

Our position

Working together to fight antimicrobial resistance

Recommendations to address the human health challenges posed by AMR



AmCham EU speaks for American companies committed to Europe on trade, investment and competitiveness issues. It aims to ensure a growth-orientated business and investment climate in Europe. AmCham EU facilitates the resolution of transatlantic issues that impact business and plays a role in creating better understanding of EU and US positions on business matters. Aggregate US investment in Europe totalled more than €2 trillion in 2016, directly supports more than 4.5 million jobs in Europe, and generates billions of euros annually in income, trade and research and development.

Executive summary

This paper presents AmCham EU's policy recommendations on how to address the global health challenge posed by antimicrobial resistance (AMR). In order to reduce the negative impact and spread of AMR, collaboration amongst all stakeholders is essential. We are fully supportive of the need to adopt a holistic approach to this complex issue, as clearly stated in the recent Communication '*A European One Health Action Plan against Antimicrobial Resistance*'.¹ In this paper we propose specific actions pertaining to human health.

The EU and its Member States can and should play a leading role in shaping and promoting the right policies against AMR. These include: antibiotic stewardship; improved and more coordinated surveillance mechanisms; full recognition and increased uptake of vaccines as a key element to decrease the use of antibiotics, but also of medical technologies, such as medical devices, in-vitro diagnostics, e-health and m-health to improve prevention, control and monitoring. Finally, and equally important, we urgently need new sustainable and predictable economic models and incentives for antibiotic, vaccine and diagnostic research and development (R&D) in order to secure appropriate investments for the future.

¹ European Commission, '*A European One Health Action Plan against Antimicrobial Resistance (AMR)*', June 2017, Available at https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

Introduction

Antimicrobial resistance (AMR) occurs when microbes evolve to resist antimicrobial medicines (antibiotics, antifungals, etc.), thereby decreasing their effectiveness.² Although AMR is a natural biological process, in recent years the inappropriate³ use of antibiotics has accelerated the emergence and dissemination of resistant bacteria. According to the World Health Organisation (WHO), if AMR is not properly addressed, we could be facing a ‘post-antibiotic era’ with limited treatment options for even the most common infections.⁴ The Review on Antimicrobial Resistance, led by Lord Jim O’Neill, estimated that ‘by 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output are at risk due to the rise of drug-resistant infections if we do not find proactive solutions now to slow down the rise of drug resistance’.⁵ In the EU, studies show that AMR is already responsible for about 25 000 deaths every year, with related healthcare costs and productivity losses exceeding 1.5 billion euro.⁶

AmCham EU welcomes the global political awareness and governance efforts around AMR, including at the EU, WHO, G7, G20, UN, and OECD level. Industry recognises that fighting AMR is a shared responsibility and is striving to do its part. The 2016 Davos Declaration and Industry Roadmap outline proactive commitments by the signatories to take action on issues under their direct control, e.g. reduce the environmental impact from the production of antibiotics; support continued commitment to global and regional-level stewardship and surveillance programmes, helping ensure antibiotics are used only by patients who need them; improve access to current and future antibiotics, vaccines, and diagnostics; explore new opportunities for open collaborations between the industry and the public sector to address challenges in R&D; and positively contribute to policy discussions around new economic models and incentives for the development of the next generation of antibiotics, vaccines, diagnostics and other innovative technological solutions that help address AMR.⁷

The EU can and should serve as a leader in addressing the global fight against AMR. AmCham EU welcomes the recent publication of the Commission’s Communication “A European One Health Action

² We mostly use the term ‘antibiotics’ (cf. ‘antimicrobials’) throughout the paper, as resistant bacteria represent the top priority for all stakeholders. However these principles could be applied to other antimicrobial medicines.

³ It is worth pointing out that any use of an antibiotic increases pressure for the development of resistance, including appropriate use. With our aging population, increase in patients with immunosuppression and increase in comorbidities, increasing appropriate use of antibiotics should also be expected.

⁴ D. Rawat, D. Nair., ‘Extended-spectrum β -lactamases in Gram Negative Bacteria’. *Journal of Global Infectious Diseases*, Sep-December 2010; 2(3): 263–274.

⁵ The Review on Antimicrobial Resistance, ‘Tackling drug-resistant infections globally’, May 2016, p. 4. Available at https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

⁶ ECDC, Technical Report ‘The bacterial challenge: Time to react’, September 2009, available at http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

⁷ See ‘Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance’, Davos, January 2016, available at https://amr-review.org/sites/default/files/Industry_Declaration_on_Combating_Antimicrobial_Resistance_UPDATED%20SIGNATORIES_MAY_2016.pdf. See also IFPMA, ‘Roadmap for Progress on Combating Antimicrobial Resistance’, September 2016, available at <http://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf>

Plan against Antimicrobial Resistance (AMR)".⁸ In this paper we present our priorities to address the main challenges in AMR policy in Europe: antibiotic stewardship, surveillance mechanisms, the role of infection prevention and vaccination in the fight against AMR, and the crucial issue of R&D incentives.

1. Preserve the effectiveness of existing antibiotics

Tackling AMR is a responsibility to be shared among a wide range of stakeholders, from EU institutions and national governments to manufacturers, healthcare professionals and patients. Antibiotic stewardship is key to preserving the effectiveness of existing treatments. We need to ensure that patients receive the right antibiotic, by the right route of administration, at the right dose, and for the right duration. Surveillance of pathogens with the early identification of changes in resistance patterns is also fundamental to implementing stewardship efforts, and is critical to physicians as they choose the most appropriate treatment for their patients. We would therefore welcome the development, in collaboration with the industry and other relevant stakeholders, of clear targets and benchmarks to define and measure good stewardship and appropriate use of antibiotics, and to measure progress in implementing the EU and National Action Plans on AMR.

Policy recommendations

AmCham EU welcomes the commitments taken by Member States in their June 2016 Council Conclusions, notably around setting up National Action Plans with measurable goals and supporting dialogue with the industry.⁹ We are encouraged by the language in the recently published EU Action Plan around 'Making the EU a best-practice region on AMR'.¹⁰ The European Commission and national governments could add significant value through, *inter alia*:

- Ensuring consistent implementation of existing EU guidelines on prudent use of antimicrobials in human medicine (2017).¹¹
- Increasing coordination and best practice sharing among Member States on the implementation of their National Action Plans, based on the 'One Health Approach'. To this end, we welcome the establishment of the 'One Health Network' and look forward to exploring ways of collaboration with industry.
- Further strengthening surveillance and monitoring of pathogens and resistance patterns.

⁸ See footnote 1. From here onwards, we will refer to it as the 'EU Action Plan' for brevity.

⁹ Council Conclusions on the next steps under a One Health approach to combat antimicrobial resistance, Brussels, 17 June 2016, available at <http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-antimicrobial-resistance/>

¹⁰ European Commission, Roadmap on the 'Commission's Communication on a One-Health Action Plan to support Member States in the fight against Antimicrobial Resistance (AMR)', October 2016, available at http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_176_action_plan_against_amr_en.pdf

¹¹ European Commission, *EU Guidelines for the prudent use of antimicrobials in human health*, June 2017, available at https://ec.europa.eu/health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf.

- Collecting data on the presence of antibiotic residues in the environment, in order to reduce the current knowledge gap on their relative impact on AMR.
- Promoting and funding specific training programmes for national authorities and healthcare professionals (HCPs) on prudent antibiotic use and proper stewardship.
- Raise awareness among healthcare professionals, patients and the wider public. European Commission data show that antibiotic consumption is higher in countries with lower levels of education and that consumption decreases as awareness of AMR increases.¹²

2. Broaden the use of vaccines and medical technologies to combat AMR

Preventing infections remains one of the most effective ways of slowing AMR. The expanded use of vaccines and medical devices (notably diagnostics) would reduce the need for antibiotics and decrease the selective pressure which produces AMR. For example, the ability to identify infections quickly and accurately, e.g. by allowing providers to distinguish bacterial from viral infections, would prevent the inappropriate use of antibiotics. Moreover, infection control programmes preventing healthcare-associated infections (HAIs) and limiting the horizontal spread of multi-resistant bacteria are essential tools in the fight against AMR.

Vaccines are essential tools in our fight against antibiotic resistant infections. For instance, a study showed that universal coverage by a pneumococcal conjugate vaccine could potentially avert 11.4 million days of antibiotic use per year for children younger than five.¹³ Alongside protecting vaccinated individuals directly, vaccines also provide indirect protection to non-vaccinated groups. Indeed, if the immunisation rate is high enough, they limit the spread of infections within a community ('herd immunity').¹⁴ Finally, vaccines do not only reduce bacterial infections but also viral infections for which antibiotics are unnecessarily prescribed. The EU Action Plan acknowledges the role of vaccination in combating AMR. Member States should implement measurable targets around prevention and vaccination in their National Action Plans.

Medical technologies such as medical devices and in-vitro diagnostics (IVDs) play a very important role in effectively preventing, diagnosing and controlling infections, thereby reducing the spread of AMR. As an example, technological solutions based on antiseptics (antibacterial sutures and implants, antibacterial incise drapes, catheters and dressing) have proved efficient in reducing healthcare-associated infections, therefore reducing the reliance on antibiotics and the development of resistance. Today, innovative medical technologies supporting the control of the horizontal spread (e.g. controlling the cleanliness of

¹² European Commission, 'Antibiotics in the EU – Use and Perceptions', Special Eurobarometer 445, April 2016, available at http://ec.europa.eu/dgs/health_food-safety/amr/docs/eb445_amr_generalfactsheet_en.pdf

¹³ R. Laxminarayan et al., 'Access to effective antimicrobials: A worldwide challenge, Antimicrobials: access and sustainable effectiveness', *Lancet*, 2016, 387: 168–75.

¹⁴ Vaccines Europe, 'The role of vaccination in reducing antimicrobial resistance (AMR)', Brussels, February 2017. Available at <http://www.vaccineseurope.eu/wp-content/uploads/2016/11/VE-policy-paper-on-the-role-of-vaccines-in-reducing-AMR-2016-FIN-1.pdf>

surfaces in hospitals or nursing homes) are being integrated into a large AMR inter-regional research project: Interreg-i41Health. Finally, e-health and m-health tools should also be considered as an important part of the solution and further applied to improve the monitoring of patients and their adherence to treatments, aiming to reduce the unnecessary use of antibiotics.

Policy recommendations

AmCham EU strongly encourages the EU and its Member States to fully utilise alternatives to antibiotics, preventive measures (e.g. vaccines) and medical technologies (e.g. medical devices and in-vitro diagnostics) as key tools to combat AMR. We recommend in particular to:

- Integrate concrete and measurable targets for life-long vaccination as a key element of National Action Plans on AMR.
- Adopt a 'life-long approach' in Member States' National Immunisation Programmes. An extended coverage and use of existing vaccines will help maximise their impact on AMR.
- Promote the development and uptake of medical technologies that help prevent, diagnose and control infections (e.g. medical devices or diagnostics).

3. Design economic models to incentivise R&D for antibiotics, vaccines and diagnostics

The discovery and development of new antibiotics, vaccines and diagnostics has not kept the pace of AMR. R&D in this area is particularly challenging, both due to inherent scientific barriers and market dynamics. Once brought to market, after costly and regulated processes lasting on average more than a decade, novel antibiotics are often held in reserve to delay the development of resistance. Furthermore, unlike other life-saving drugs, antibiotics are only given to patients for a short period of time (four days to six weeks). In order to repopulate the antibiotic pipeline, new economic models are needed. They should capture the full value of these critical medicines, provide an attractive return on investment and align with stewardship (for example by reducing the proportion of manufacturer revenue from antibiotic sales volume).

There is global consensus that a mix of different and complementary incentives is needed, acknowledging however that there is no 'one-size-fits-all' solution and that policies should be tailored to each specific national context. Significant efforts have been dedicated so far to mechanisms that reduce financial risk of companies by providing funding and expertise for R&D ('push' incentives). While these efforts should certainly continue, we believe these need to be complemented by market-based 'pull' mechanisms in

order to create a sustainable basis for investment.¹⁵ ‘Pull’ incentives designed to reward companies who successfully bring to market products addressing a high unmet medical need are crucial for further advances in the field. Potential examples are market-entry rewards (MERs) or novel IP mechanisms, such as transferable exclusivity extensions (TEE) coupled with appropriate public health safeguards to ensure appropriate stewardship and access. Companies are actively contributing to the current policy debate, working with individual Member States on new economic models for AMR-focused antibiotic R&D. In addition to new reward models for antibiotics, specific ‘pull’ incentives should be developed for vaccines, for use in larger populations. These could include advance market commitments (AMC) in developing countries and early commitments from the National Recommending bodies and payers in developed countries.

Without sufficiently strong ‘pull’ incentives, the existing and future ‘push’ efforts are unlikely to create a predictable and sustainable environment that would encourage private companies to devote the necessary resources to the development of critical new antibiotics needed to address AMR. When reflecting on how to develop policies to incentivise R&D in this area, AmCham EU supports the principles the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) presented in January 2017¹⁶. These highlight the need for clear definitions and criteria for products that would earn a ‘pull’ incentive, which should be established in collaboration with stakeholders. This is critical so as to enable the industry to focus resources where unmet medical need is highest. A predictable, reliable and sustainable funding scheme is also crucial to support R&D and incentivise long-term investments.

AmCham EU would also welcome increased international alignment between regulatory authorities such as European Medicines Agency (EMA), US Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA), and through the Transatlantic Task Force on Antimicrobial Resistance (TATFAR). We would also encourage as further dialogue between regulators and the industry on accelerated pathways and other regulatory incentives to speed up the development and approval of highly needed antibiotics, vaccines and diagnostics. Specifically, we would welcome continued dialogue with the EMA and further guidance on PRIME (PRiority MEDicines) eligibility for antibiotics. This includes exploring the eligibility criteria for PRIME in light of the way antibiotics are currently developed, and greater clarity on the application of the ‘unmet medical need’ definition, in order to increase the probability that antibiotics might qualify for PRIME in the future. No less importantly, the added value of new innovative antibiotics and vaccines for society should be adequately recognised.

¹⁵ The need for ‘pull’ incentives was also highlighted in a recent report by the London School of Economics and Political Science (LSEPS), commissioned by the Swedish Government. See LSEPS, ‘Policies and incentives for promoting innovation in antibiotic research’. Available at:

<http://www.lse.ac.uk/LSEHealthAndSocialCare/impacts/LSEHealthNews/News%20Attachments/Policies%20and%20incentives%20report.pdf>

¹⁶ IFPMA, ‘Sustainable models to overcome the challenging economics of antimicrobial R&D’, January 2017, http://www.ifpma.org/wp-content/uploads/2017/01/IFPMA_AMR_Policy_Position_January_2017_FINAL.pdf

At EU level, there has been important progress to facilitate antibiotic development through regulatory reforms implemented by the EMA. However, HTA and reimbursement systems at Member State level do not yet fully capture societal benefits nor support appropriate use of novel antibiotics. As stressed in the EU Action Plan, the Commission could better involve Member States' HTA bodies in AMR-related discussions to raise their awareness of AMR and facilitate new approaches when assessing the added value of new antibiotics and alternatives, diagnostics or a combination thereof.

Policy recommendations

Further to the EU Action Plan on AMR, we recommend that the EU and Member States:

- Clearly define the priorities and targets of incentives for the development of new antibiotics and vaccines against AMR pathogens. This may be implemented through an EU Priority Pathogens List, aligned with the WHO list, which would be defined in collaboration with all stakeholders, including the industry. In parallel, the characteristics of new agents that would earn a 'pull' reward should be developed.
- Constructively engage with stakeholders, to elaborate at EU and national level 'push' and especially 'pull' incentives for R&D, acknowledging that there is no 'one-size-fits-all-approach'.
- Support pilots and implementation of new economic models and incentives at EU and Member State level to boost the development of new antibiotics, alternatives, vaccines and diagnostics.
- Consider automatic acceptability of new antibiotics and vaccines addressing serious, life-threatening and multi-drug resistant (MDR) infections caused by resistant pathogens for accelerated regulatory review. Explore opportunities for greater inclusion of such products into accelerated pathways such as PRIME and Adaptive Pathways.
- Develop new or improved HTA approaches and foster methodological consensus-building to appropriately value novel antibiotics.
- Explore greater acceptance of innovative clinical trial protocols and a willingness to run trials with evidence that recognises the unique characteristics and value of antibiotics.
- Define (a) regulatory pathway(s) to:
 - approve drugs for multi-drug resistant pathogens that are relatively rare but expected to increase in the near future;
 - approve alternative antiseptic solutions to be used in prevention strategies (prophylactic) in replacement of antibiotics.

Conclusion

Combating AMR is a shared societal challenge. AmCham EU member companies are striving to do their part and will continue to do so, in collaboration with all stakeholders. The EU Action Plan on AMR is a good first step, but much work still needs to be done notably to:

- Promote antibiotic stewardship.

09/10/2017

- Expand and better coordinate surveillance tools and increase our knowledge of the mechanisms of resistance.
- Advocate for a broader and more effective use of vaccines, alternatives to antibiotics, and new technologies such as medical devices and diagnostics.
- Develop and implement new economic models and incentives to promote antibiotic, vaccines and medical devices (including diagnostics) R&D, which appropriately reward the results of investment in areas with high unmet need.