clear potential to tackle AMR in the agricultural sector. AIM welcomes the ambitious target to reduce overall EU sales of antimicrobials for farmed animals and in aquaculture by 50% by 2030. The Common Agricultural Policy (CAP) can also contribute to achieving farm practices which prevent the development of antimicrobial resistance.

The industrial causes of AMR in the pharmaceutical supply chain should not be overlooked. Pollution in the supply chain has been identified as a major cause of the spread of AMR (notably the dumping of active antimicrobial compounds into the environment).¹⁸ Antimicrobial manufacturing facilities in global supply chains should be a specific a point of focus. Part of the pharmaceutical industry has recognised the problem and an Industry Roadmap to combat AMR was issued in 2016. While this step forward is to be welcomed, the statement was not endorsed by all companies. Binding measures are necessary to ensure a coordinated approach.

- **Implement delinkage models to develop new antimicrobials.**

In order to increase the level of investment in antimicrobials, prevent overselling and provide long-term supply continuity, AIM is in favor of a model that delinks R&D costs and innovation from price and sales volumes. A market entry reward (MER) system is suggested by a number of reports and many journal articles as a solution^{19, 20, 21, 22, 23, 24}. For instance, the Health Impact Fund²⁵ has developed a concept where a pharmaceutical company can receive initially (minimum) incentives to cover some of the expenses for (efficient!) R&D and to set up a supply system. Later, the annual payments may

¹⁸ Antimicrobials in Agriculture and the Environment : Reducing Unnecessary Use and Waste, The Review on Antimicrobial Resistance, Chaired by Jim O’Neill. December 2015, available at: <https://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf>

¹⁹ Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The Review on Antimicrobial Resistance, Chaired by Jim O’Neill. May 2016, available at: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf, p. 1.

²⁰ 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, Clin Infect Dis 2017; 65(8): 1378-1382.

²¹ Towse A, Hoyle CK, Goodall J, Hirsch M, Mestre-Ferrandiz J, Rex J H. Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. Health Policy 2017; 121 (10), 1025-1030, available at: <https://pubmed.ncbi.nlm.nih.gov/28888660/>

²² Outterson K, Gopinathan U, Clift C, So AD, Morel CM, Røttingen JA. Delinking Investment in Antibiotic Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality. PLoS Med, 2016; 13(6):e1002043, available at: <https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002043>

²³ Health Impact Fund, Delink the price of drugs from the cost of research, Health Impact Fund, Accessed September 2020: <https://healthimpactfund.org/en/>

²⁴ Challenges to Tackling Antimicrobial Resistance: Economic and Policy Responses. (Anderson M, Cecchini M, Mossialos E, eds.). Cambridge: Cambridge University Press, European Observatory on Health Systems and Policies; 2020. doi:10.1017/9781108864121, available at: http://www.euro.who.int/_data/assets/pdf_file/0007/432790/Challenges-to-tackling-antimicrobial-resistance.pdf?ua=1

²⁵ Health Impact Fund, Delink the price of drugs from the cost of research, Health Impact Fund, Accessed September 2020: <https://healthimpactfund.org/en/>

increase depending on the outcome of post-marketing data on effectiveness, resistance profiles and stewardship arrangements. AIM believes that this could be one possible way forward.

Every member state could contribute financially (when possible and according to their means) and/or implement measures in line with the WHO's global plan of action on antimicrobial resistance. The organization would be done by a global coordination body (that could be hosted by the WHO) which is owner of the intellectual property, to avoid any issue of access. This body directs the research towards the most needed antibiotics. The antibiotic should meet predefined criteria and the developer would adhere to post-market authorisation conditions related to sustainability and patient access. In this model, the shareholders are governments and return on investment are affordable medicines and global access. Developing antibiotics is not cheap. Various studies calculated that the required budget for pull incentives would range from USD 1 billion to – USD 2 billion per antibiotic^{26, 27, 28}. Hence, developing 10 to 15 antibiotics within 10 years²⁹ would require approximately EUR 10-30 billion. But taking into account the impact to the global economy if no new efficacious antibiotics are available, it would be a reasonable investment.

- ***Think global.***

International collaboration on AMR should be intensified. Both European and international organisations should provide support to developing countries.

In an increasingly interconnected world, tackling AMR will require a global effort. Intensive exchanges and movement of people and food show that AMR does not stop at borders and requires a wide international collaboration between Member States, European Institutions but also global organisations like the World Health Organisation, the World Organisation for Animal Health and the Food and Agriculture Organisation of the United Nations.³⁰

In its One Health Action Plan, the European Commission recognizes that the economic and social impact of AMR is even greater in developing countries. AIM agrees that the EU can play a key role in raising awareness, sharing experiences and supporting capacity building in those countries. EU aid and cooperation activities should keep those objectives in mind so as to contribute to strengthening health systems and to implementing the Sustainable Development Goals in developing countries, including through the fight against AMR.³¹

²⁶ Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The Review on Antimicrobial Resistance, Chaired by Jim O'Neill. May 2016, available at: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf, p. 1.

²⁷ Towse A, Hoyle CK, Goodall J, Hirsch M, Mestre-Ferrandiz J, Rex J H. Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy* 2017; 121 (10), 1025-1030.

²⁸ Driving reinvestment in R&D for antibiotics and advocating their responsible use. Drive AB, March 2018. <http://drive-ab.eu/news/drive-ab-report/>

²⁹ Challenges to Tackling Antimicrobial Resistance: Economic and Policy Responses. (Anderson M, Cecchini M, Mossialos E, eds.). Cambridge: Cambridge University Press, European Observatory on Health Systems and Policies; 2020. doi:10.1017/9781108864121, available at: http://www.euro.who.int/_data/assets/pdf_file/0007/432790/Challenges-to-tackling-antimicrobial-resistance.pdf?ua=1

³⁰ One Health Action Plan Against Antimicrobial Resistance, European Commission, European Commission, June 2017. available at: https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf, 2017, p. 18

³¹ One Health Action Plan Against Antimicrobial Resistance, European Commission, European Commission, June 2017. available at: https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf, 2017, p. 20