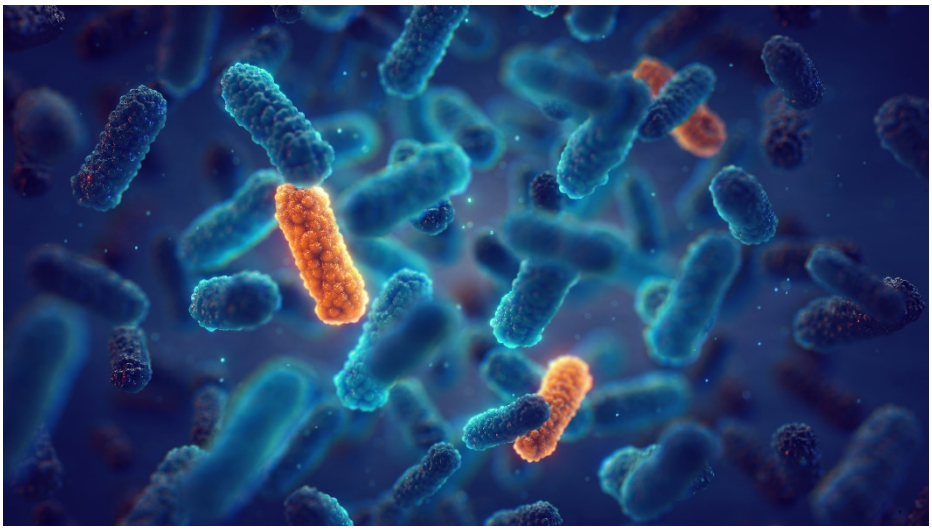
WORKSHOP PROCEEDINGS

ENVI Health Working Group

European Parliament

Antimicrobial resistance - New incentives to improve the accessibility and availability of antimicrobial medicinal products



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Antimicrobial resistance - New incentives to improve the accessibility and availability of antimicrobial medicinal products

Abstract

These proceedings summarise the presentations and discussions before the European Parliament's Health Working Group as part of the workshop on 'New incentives to improve the accessibility and availability of antimicrobial medicinal products', held on 26 October 2022. The five presentations touched, inter alia, upon the burden of AMR, the current research on development of antimicrobials, and incentive models.

These workshop proceedings were provided by the Policy Department for Economic, Scientific and Quality of Life Policies for the European Parliament Committee on the Environment, Public Health and Food Safety (ENVI).

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AMR	Antimicrobial resistance
COVID-19	Coronavirus Disease 2019
EC	European Commission
ECDC	European Center for Disease Prevention and Control
EEA	European Economic Area
ENVI	European Parliament Committee on the Environment, Public Health and Food Safety
EMA	European Medicines Agency
EP	European Parliament
EPP	European People's Party
EU	European Union
EU-JAMRAI	European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections
GARDP	Global Antibiotic Research and Development Partnership
GBD	Global Burden of Disease
HAI	Healthcare-associated infections
HERA	Health Emergency Preparedness and Response Authority
LMIC	Low- and middle-income countries
MEP	Member(s) of the European Parliament
MSE	Micro- and small enterprises
NIPH	Norwegian Instutute of Public Health
OECD	Organisation for Economic Co-operation and Development
PPP	Purchasing power parities

Q&A	Questions and answers
R&D	Research and development
S&D	Socialists & Democrats
SME	Small and Medium-sized Enterprise(s)
TEE	Transferable exclusivity extension
USD	United States Dollar
WHO	World Health Organization
WHO EURO	World Health Organization's Regional Office for Europe

EXECUTIVE SUMMARY

Background

The workshop on 'Antimicrobial resistance - New incentives to improve the accessibility and availability of antimicrobial medicinal products' was held on 26 October 2022 in Brussels, before the Health Working Group of the European Parliament's Committee on the Environment, Public Health and Food Safety (ENVI).

The workshop convened leading experts in the field - from the World Health Organization, the medical profession, innovating SMEs, academic research in Public Health and civil society advocacy. The five speakers presented diverse perspectives on the current state of play of research and development of new antimicrobial medicinal products and availability of old products in Europe and shared their respective expertise and conclusions on concrete actions needed with the Members of the Health Working Group.

Aim

The workshop was conceived to provide the European Parliament with a comprehensive and multidisciplinary overview of the European and global situation on the research and discovery of antimicrobial medicinal products for human use and on the specific challenges faced by research on antimicrobials, as well as to present the current discussions on the way forward to stimulate research and development in this field, in the context of the upcoming revision of the European pharmaceutical legislation.

Main discussions

Current and projected burden of AMR

The speakers all confirmed the growing risk and concern represented by antimicrobial resistance (AMR) for populations and economies in Europe and globally. The co-chairs of the Health Working Group qualified AMR as a 'silent pandemic', and a possible 'COVID-19 2.0'.

The European Centre for Disease Prevention and Control and the World Health Organization's joint report on AMR for 2022 record 670 000 infections due to resistant bacteria and approximately 33 000 deaths per year in the EU/EEA region[1]. The death toll directly attributable to resistance was estimated to reach 1.27 million deaths worldwide in 2019. In addition, the global economic cost of AMR is significant, estimated to amount to USD PPP 3.5 billion per year on average between 2015 and 2050. The results of the OECD's research highlight that the cost of inaction is high compared to the human (large number of deaths avoided) and economic (higher return on investment) benefits of acting.

According to the medical community, it is crucial to have access to a wide pharmacopeia of narrow- and broad-spectrum antimicrobial medicinal products to best treat patients and to prevent the acceleration of resistance. The consequences of AMR are potentially far-reaching, and AMR negatively impacts the health outcomes of both patients treated for a critical infection inside or outside of a hospital, and patients undergoing routine surgeries for which antimicrobials are used as prophylaxis.

[1] European Centre for Disease Prevention and Control and World Health Organization's Regional Office for Europe, 'Antimicrobial resistance surveillance in Europe 2022, 2020 data'. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/ECDC-WHO-AMR-report.pdf. Based on Cassini, A., *et al*, 'Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis', Lancet Infect Dis 2019; 19: 56–66.

However, medical practitioners face issues of availability on 'old' (generic) antibiotics in the EU, due to a large extent to fragile globalised supply chains and to the deregistration of certain products by marketing authorisation holders. The consultations conducted in the context of EU-Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU JAMRAI) confirm that shortages of existing antibiotics are a serious problem, and that many countries report essential current antibiotics being withdrawn from their national markets. Furthermore, regarding newly approved antibacterials, a delay is observed between approval and commercial launch, as well as strong disparities in the availability of the products across EU Member States, including antibiotics considered essential in WHO's essential medicines list.

The number of recently approved antibacterial agents and of those currently in clinical and preclinical developments is considered insufficient by the WHO to address the emergence and spread of antimicrobial resistance infections, in particular considering the high failure rate in the development process.

Challenges of research and development on antimicrobials

The process for research and development of new antimicrobials is characterised by an increasing cost of development along the development phases of a product, combined with a decreasing number of candidates due to failures to show safety or clinical efficacy.

The antibacterial drug discovery in Europe is dominated by small- and medium-sized enterprises, which are behind around 80% of drugs in development, including in clinical development. Larger pharmaceutical companies have left the field, which can be explained by the limited profitability compared to other medical fields and the limited forecast revenues on antibacterial medicinal products.

In recent years, improvements of the environment for research and development have been made in the EU and the preclinical pipeline is stronger than it has been in decades, in particular via the multiplication of 'push' incentives. The discovery of novel antimicrobial products remains, however, insufficient and 'pull' incentives could provide long-term / sustainable perspectives of financial return to those who invest in research and development.

The central challenge for policymakers is to determine which incentives are most appropriate to boost the discovery of novel antimicrobials, and at which point of the R&D process the public intervention is the most impactful.

Recommendations

A consensus emerged in the discussions on the urgent need for Europe to take actions for its citizens, and on assuming a share of the global responsibility.

Furthermore, it is crucial to uncouple how much revenues a specific antibiotic will generate from the level of sales for this antibiotic. The **principle of delinking** the financial return for developers of antibiotics from the volume of antibiotics consumed received undisputed support among speakers. This should help conciliating the contradictory objectives of, one the one hand reducing the consumption (via antimicrobial stewardship policies), and one the other hand, incentives to produce new antimicrobial medicinal products with low sales and profitability prospects. In this context, two pull incentive instruments which could be implemented at EU level have been discussed during the workshop:

- **Transferable Exclusivity Extensions (TEEs)** which are tradable vouchers awarded to the innovator of a novel antimicrobial, meeting specifications that can then be used to extend the monopoly time period of any patented medicine. They can either be applied by the awardee to another medicinal product of its own portfolio or sold to another company.

This model is supported by the innovative pharmaceutical industry, including the BEAM Alliance, as a readily actionable mechanism to reward innovation, where the duration of the exclusivity can be tailored, and whose operation can be centralised at European level. The award of TEEs would be conditioned on the fulfilment of eligibility criteria, in particular the capacity of the product to address an unmet medical need and its innovative character. However, public health and civil society representatives at the workshop consider that the TEE model would lead to potential high cost for Member States, due to, *inter alia*, a prolongation of high prices of non-related medicines and the absence of a guarantee for the healthcare system regarding access to the products. The lack of legal precedent and significant opportunities for speculation were also considered as additional risk factors for this pull incentive.

As an alternative to TEEs, ReAct proposed gradually awarded rewards/prizes along milestone achievements in the development of antimicrobial products, to facilitate the pathway from preclinical to clinical stages, and to ensure sustainable access to a new medicinal product. Their recommendations included a stronger public leadership for public health needs-driven R&D with a non-profit (global/EU) coordination entity for antibacterial drug discovery and increased public oversight and control of end products (production, procurement, distribution and patient access).

- The **Annual Revenue Guarantee** is a predictable and increased revenue for producers of marketed antimicrobial pharmaceutical products with proven public health value, delinking revenues from sale volumes.

This model studied in the context of the EU-JAMRAI aims at securing revenues for producers of antimicrobial medicinal products, while ensuring stable access to important antibiotics for healthcare systems. It has been designed to work independently from national health processes (health technology assessment, pricing, and procurement). It is adaptable to ensure access to both old and new antibiotics. BEAM Alliance, however, considers that this model is difficult to implement in Europe and may lead to freeriding behaviours when implemented in a multi-country setting.

Beyond the discussion on the specific incentive models, WHO and ReAct Europe stressed the need for the adoption of a holistic and multilateral approach. ReAct supported an 'end-to-end approach' away from market-based rationales but requiring public authorities to coordinate and control the research and development process in a public health needs-driven manner, including the provision of funding in a more sustainable way, as well as of mentorship, training and coordination in early research stages.

1. BACKGROUND ON AMR AND R&D

When exposed to antimicrobial pharmaceutical products (incl. antibiotics), microorganisms may evolve to survive and lose sensitivity to treatments via different biological processes, usually referred to as **antimicrobial resistance (AMR)**. The resulting impossibility to treat such drug-resistant infections with the existing drugs creates serious health risks for persons affected either via regular pathways (primarily person to person, between people and animals, and via food from animal origin), or by **healthcare-associated infections (HAI)**, e.g. when undergoing routine medical procedures.

"Antibiotic resistance is growing, and we are fast running out of treatment options. If we leave it to market forces alone, the new antibiotics we most urgently need are not going to be developed in time."

Marie-Paule Kieny, WHO's former Assistant Director-General for Health Systems and Innovation, 2017.

State of play on antimicrobial resistance and availability of medicinal products

The emergence of drug-resistant microorganisms with new resistance mechanisms is a growing health threat of global scale. Infections with bacteria having developed resistance to antibacterial products accounted for an estimated 33 000 attributable deaths in Europe in 2015[2], and based on the latest predictive statistical models, 4.95 million deaths are associated with bacterial resistance worldwide (including 1.27 million directly attributable to bacterial resistance)[3]. The latest research conducted by European agencies confirms the strong link between antibacterial drug consumption and the development of bacterial resistance[4]. Beyond drug-resistant bacteria, antimicrobial resistance can also develop with health-threatening fungi, viruses and protozoa.

Many preventive measures can reduce the development of antimicrobial resistance. For example, ensuring that a patient only receives an antibiotic when necessary, and after the diagnosis of a bacterial pathogen. Using narrow-spectrum antibiotics is preferable because they kill fewer of the body's commensal bacteria. Yet this presupposes that all antibiotics are accessible to medical professionals, which unfortunately is often not the case. Shortages of older and effective antibiotics (especially those that are narrow spectrum or for children) are common, due in particular to limited profitability and fragmented markets[5]. This has likely led to supplier consolidation and a dependence upon low-cost production outside of Europe. Yet, it is near impossible to confirm or to proactively identify supply vulnerabilities because supplier information is not transparently available[6]. The end result is that physicians may need to prescribe a broader-spectrum antibiotic than therapeutically warranted, thereby contributing to the development of antibiotic resistance.

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2 Cassini, A, Högberg. LD, Plachouras, D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis, The Lancet Infectious Diseases 2019; 19(1): 56-66.

3 Murray, JLC, et al, *Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis*, The Lancet, Vol. 399, Issue 10325, p. 629-655. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext#%20.

4 European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA), *Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA*. Available at: https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2021.6712.

5 World Health Organization, *Meeting report 'Antibiotic Shortages: Magnitude, Causes and Possible Solution'*, 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf.

European Commission, Directorate-General for Health and Food Safety, Jongh, T, Becker, D, Boulestreau, M, et al, *Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised)*. Available at: https://op.europa.eu/en/publication-detail/-/publication/1f8185d5-5325-11ec-91ac-01aa75ed71a1/language-en/format-PDF/source-245338952.

6 Ardal, C, Baraldi, E, Beyer, P, Lacotte, Y, Larsson, DJ, Ploy, MC, Rottingen, JA, Smith, I, *Supply chain transparency and the availability of essential medicines*, Bull World Health Organ., 2021. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8085627/.

Availability is also a problem for new antibiotics. Three antibiotics included on World Health Organization's Essential Medicines List and approved by the European Medicines Agency (EMA) after 2016 were unavailable in almost all EU countries as of the end of 2020[7]. The centralised authorisation procedure under EMA does not necessarily lead to the marketing of new products in all Member States, creating unequal access to new drugs, usually caused by profitability issues and affordability of expensive new drugs.

In parallel to the actions to prevent the development of resistant pathogens and to the adoption of non-pharmaceutical mitigation measures, a fundamental aspect to limit health risks linked to AMR is to improve **the availability and access to new antimicrobial products.** There are, however, several barriers that limit their accessibility and availability. First, research is experiencing difficulties in discovering new antimicrobial products. Despite broad national financial support to academic research worldwide, no new *classes of antibiotics* have been discovered since the 1980s. The World Health Organization (WHO) reports that between mid-2017 and 2020, there have only been 11 new antibiotics approved in the United States or the European Union (or both). In addition, the newly discovered products are considered to have limited clinical benefits over existing treatments and are often not responding to unmet medical needs. The WHO reports that 'overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance'[8].

The availability of new antimicrobial products is also hindered by the lack of investment from the pharmaceutical industry in research due to the lack of profitability of such new products compared to other medical fields such as cancer or immunology. This is illustrated by the withdrawal of the pharmaceutical industry from development of antimicrobials, and failures by small developers to cover the costs of R&D, even for companies making ground-breaking discoveries[9]. Alternative models which do not rely solely on profitability have been proposed, for a sustainable development of antibiotics[10].

European initiatives on the fight against AMR

The European Union's action on combatting AMR relies on successive action plans, such as the 2011 Action Plan against the rising threats from Antimicrobial Resistance[11], and the 2017 **European One Health Action Plan against Antimicrobial Resistance** (AMR)[12]. One of the key objectives of the current strategy is to 'boost research, development and innovation on AMR', both in the human health and animal health sectors. The European Commission aims at achieving this boost via various and new funding instruments for research and partnerships, such as the New Drugs for Bad Bugs (ND4BB) programme and the AMR Accelerator, which entails public funding within a public-private partnership between industry, academia and biotech organisations.

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7 Outterson, K, Orubu, E, Rex, J, Ardal, C, Zaman, M, Patient Access in 14 High-Income Countries to New Antibacterials Approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010-2020, in Clinical Infection Diseases, Vol. 74 Issue 7, 2022. https://academic.oup.com/cid/article-abstract/74/7/1183/6319400/.

World Health Organization, *2020 Antibacterial agents in clinical and preclinical development*, An overview and analysis. Available at: https://apps.who.int/iris/rest/bitstreams/1341746/retrieve.

9 Årdal, C, Lacotte, Y, Ploy MC, (on behalf of EU-JAMRAI), *Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe*, Clinical Infectious Diseases, Volume 71, Issue 8, 15 October 2020, Pages 1994–1999. Available at: https://academic.oup.com/cid/article/71/8/1994/5736365?guestAccessKey=4b09d6a0-1dda-49e7-9de7-2ca4299da1a3.

10 REVIVE, Global Antibiotic Research and Development Partnership (GARDP), *The non-profit future of antibacterial R&D – by Brad Spellberg*, Available at: https://revive.gardp.org/the-non-profit-future-of-antibacterial-rd-by-brad-spellberg/.

11 European Commission, Communication from the Commission to the European Parliament and the Council on an Action plan against the rising threats from Antimicrobial Resistance, COM(2011) 748.
Available at: https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:52011DC0748.

12 European Commission, Communication from the Commission to the Council and the European Parliament on A European One Health Action Plan against Antimicrobial Resistance (AMR), COM(2017) 339.
Available at: https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A52017DC0339.

On the development of new therapeutics and alternatives, the aim is to enhance the discovery of new antimicrobial drugs and alternative approaches (e.g. repurposing of old antimicrobials, combination therapies), with an emphasis on SMEs' innovation capacities. Nevertheless, the European Court of Auditors underlines the high level of financial support for research in the EU (EUR 1.5 billion since 2004) but also the lack of breakthrough, and the persistence of market failures in antimicrobial research and development[13]. The high level of financial support is not sufficiently focussed on the discovery of new antibacterial therapies but is a more general support of research.

The 2017 Plan also includes actions related to non-financial support to research, i.e. facilitating data-sharing across research organisations, support on the conduct of clinical trials and on the use of digital technologies in the development of therapeutics and alternative approaches, as well as coordination of national research under the Joint Programming Initiative on Antimicrobial Resistance[14]. It is complemented by national actions plans / strategies within Member States called for by the World Health Organization[15].

The 2020 **Pharmaceutical Strategy for Europe** of the European Commission[16] also describes the lack of development of antimicrobials as one of the greatest unmet medical needs of global concern. It recalls the antimicrobials paradox, according to which incentives and interests of the pharmaceutical industry to develop new products are constrained by the public policy strategies to reduce excessive and inappropriate use and keep consumption to a minimum, as well as the strategy of healthcare professionals to use innovative antimicrobials only as a last resort to prevent rapid emergence of resistance and only if clearly indicated by a diagnostic result. This strategy highlights the need for incentivisation (e.g. pull incentives to provide a viable market to the industry) and new pricing systems, to be integrated into the work of the EU Health Emergency Response Authority (HERA) and in the current evaluation of the general pharmaceutical legislation. It also aims to improve access to generic medicines including through innovative procurement approaches and seeks to understand the root causes of deferred market launches.

Besides, the fight against AMR is incorporated in **other strategies and actions** of the European Union aimed at reducing the use of antimicrobials or its presence in the environment, e.g., the European Union Strategic Approach to Pharmaceuticals in the Environment[17] and the Farm to Fork Strategy (aiming at reducing by 50% the overall EU sales of antimicrobials for agriculture by 2030)[18] and the adoption of restrictive measures on their use in the Veterinary Medicinal Products Regulation[19] and Medicated Feed Regulation[20].

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13 European Court of Auditors, Special Report 'Addressing antimicrobial resistance: progress in the animal sector, but this health threat remains a challenge for the EU'. Available at: https://op.europa.eu/webpub/eca/special-reports/amr-18-2019/en/.

14 European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections, webpage 'Vision / Mission'. Available at: https://eu-jamrai.eu/vision-mision/.

15 World Health Organization, Library of AMR national action plans. Available at: https://www.who.int/teams/surveillance-prevention-control-AMR/national-action-plan-monitoring-evaluation/library-of-national-action-plans.

16 European Commission, Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on the Pharmaceutical Strategy for Europe, COM(2020) 286. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52020DC0761.

17 European Commission, Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee on a European Union Strategic Approach to Pharmaceuticals in the Environment, COM(2018) 128. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52019DC0128.

18 European Commission, Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on A Farm to Fork Strategy for a fair, healthy and environmentally-friendly food system, COM(2020) 381. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52020DC0381.

19 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, OJ L 004 7.1.2019.

20 Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2019 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) No 183/2005 of the European Parliament and of the Council and repealing Council

The research conducted by the **EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections** (EU JAMRAI) points at the need for another approach to tendering, based on multi-award tendering to strengthen the supply of existing antibiotics, rewards for independent supply chains, and departure from price as the sole criterion. With regard to the supply of antimicrobials for unmet medical needs, JAMRAI recommends furthering the support to research and development grants under the coordination of HERA, and of pull incentives for small market antibiotics (e.g., novel antibiotics and older, fragile markets like for children's formulations).[21]

In its **September 2018 Resolution** on the European One Health Action Plan against Antimicrobial Resistance (AMR)[22], the European Parliament called for investments both in new antibiotics as well as in alternatives to antimicrobials (e.g. vaccines). The EP highlighted that 'the usual business model for developing medicines is not suitable for antibiotic development'. In this regard, it called for a delinking of R&D models from profitability linked to volumes sold, as suggested by the work of the World Health Organization, the World Intellectual Property Organization and the World Trade Organization. It also emphasised the need for a combination of push and pull incentives.

Most recently, on 5 September 2022, a subgroup of the **AMR One Health Network**, gathering government experts of the Member States of the public health, animal health and environmental sectors, has published a report in which policy suggestions for actions by the EC on AMR are formulated[23], following up on Commissioner Kyriakides' announcement of a new policy initiative on AMR in January 2022. With regard to **accessibility and availability** of medicinal products, the suggested actions set as priorities are:

- Ensuring continued **availability and accessibility of 'old', narrow-spectrum antimicrobials** via a stable supply chain to avoid the shortages experienced in the recent years. Another proposal suggests including secure supply of antibiotics in the upcoming international instrument on pandemics. Another suggests an EU-wide agreement with pharmaceutical companies to secure the supply of a list of antibiotics with special medical value.
- Working on the availability of antibiotics, both for humans and animals, especially when there is a lack of commercial interest, via **new incentives and levers**. Another proposal suggests push and pull incentives in relation to economic incentives, procurement, legal and regulatory aspects and increasing transparency to assure effective early warning systems, and reinforced research.
- Ensuring accessible and affordable **rapid diagnostic tools** and rapid antibiograms for animal health professionals.
- Examining issues with the availability of first line / lower priority antimicrobials (veterinary sector).

Directive 90/167/EEC, OJ L 4/1 7.1.2019.

21 EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (JAMRAI), *A Strategy for implementing multi-country incentives in Europe to stimulate antimicrobial innovation and access*. Available at: https://eu-jamrai.eu/wp-content/uploads/2021/03/EUjamrai_D9.2_Strategy-for-a-multi-country-incentive-in-Europe_INSERM-FHI.pdf.

22 European Parliament resolution of 13 September 2018 on a European One Health Action Plan against Antimicrobial Resistance (AMR), 2917/2254(INI), OJ C 433m 23.12.2019, p. 153-172.

23 EU AMR One Health Network, *Final report – Subgroup established under the EU AMR One Health Network to formulate suggestions for AMR Actions*, 5 September 2022. Available at: https://health.ec.europa.eu/latest-updates/final-report-subgroup-established-under-eu-amr-one-health-network-formulate-suggestions-amr-actions-2022-09-05_en.

2. WORKSHOP PROGRAMME

The workshop consisted of two parts with a total of five presentations:

Part one: State of affairs, global situation and current needs in the EU

The burden of AMR in Europe and globally: prioritisation of antimicrobials beneficial for the global One Health
Sarah Garner (World Health Organization)

Patients' needs for antibiotics and medical strategies to optimise the use of antimicrobial products
Thomas Tängdén (University of Uppsala)

Part two: Incentives and support for research, potential policy developments at EU level

The central role of SMEs in research and development: the case for SME-compatible pull incentives
Marc Gitzinger (BEAM Alliance)

Securing access to new (and old) antibiotics through an annual revenue guarantee
Christine Årdal (NIPH/EU-JAMRAI)

Achieving sustainable access to antibiotics through public leadership and an end-to-end approach to research and drug discovery
Kerstin Åkerfeldt (ReAct Europe)

3. SUMMARY OF THE PRESENTATIONS

The workshop was chaired by the co-chairs of the Committee's Health Working Group, MEP Sara Cerdas and MEP Dolors Montserrat.

Opening remarks

MEP Sara Cerdas introduced the workshop by recalling the significance of AMR, called by some the '**silent pandemic**'. The purpose of this workshop is to gather first-hand inputs from experts (patients, medical professionals, industry, academics and policy makers) about this growing European and global issue. The co-chair of the Health Working Group finally raised the central question of whether Europe is doing enough, and whether AMR can be considered a '**COVID-19 2.0**'.

3.1. The burden of AMR in Europe and globally: prioritisation of antimicrobials beneficial for the global One Health

This presentation was given by Sarah Garner, Senior Policy Advisor at WHO's Regional Office for Europe.

- **State of affairs on the global antimicrobial resistance situation: Geographical differences in the burden of resistance and global development of resistance**

The presenter provided key figures on AMR, its burden, and the possible way forward: In 2019, **1.27 million deaths were caused by AMR worldwide**[24]. The cost of AMR is not limited to fatalities, and OECD and World Bank estimates have suggested that between 2015 and 2050, **AMR would cost up to USD (PPP) 3.5 billion** per year on average to the healthcare services of the 33 countries included in the analysis[25]. Data from the OECD also shows in parallel that **investing 2 USD (PPP) per capita per year** in a comprehensive package (hygiene, ending over-prescription, rapid testing, delayed prescription, mass media campaigns) could reduce AMR-related mortality, pay for itself within just one year and even save more than the cost of AMR itself, i.e., USD 4.8 billion per year in OECD countries.

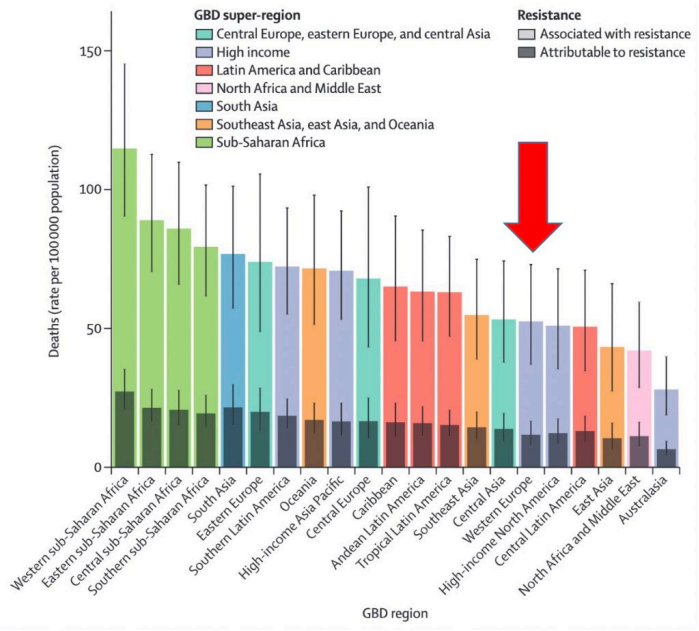
As shown in Figure 1, Europe is neither the worst nor the best regarding the patterns and prevalence of AMR globally. Strong differences exist between the 21 (global burden of disease) regions[26], but all regions could show better progress in the fight against AMR.

[24] Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. The Lancet Infectious Diseases 2019; 19(1): 56-66.

[25] Organisation for Economic Co-operation and Development, 'Stemming the Superbug Tide, Just A Few Dollars More', 2018, available at: https://www.oecd-ilibrary.org/social-issues-migration-health/stemming-the-superbug-tide_9789264307599-en.

[26] Regions defined pursuant to the Global Burden of Disease (GBD) regional classification system.

Figure 1: All-age rate of deaths attributable to and associated with bacterial antimicrobial resistance by GBD region, 2019



Source: Antimicrobial Resistance Collaborators (2022), Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, The Lancet.

Focusing on Europe, antimicrobial resistance (AMR) remains a major public health concern in the WHO European Region according to the ECDC and WHO's 2022 surveillance report on AMR. AMR is widespread, although the situations **vary widely depending on the bacterial species**, **antimicrobial group and geographical region**. A north-to-south and west-to-east gradient is generally observed, with higher AMR percentages in the southern and eastern parts of Europe. The full report provides pathogen- and country-specific data on the prevalence of resistance in European countries[27].

- **Risks and costs of the research and development (R&D) process**

In light of the growing global antimicrobial resistance, the development of new antimicrobial medicinal products is essential. However, the process for the research and development of new antimicrobials is a delicate subject and it is important to have a proper system of incentives in place. For normal medicinal products, the price of development goes up along development phases (basic research, first-in-humans research, clinical trials), and the number of potential candidates decreases at every single stage. The current discussions at WHO EURO revolve around the **methods for the public sector to 'de-risk' this R&D process**.

The development of medicinal products can be seen as a '**relay race'**, which used to be relatively **simple and linear**: universities did the basic research and passed it onto larger companies who implemented the development stage. This linear process of this relay race has been disturbed: Over time, the way companies operate changed a lot due to **outsourcing** and **blurring the private and public sectors** at the early stages (universities spinning out, incubators, hubs for particular diseases or specific countries). The cost of clinical trials is contracted out to research organisations who need to make a profit on their activity. A lot of risk is borne by the public sector and the prices are going up.

[27] European Centre for Disease Prevention and Control (ECDC) and World Health Organization's Regional Office for Europe (WHO EURO), Antimicrobial resistance surveillance in Europe 2022 (2020 data), available at: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2022-2020-data.

The questions which should be asked, are therefore: Which are the most appropriate incentives, and at which point of the relay race?

- **Need for new antibiotics against critical priority pathogens and indications**

In the *2021 Antibacterial agents in clinical and preclinical development: an overview and analysis*, the WHO mapped antibacterial agents in development at clinical and preclinical development stages and observed that, at each phase, smaller and smaller numbers of candidates for antibacterials are observed. The report concluded that **recently approved antibacterial agents, and those in the different stages of clinical development, are still insufficient** to address the emergence and spread of antimicrobial-resistant infections. While the preclinical pipeline features some innovative products, only a fraction of these is likely ever to come to market due to the high failure rate characteristic of the drug development process.

Candidate antibacterials against the critical pathogens, as defined in WHO's list of critical pathogens, are also lacking. The WHO has developed a list of priority pathogens (i.e., families of bacteria causing great threats to human health) against which new antibiotics must be developed, with the group of **critical priority** pathogens (*Acinetobacter baumannii*; *Pseudomonas aeruginosa*; *Enterobacteriaceae*) as most urgent priority. Furthermore, over 80% of newly approved antibiotics belong to **existing antibiotic classes** where resistance mechanisms are established. In a same class of antibiotics, **antimicrobial resistance can be transferred easily**. Considering these observations, **other mechanisms to manage AMR are needed** to diversify the armamentarium.

For instance, one of manner in which AMR can be controlled is **antimicrobial stewardship**, i.e. a coherent set of actions which promote the responsible use of antimicrobials. This definition can be applied to actions at the individual level as well as the national and global level, and across human health, animal health and the environment[28].

- **The World Health Organization's AWaRe tool (Access Watch and Reserve)**

The WHO has adopted an **advisory list of essential medicines**, which should be available and accessible in all countries to meet the populations' healthcare needs. For AMR, the starting point was the preparation of a list of common infections, indicating which **antibiotics of choice** should be available to treat them. At the same time, a list of **reserve list of antibiotics** was also drawn, which should be used as a last resort when all other antibiotics have failed.

3.2. Patients' needs for antibiotics and medical strategies to optimise the use of antimicrobial products

This presentation was given by Thomas Tängdén, Senior consultant and associate professor of infectious diseases at Uppsala University Hospital.

- **A medical perspective on the importance of antimicrobials for patients' health: Illustration of the clinical importance of resistance by two clinical cases**

Antimicrobial resistance is complex and can be caused by many different genes and mutations, occurring in different bacterial species, causing non-susceptibility to a large number of antibiotics. Illustrating the causes and consequences of AMR by two clinical cases provides clearer insights:

[28] World Health Organization, *Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries, a WHO practical toolkit*, 2019, available at: https://apps.who.int/iris/bitstream/handle/10665/329404/9789241515481-eng.pdf.

Clinical case 1: 22-year-old woman, with fever and flank pain. Lab results and physical examinations suggest a urinary tract infection. The patient is not critically ill and oral antibiotics should be enough.

The two central preliminary questions before treating this patient would be: *what bacteria cause the infection*, and *what antibiotics are effective*? However, this information is rarely available when starting a treatment. In practice, medical practitioners try to understand (1) the probable **source or origin of infection** (urinary tract), (2) **what bacteria** usually cause this infection (medical training, resistance surveillance data), (3) **patient factors** that increase the risk of resistance (e.g. previous infection with resistant bacteria, international travel to countries with high resistance levels, recent hospitalisation, or antibiotic treatment), (4) **other considerations** for the treatment (e.g. allergies, pharmaceutical interactions, pre-existing conditions).

- **Types of antibiotics needed to treat patients in the EU, and types of therapies (empirical therapies vs. pathogen-specific therapies)**

Appropriate use of antimicrobial agents involves obtaining an accurate diagnosis, determining the need for and timing of antimicrobial therapy, understanding how dosing affects the antimicrobial activities of different agents, tailoring treatment to host characteristics, using the narrowest spectrum and shortest duration of therapy, and switching to oral agents as soon as possible. In addition, nonantimicrobial interventions are equally or more important in some cases and should be pursued diligently in comprehensive infectious disease management[29]. In absence of microbiological results, **empirical therapy** is used (as opposed to targeted pathogen-specific therapy) and relies heavily on treatment recommendations and resistance surveillance data.

- **Empirical antibiotic therapy** is often given to patients who have a proven or suspected infection, but where the responsible organism(s) or bacteria have not yet been identified.
- **Pathogen-specific antibiotics** can only be used against a specific pathogenic species/genus rather than a general disease category like sepsis or urinary tract infections (UTI). In most cases, the use of such drugs would require the identification of the pathogen and sometimes a specific resistance mechanism, which would need a rapid diagnostic infrastructure and is often difficult for medical reasons. This approach may show parallels to newer cancer drugs that are marketed with companion diagnostics[30]. This type of therapy has been used for the treatment of tuberculosis and against *Clostridioides difficile*. **Patient-specific approaches** go a step further and require specific diagnostic capabilities and adjustment of therapies to an individual patient which requires a highly developed diagnostic and healthcare system infrastructure.

The **risk of resistance** [increased by wide-spectrum antimicrobials] and the **severity of the patients' illness** are put in balance in the choice of the therapy. For critically ill patients, even a low risk of resistance can have severe medical consequences and broad-spectrum treatments which are active against many bacterial species are needed to improve patient outcomes and reduce mortality. For mild infections, standard treatment and narrow-spectrum therapies are sufficient, even if a small risk of resistance exists.

Three antibiotics are considered for the case of the 22-year-old patient with fever and flank pain: (1) co-trimoxazole, well tolerated by patients but with a resistance rate > 20%, (2) ciprofloxacin, with collateral damage on gut microbiome and resistance development but inferior resistance rate >12%, and (3)

[29] Leekha S, Terrell CL, Edson RS, *General principles of antimicrobial therapy*, Mayo Clin Proc. 2011 Feb, available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3031442/.

[30] Maxson T, Mitchell DA, *Targeted Treatment for Bacterial Infections: Prospects for Pathogen-Specific Antibiotics Coupled with Rapid Diagnostics*, in Tetrahedron, June 2016, available at: https://pubmed.ncbi.nlm.nih.gov/27429480.

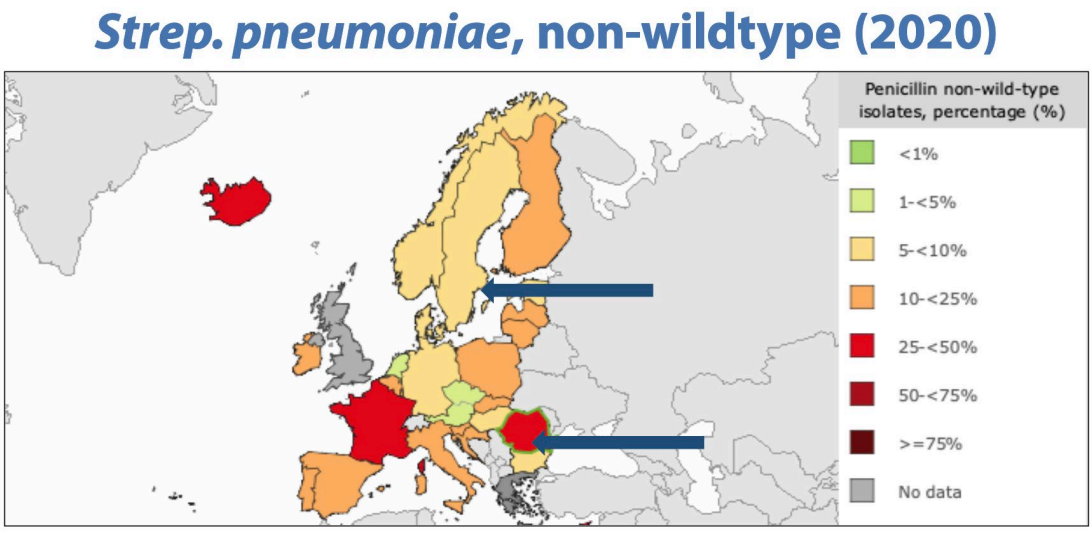
ceftibuten, which is well tolerated and a resistance rate of 5%. The best option is ceftibuten, but this generic old antibiotic has been **withdrawn from the market** (**deregistered**). Medical professions are forced to use second- or third-best antibiotics, resulting in both **worse outcomes for patients** and **accelerated resistance**.

Shortages and deregistration of generic antibiotics is increasing worldwide, affecting both commonly used antibiotics and those used in critically ill patients in intensive care units. Shortages are due to a great number of factors (e.g. commercial, manufacturing or quality issues), but the primary reason is a **fragile supply system** for 'old' antibiotics, relying on too few producers and providers of essential medicines.

Clinical case 2: 45-year-old woman, with coughing, high fever and shivering, who recently moved from Romania to Sweden. Blood tests and x-rays suggest bacterial pneumonia. The standard empirical treatment did not relieve the symptoms. The culture results showed a growth of resistant pneumococci, which prompted a shift to targeted therapy which did not prevent severe medical complications and discharge only after five weeks.

The second clinical case illustrates that resistance rates vary greatly between patient populations, healthcare settings, countries, and continents. Major differences exist across Member States within EU. This is true for, e.g., pneumococci, with a stark difference for instance between Romania and Sweden, but the variability is even stronger in gram-negative bacteria[31]. As shown in Figure 2 below based on ECDC data, resistance rates of specific bacteria such as Streptococcus pneumoniae vary greatly across Member States.

Figure 2: Resistance rate of Strep. Pneumoniae, non-wildtype isolates, to penicillin in 2020



Source: European Centre for Disease Prevention and Control (ECDC), Surveillance Atlas of infectious diseases.

[31] **Gram-positive vs. Gram-negative bacteria**: The outer membrane of Gram-negative bacteria is structurally different from Gram-positive bacteria and is an important reason for resistance to a wide range of antibiotics. The outer membrane of Gram-negative bacteria limits the access of antibiotics to their intracellular target. All the critical priority pathogens of the WHO global priority pathogens list of antibiotic-resistant bacteria are Gram-negative bacterial pathogens. Gram-negative bacteria cause significant morbidity and mortality worldwide. They can cause serious diseases in humans, especially in hospitalised and immuno-compromised individuals. Nosocomial (hospital-acquired) infections caused by Gram-negative bacilli are the most challenging issue for health care professionals due to resistance to antibiotics.

Table 1 below presents the consequences of antimicrobial resistance from the perspectives of patients, prescribers, and the healthcare system, in terms of human and financial costs.

Table 1: Consequences of antimicrobial resistance from a medical perspective

Consequences of antimicrobial resistance from a medical perspective	
Patients	Mild infections: • Worse treatment conditions: Intravenous antibiotics and hospitalisation • Treatment failures
	Severe infections: • Complications • Prolonged hospitalisation / admission in intensive care units • Treatment failures • Increased mortality
Prescribers	• Increasing resistance rates trigger the use of broader-spectrum antibiotics, which accelerates resistance • Non-evidence-based treatments must be used
Healthcare system	• Need for more patient beds • Higher costs

Source: Presenter's own elaboration.

Finally, it must be highlighted that resistance is not only a threat in the management of common infections but also a hazard to **many disciplines of modern medicine that depend on antibiotics** to prevent and treat infections, such as neonatal care, chemotherapy for cancer and major surgeries.

Take home messages

1. The consequences of AMR extend far beyond common infections and mortality estimates.
2. Precision treatment requires a broad panel of antibiotics with different spectra of activity and formulations.
3. The lack of generic antibiotics is an unnecessary added problem and can be solved by political decisions.

Finally, money alone is not the solution, and engaging with healthcare professionals is paramount to ensure that political actions meet patients' medical needs.

3.3. The central role of SMEs in research and development: the case for SME-compatible pull incentives

This presentation was given by Marc Gitzinger, President of BEAM Alliance.

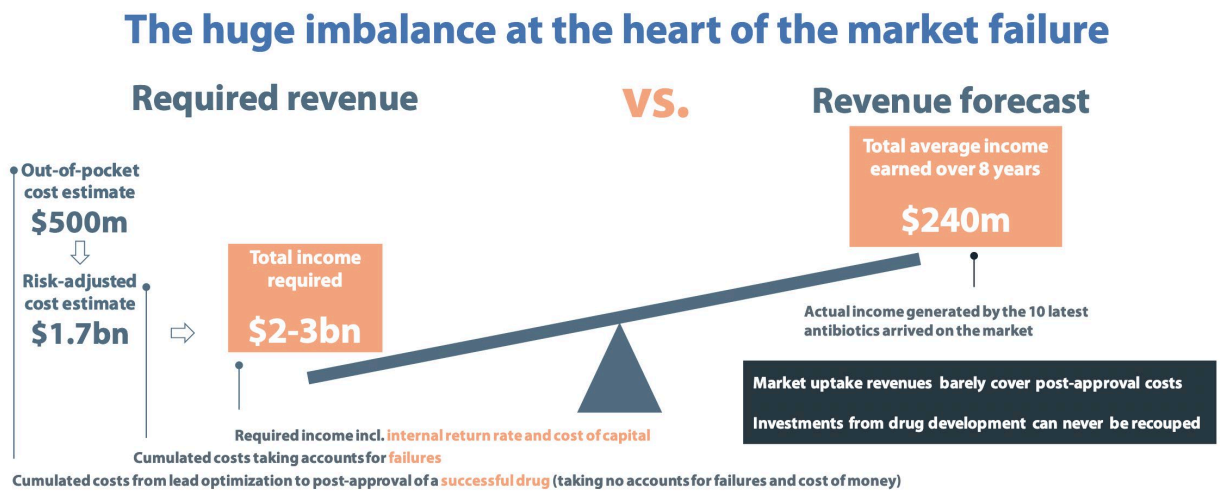
The presentation started with a brief introduction of BEAM Alliance, the Alliance of Biotech companies from Europe innovating in Anti-Microbial Resistance research. The Alliance represents 70 SMEs (mostly MSEs) in Europe (and Israel) which are still active in the development on novel antimicrobial drugs and diagnostics, working on advocacy to highlight the issue of AMR and the identification of solutions to overcome this great unmet medical need.

- **The central role of SMEs in the research and development (R&D) on antibacterial medicinal products: a critical player in a critical situation**

According to the WHO study on pipelines of antibacterial candidates, SMEs hold around 80% of drugs in development, including clinical development. A lot of the larger pharmaceutical companies left the field, as the business case is impossible to defend: the risk-adjusted cost of development is estimated

around $1.7 billion[32] for actual revenues that do not exceed $240 million per year over the first 8 years[33]. This prevents the private sector to make significant investments in the developments of novel products. The figure below illustrates the financial situation at the onset of the imbalance between revenues required and revenues forecast in the development of antimicrobial medicinal products.

Figure 3: The huge imbalance at the heart of the market failure



Sources: Presenter's own elaboration, on the basis of Outterson, K, *Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines*, Health Affairs 2021, 40(11), 1758-1765; Boston Consulting Group Report 2022, *The Case for a Subscription Model to Tackle Antimicrobial Resistance*; and Rahman et al, *Market concentration of new antibiotic sales*, J Antibiot 74, 421-423 (2021).

Looking at the role of SMEs, the situation in the normal biotech and drug development environment is the following: SMEs often take innovation from the academic sector, bring it forward into clinical development, and large pharmaceutical companies normally pick these drugs up, ensuring global approval and access to these medicines. This chain is broken in the current development of antimicrobials, and SMEs have to nearly go all the way, due mainly to the focus on the market for generics with low prices and low volumes of sales (by virtue of stewardship policies).

- **The need for sustainable scientific and financial support for SMEs in the EU: SME-compatible pull incentives mechanisms**

Responding to MEP Sara Cerdas' question on whether enough is done in Europe to fight AMR, the president of BEAM Alliance observed that the situation has improved. In particular, push incentives (supporting R&D and reducing a developer's cost and risk of researching and developing new drugs either by lowering the costs, decreasing the barriers to participation or by sharing the costs/risks across multiple parties) have been put in place and awareness is growing. However, most importantly, SMEs need **pull incentives**, i.e. improving the economic situation and give a perspective to companies developing novel antibiotics that they will be able to obtain a return on their investment. Pull mechanisms reward the successful development of a drug by increasing or ensuring future revenue. It

[32] Outterson, K., '*Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines*', in Health Affairs 2021 40:11. https://www.healthaffairs.org/doi/10.1377/hlthaff.2021.00688?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

[33] Rahman, S., *et al*, 'Market concentration of new antibiotic sales', in The Journal of Antibiotics, 2021, https://www.researchgate.net/profile/Chantal-Morel-2/publication/349767267_Market_concentration_of_new_antibiotic_sales/links/60891c248ea909241e2c7e69/Market-concentration-of-new-antibiotic-sales.pdf.

can be achieved through market-making (financial) tools or market-shaping (lego-regulatory policies) rewards.

To achieve successful pull incentives, Marc Gitzinger stressed the importance of **delinking the financial reward for developers from the volumes of antibiotics** sold to ensure appropriate stewardship and that access is given to patient. Delinkage consists in decoupling the cost of investment in research and development on antimicrobial resistance from the price and volume of sales to facilitate equitable and affordable access to new antibiotics. The concept has been endorsed by the United Nations General Assembly and the G20[34].

Furthermore, if the EU adopts a pull mechanism, it should be (1) **rapidly implementable**, (2) it must **reward innovation**, and (3) it must be of **sufficient magnitude** and **predictable**.

Furthermore, the eligibility criteria to define an eligible novel product must be innovative and address a medical need (based on patient utility). They also should avoid setting unrealistic targets for SMEs (guardrails, e.g., in terms of manufacturing, access and availability), and second and third-in-class of novel antibiotics should be rewarded in light of their use for patients and healthcare system (e.g., ease of use, or side-effect profiles).

In the view of the SMEs represented by BEAM Alliance, the most readily actionable mechanism to reward innovation are TEE (Transferable exclusivity extension) vouchers, defined as tradable vouchers awarded to the innovator of a novel antimicrobial, meeting specifications that can then be used to extend the monopoly time period of any patented medicine. They can either be applied by the awardee to another medicinal product of its own portfolio or sold to another company.

BEAM Alliance considers that TEEs constitute a fast and centralised procedure (including at EU level), and the reward amount is predictable, which can be controlled by certain guardrails. Although this model is not necessarily perfect, it outweighs the disadvantages of the subscription model for SMEs. In the view of BEAM Alliance, annual revenue guarantees (also known as subscription models, described below) are difficult to implement in Europe, as they need alignment of 27 Member States, and face free riding issues[35] when implemented at a multi-country level.

Take home messages

1. Time plays against us: running out of treatment options for several patient groups and it takes time to develop a new antibiotic.
2. Size matters: Europe has a responsibility at global level, and well-published numbers exist on what is needed in terms of pull mechanisms, and Europe's fair share is between EUR 0.6 and 1.2 bn per new antimicrobial product (i.e. EUR 3 per EU inhabitant).
3. A pan European TEE is needed: It can be combined with national subscription models to ensure access at national level (as done successfully in Sweden), i.e., a hybrid model.

3.4. Securing access to new (and old) antibiotics through an annual revenue guarantee

This presentation was given by Christine Årdal, Senior Researcher at the Norwegian Institute of Public Health (NIPH).

[34] United Nations' Interagency Coordination Group on Antimicrobial Resistance (IACG), Discussion paper on 'Antimicrobial resistance: Invest in innovation and research, and boost R&D and access', 2018, available at: https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/iacg-amr-invest-innovation-research-boost-rd-and-access-110618.pdf.

[35] Some countries may be reluctant to financially contribute to a common reward, *e.g.,* because the targeted pathogens would be of low incidence in their own country for now, while benefiting from the positive impact brought by the awarded antimicrobial containing the spread of the resistance.

- **Discussion on the importance of stimulating antibiotic innovation for unmet public health needs, but also securing access to important antibiotics in every country**

Access to essential antibiotics is fragile.

As part of the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU JAMRAI), in-depth interviews have been conducted with policy makers in thirteen countries, including 10 European countries. The conclusions of this consultation are that:

- 12 of 13 countries report that **shortages of existing antibiotics are a serious problem** nationally.
- 8 of 13 indicate that these shortages result in greater use of broad-spectrum antibiotics (thereby increasing AMR).
- 8 of 13 countries reported that companies recently decided to stop marketing an essential, existing antibiotic in their country, mostly narrow-spectrum antibiotics.

On the basis of these conclusions on access to antibiotics, an analysis of newly approved (new molecular entity) antibacterials in high-income countries showed that (1) a significant period of time is observed between approval and commercial launch, and that (2) approval by the EMA does not result in a commercial launch in all EU Member States (e.g., *Cefiderocol*, for the treatment of complicated urinary tract infections). When looking at the three antibiotics considered essential in WHO's essential medicines list, access problems are also observed.

- **Critical analysis of the TEE vouchers, proposed by the pharmaceutical industry to stimulate antibiotic innovation**

In order to secure access, there is thus a need for the public sector to **pay for predictable access**, **not consumption**, via '**delinked pull incentives'**, which provide revenues independently of unit sales.

Regarding the choice of the specific pull incentive, the model of transferable exclusivity extensions (TEE), supported by BEAM Alliance, may stimulate antibiotic innovation, but will likely be extremely and unpredictably costly. The consequence of this model is the possibility of extending a monopoly on certain treatments (e.g., expensive cancer treatments, or BioNTech COVID-19 vaccine), which would be extremely costly. Industry numbers, also used by the European Commission, assume that 1 to 3 vouchers would be awarded annually, whereas only one antibiotic candidate in the entire clinical pipeline today is considered innovative against critical priority pathogens, rewarding antibiotics of questionable public health value, and impacting only small patient groups.

Furthermore, the TEE model does not ensure availability in most or all European countries. As a one-off transaction, there is almost no way to ensure access. The industry is calling for both a TEE and access mechanism, ramping up the European price to billions or tens of billions of euros per antibiotic. Finally, setting out such a mechanism in pharmaceutical legislation limits flexibility to test this unprecedented model.

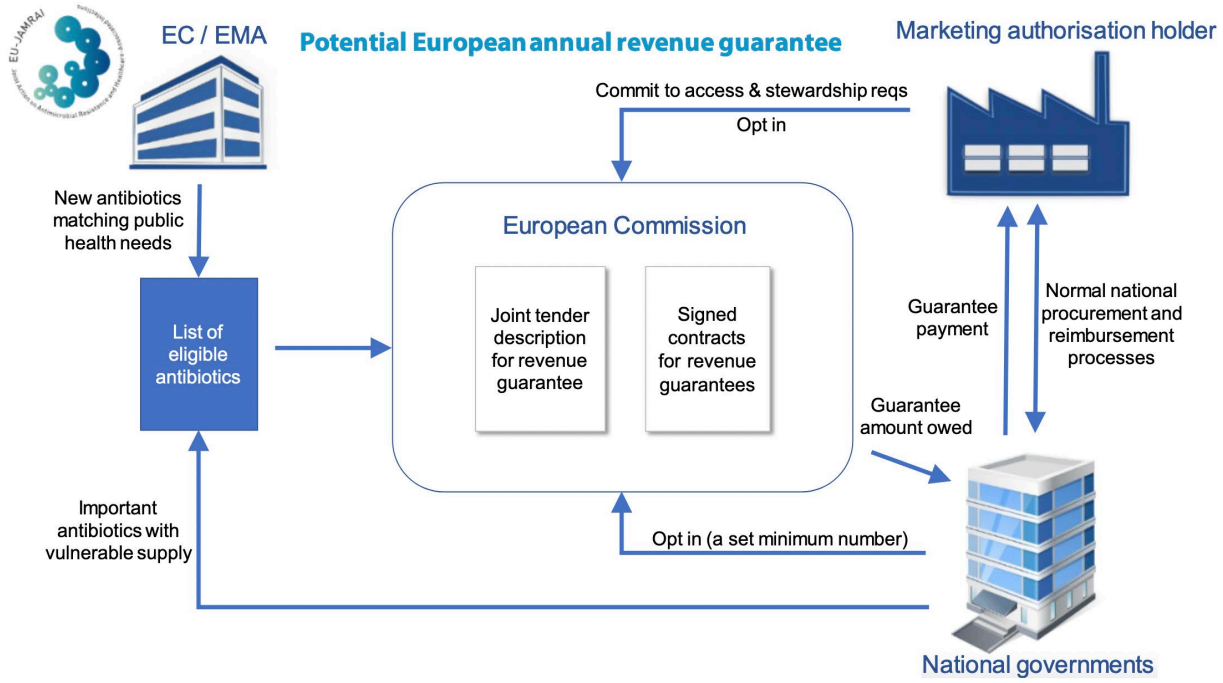
- **Presentation of the proposal by EU-JAMRAI of an EU-wide annual revenue guarantee, not only to stimulate innovation but also to secure access**

Annual revenue guarantees (also called subscription-based models) are 'pull' incentives consisting in providing **predictable and increased revenues** for producers of marketed antimicrobial pharmaceutical products with proven public health value, delinking revenues from sale volumes. They secure states' access to important products and furthermore create incentives for large pharmaceutical

companies not to abandon antibacterial development while preventing bankruptcy of small innovators[36].

The annual revenue guarantee ensures access to the selected important antibiotics while operating **independently from national health processes** (HTA, pricing and procurement). To support this option, 11 of 13 countries interviewed in the context of the EU JAMRAI research support a 'common, multinational incentive, so long as it is independent from national medicine pricing, procurement and reimbursement processes. Other advantages of an annual revenue guarantee include **rewarding success** for those who obtain regulatory approval and can ensure **profitability for innovators of both old and new antibiotics**. The figure below presents the functioning of the model proposed by EU JAMRAI, including the role of the respective stakeholders (EC, EMA, MAH, and national governments).

Figure 4: Proposed model for a European annual revenue guarantee



Sources: Årdal, C., et al, on behalf of the EU-JAMRAI, *National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation*, Antibiotics 2021, 10(6), 749; and Slovenian Presidency of the Council of the European Union 2021, *Policy brief: Improving access to essential antibiotics*.

Take home messages

1. Europe needs to test new incentives to secure access to important antibiotics, both old and new.
2. If designed well, this incentive will also stimulate innovation.
3. An annual revenue guarantee seems to be the most promising option, aligned with Member States' expectation, and with the ability to adjust over time based upon lessons learned.

[36] For example, Sweden has signed agreements with suppliers of five newly marketed antibiotics for an annual revenue guarantee. Hospitals continue to purchase as normal, while the pilot study fund pays the difference between the guarantee and actual sales. This pilot ran between July 2020 and July 2022. Producers are guaranteed an annual revenue, with the difference between the guarantee and actual annual sales paid through the new incentive. If sales exceed the guarantee's amount, the innovator keeps the additional revenues as well as receiving a 10% bonus so long as all contractual conditions have been met. Sweden has entered into two-year contracts with the antibiotic producers and has included national access and stewardship provisions.

3.5. Achieving sustainable access to antibiotics through public leadership and an end-to-end approach to research and drug discovery

This presentation was given by Kerstin Åkerfeldt, Policy Expert at ReAct Europe.

ReAct observed 30 years of standstill in developing new antibiotics and of the failure of the traditional market-based financing model for research and development of new antibiotics. Following the Swedish Presidency of the Council of the European Union in 2009, React arranged an international conference on the global need for new antibiotics, which became central for the first EU Action Plan on AMR. Despite the efforts, the response has not reached the scale and urgency to address the standstill.

- **Urgent need for developing new antibiotics and managing responsible use**

In light of the urgency of developing new antibiotics and managing a responsible use, there is a strong case for multilateral action and stronger public leadership, at international level and through the EU, considering the global nature of this cross-border threat.

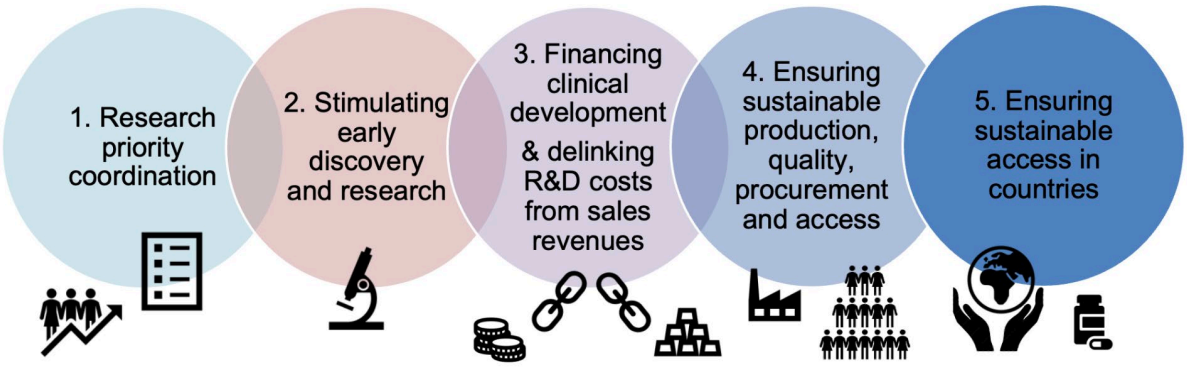
For ReAct, it is a mistake to solely focus on incentives to develop new products when trying to address the lack of new antibiotics. New drugs are precious and should be used responsibly, and global access should be ensured. The way drugs are used and managed in different countries around the globe should follow the axiom '**Access without excess**'.

The image of a leaking bucket has been used to describe the importance of closing the holes in the management of AMR by preventing overuse, misuse and lack of access to antibiotics, but also by adopting preventative measures (e.g., water and sanitation) before introducing new antibiotics. Otherwise, new drugs could be 'burned' too fast. Therefore, ReAct advocates for a holistic approach to AMR, i.e. the 'end-to-end approach' described below.

- **Key challenges in the current model – taking an end-to-end approach**

As illustrated in the figure below, ReAct's recent report *Ensuring sustainable access to effective antibiotics for everyone - everywhere*[37] outlines five key challenges in the development of antimicrobial products, which should be resolved in an **'end-to-end' approach**:

Figure 5: ReAct's end-to-end approach



Sources: Presenter's own elaboration.

[37] ReAct Europe, 'Ensuring sustainable access to effective antibiotics for everyone – everywhere', 2021, available at: 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.

ReAct's end-to-end approach for a successful R&D on antimicrobial medicinal products requires:

(1) **setting research priorities** to address the most important global unmet health needs, in line with WHO's priority pathogens list, whereas today only 1/3 target these pathogens and only a fraction is innovative.
(2) **overcoming the barriers in early discovery and research**.
(3) **financing clinical development** and **delinking** R&D costs from sales revenues (away from the market-based model).
(4) **ensuring sustainable production, quality, procurement and registration** of new antibiotics to prevent shortages. The current model is not fit for purpose.
(5) **ensuring sustainable access globally** by national governments and by global governance, while preventing misuse and overuse.

- **The scientific and structural challenges in early drug discovery – dry pipeline**

More specifically with regard to the second point of the **end-to-end approach** on early discovery and research, Kerstin Åkerfeldt highlighted the significant scientific challenges which hamper the development of new antibiotics, shown by the lower yield in discoveries compared to other medical fields. Finance and expertise have disappeared from this field, as large pharmaceutical companies have withdrawn in the last 20 years, focusing on areas with higher economic returns. The structural issues include limited and short-term funding, lack of mentorship and training and insufficient coordination of research. A sole focus on late-stage incentives (e.g. pull incentives) will likely fail to address these challenges.

- **The global perspective**

The COVID-19 pandemic has uncovered the existence of deep global health inequities and highlighted the cross-border nature of health threats. There needs to be a new system which by design serves the health needs of rich and poor patients. **Access to effective life-saving antibiotics** should be at the core of everyone's right to health. As a strong economic area, the EU has a strong global responsibility and role to play. Prior to the COVID-19 pandemic, European Commission President Ursula von der Leyen missioned Commissioner for Health and Food Safety Stella Kyriakides to work on a global agreement on use and access to antimicrobials. According to ReAct, the global instrument pandemic preparedness should include AMR.

To achieve these goals, governments must take a bigger responsibility and adopt an end-to-end approach to change the way antimicrobials are managed and used, through far more public intervention and direction. A rules-based global governance system and a commonly defined playbook is needed to ensure that individual governmental actions can be coordinated and thereby more effective.

- **Concrete recommendations for EU action**

Kerstin Åkerfeldt presented the five most pressing recommendations by ReAct for action at EU level.

Stronger public leadership for more efficient and public health needs-driven R&D. It can be reinforced by a focus on global governance and coordination (particularly for early-stage R&D), but also exploring alternative models in which non-profit and public actors play a key role. A global entity for systematic coordination of antibiotics R&D should be established, e.g., as a non-profit European centre for antibacterial drug discovery.

Increased push funding for early stage for targeted drug discovery and translational research. This should promote sharing of data and compound libraries, coordination, transparency, and attached

sustainable funding conditions. Ideally, it should also be combined with technical mentorship and training (pipeline coordinators like ENABLE and GARDP[38]).

Alternative pull incentives (rather than TEE vouchers) for late-stage clinical development, through targeted and **gradually awarded "milestone" prizes** that could move the process forward more efficiently from preclinical to clinical. Milestone-based prizes are rewards paid to developers upon the successful completion of key R&D steps (e.g., phase 1 clinical studies). Since they reward success, the risk to the funder is lower. In addition, milestone prizes allow the funder to steer the direction of research by defining the conditions under which such prizes are paid out. Milestone prizes can also be linked with end product profile attributes set out in Target Product Profiles (TPPs).

Increased public control and oversight of production, procurement, distribution and patient access to ensure sustainable access.

Inclusion of LMICs in global agreements as part of developing solutions to make sure they are going to be able to access and manage the drugs.

[38] Pipeline coordinators are public or non-profit organisations that closely monitor the development of antibiotics, identify gaps in the pipeline and actively support (or directly conduct) R&D projects to fill these gaps with considerable flexibility in terms of tools and solutions applied. Usually, pipeline coordinators involve both public and private actors in various forms of collaboration. Examples of such pipeline coordinators are: ENABLE, GARDP and CARB-X[38].

4. DISCUSSIONS AND Q&A

Members of the European Parliament and participants to the workshop could raise questions to the expert-speakers during two Q&A sessions. The discussions are presented below:

- **Remarks by MEP Petar Vitanov**

The MEP stressed the great importance of antimicrobial resistance, as well as of communication on this topic, as there are lots of speculations. He stressed that the solution requires significant and targeted funding of the fundamental research. As European legislators, MEPs should insist on the need for governments and European institutions to intervene in research and innovation, on stabilising the supply chains (shortages of components of antibiotics), and on supporting the pharmaceutical industry to maintain the availability of certain antibiotics, both for humans and animals.

- **Remarks by Rosa Castro, European Public Health Alliance (EPHA)**

Rosa Castro raised a question addressed to Marc Giztinger (BEAM Alliance) on the basis of BEAM Alliance's request for a rapidly implementable and predictable remedy to the lack of antimicrobials in the pipelines. She argued that transferable exclusivity extensions are rather unpredictable on the side of national payers. Considering the magnitude of AMR as a global issue, which can affect any citizen, she argued that Europe should be more ambitious.

Co-chair **MEP Dolores Montserrat** agreed that Europe needs to step up the actions undertaken, in view of patients suffering from multi-resistant bacteria in hospitals, and possible consequences of the healthcare systems worldwide (reliance on antibiotics for many treatments, e.g., wisdom tooth).

- **Remarks by Giuliana Pennisi, Medicines for Europe**

Medicines for Europe is the European off-patent medicines association, representing producers of generics, biosimilars and value-added medicines. They supply 70% of prescribed medicines on the European market. She underlined that:

1/ Medicines for Europe supports actions to ensure the availability of medicines to avoid prescription of wide-spectrum antibiotics, contributing to AMR. In this regard, there is a need for sustainable policies. In the study commissioned by the European Commission on Future-proofing pharmaceutical legislation, a link is evidenced between medicine shortages and economic root-causes.

2/ Medicines for Europe does not support transferable exclusivity vouchers, as supported by the Health Ministers' Council Conclusions of 2021. It will create legal uncertainty for payers/healthcare systems and for the off-patent industry and will create delays in access to medicines for patients.

Co-chair **MEP Dolores Montserrat** recalled the upcoming discussions on the legislative package on pharmaceutical legislation (including orphan medicines, substances of human origin), provisionally scheduled to take place in the first semester of 2023.

Marc Gitzinger, BEAM Alliance, specified on this point of discussion that TEEs must be announced at least two years before implementation to give security to the off-patent industry.

- **Further remarks by Marc Gitzinger, BEAM Alliance**

Marc Gitzinger identified the common messages across speakers: action needs to be taken, and relatively fast; and Europe plays a central role in the bigger picture. The question is now how to implement this in European legislation.

Concerning the TEE model proposed by the industry, he argued that the size of the award should be guided by the duration of the extension, which can be flexible between 6 and 12 months. No matter the instrument selected, the reward for new antimicrobials should remain between USD 0.6 and 1.2 bn.

Concerning joint procurement, he cautioned that this would be very difficult to implement in Europe, will necessitate a lot of time, and probably will not be implemented by all MS due to the HTA systems being circumvented.

- **Further remarks by Christine Årdal, Norwegian Institute of Public Health**

Christine Årdal agreed that improvements have been made and achievements have been reached especially in the last five years:

- the clinical pipeline is stronger than it has been in decades thanks to push funding (see, e.g., Carb-X - the 'Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator' global nonprofit partnership focused on supporting antibacterial research).
- mechanisms for access and research and development for LMICs through the 'Global Antibiotic Research and Development Partnership' (GARDP). For the first time, a new antibiotic which is considered for critical priority pathogens and considered innovative will be made available to LMICs at the same time as high-income countries.

The reason for the adoption of pull incentives is to avoid the public sector to take the full bill of antibiotic innovation, which is scientifically risky and where most candidates fail. The idea with pull incentive is to have the private sector back investing in antibiotics. This needs to be done quickly.

The Health Emergency Preparedness and Response Authority (HERA) has commissioned a report, where the annual revenue guarantee will be examined in closer detail, due out in early 2023. She also noted that joint procurement can be implemented quite rapidly in Europe, as shown during the COVID-19 pandemic.

Christine Årdal also warned of the possible negative consequences of setting out a mechanism such as TEE in EU's pharmaceutical legislation, i.e., high risk of unintended consequences (e.g. wrong eligibility criteria).

Closing remarks

MEP Dolors Montserrat closed the workshop by thanking the speakers and recalling the conclusion of the Lancet's study establishing a comprehensive and detailed assessment to date of the burden of AMR in Europe. The mitigation strategies against AMR will require high-quality surveillance, networks, and advanced knowledge of its true burden. This can support the research and development of new antibiotics and treatment, to find a way out of this 'silent pandemic'. The Director of HERA, Pierre Delsaux, announced a European Union Action Plan. The EU needs to establish a balanced system between industry competitiveness and incentives, access to innovation and sustainability of healthcare systems.

WORKSHOP PRESENTATIONS

Part one: State of affairs, global situation and current needs in the EU

1. **The burden of AMR in Europe and globally: prioritisation of antimicrobials beneficial for the Global One Health**, by Sarah Garner (World Health Organization's Regional Office for Europe).

2. **Patients' need for antibiotics and medical strategies to optimise the use of antimicrobial products**, by Thomas Tängdén (Uppsala University Hospital).

Part two: Incentives and support for research, potential policy developments at European level

3. **The central role of SMEs in research and development: the case for SME-compatible pull incentives**, by Marc Gitzinger (BEAM Alliance).

4. **Securing access to new (and old) antibiotics through an annual revenue guarantee**, by Christine Årdal (Norwegian Institute of Public Health/EU-Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections)

5. **Achieving sustainable access to antibiotics through public leadership and an end-to-end approach to research and drug discovery**, by Kerstin Åkerfeldt (ReAct Europe).

ACCESS TO THE FULL CONTENT OF THE PRESENTATIONS IS ALSO AVAILABLE HERE:

ENVI HEALTH WORKING GROUP – WORKSHOP ON ANTIMICROBIAL RESISTANCE:
https://www.europarl.europa.eu/committees/en/envi-health-working-group-workshop-on-an/product-details/20220921WKS04381

SHORT BIOGRAPHIES OF THE SPEAKERS

Sarah Garner

Senior Policy Advisor, WHO Regional Office for Europe

Sarah Garner, PhD, is a global access policy pharmacist specialised in multi-sector engagement with regulatory science, R&D, HTA, health systems strengthening including procurement and supply chain. Ms Garner has 14 years of experience with national and international policy and strategy development in the pharmaceutical sector and operational management of multidisciplinary teams. Her previous roles have included Pharmacist Lead for the UK Government's Special Advisory Committee on Antimicrobial Resistance. She is technically leading the Oslo Medicines Initiative (https://www.omi-euro.org/) and has previously led policy and research work-packages of major EU public-private research partnerships funded by the Innovative Medicines Initiative. Her research and policy experience include new development mechanisms for medicines for unmet need, the use of digital information / real-word data in pharmaceutical development, regulatory and HTA decision-making methodology and disinvestment (low-value care).

The Regional Office for Europe of the World Health Organization and its teams on Control of Antimicrobial Resistance and on Access to Medicines and Health Products provide support to research, surveillance and awareness-raising on antimicrobial resistance, in particular in the context of WHO's 'One Health' approach, and run campaigns such as the World Antimicrobial Awareness Week.

Thomas Tängdén

Senior consultant and associate professor of infectious diseases, Uppsala University Hospital

Thomas Tängdén (MD, PhD) is an infectious disease physician and research group leader, chair of the Swedish Strategic Programme against Antibiotic Resistance (Strama), project leader of PLATINEA 2.0 – a collaborative project promoting availability and individualised use of existing antibiotics, chair of the PK/PD study group of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and medical advisor of the global resistance network ReAct. He has authored national and European treatment recommendations, e.g., for infections caused by multidrug-resistant Gram-negative bacteria. His research includes clinical trials, interventions to improve antibiotic use at hospitals, pharmacokinetic studies to optimise antibiotic dosing, mapping of resistance development and negative effects on the gut microbiota during antibiotic therapy, and laboratory studies to find new diagnostic and treatment strategies to overcome multidrug resistance, for example by using antibiotic combinations.

The Swedish Strategic Programme against Antibiotic Resistance (Strama) is a network of healthcare professional supported by the Swedish government that works in collaboration with the Public Health Agency of Sweden. Its overall aim is to secure effective treatment of bacterial infections for the current and future generations. Strama provides evidence-based treatment recommendations and promotes rational use of antibiotics at the national and local levels.

PLATINEA 2.0 is a multisectoral collaboration platform publicly funded by Sweden's Innovation Agency (Vinnova), The main objectives of the initiative are to ensure sustainable access and guide individualized use of antibiotics, thereby prolonging the lifespan of the existing drugs.

Marc Gitzinger

President, BEAM Alliance

Marc Gitzinger is Chief Executive Officer and co-founder of BioVersys. He has over 10 years of experience in the biotech industry, having launched a university spin-off in the field of antimicrobial resistance and growing it into a multi-asset early clinical stage company addressing unmet medical needs in infectious disease such as tuberculosis and hospital acquired Acinetobacter infections. He is also President of the board of the BEAM Alliance, a European association representing over 60 European and international SMEs active in antimicrobial research and development and board member of the AMR Industry Alliance. Marc is co-author on several scientific publications and patents in the field.

The BEAM Alliance (Biotech companies from Europe innovating in Anti-Microbial resistance research) represents over 60 small and medium-sized European companies involved in developing innovative products and kits to tackle antimicrobial resistance (AMR), including small molecule antibiotics, biologics, products with a prophylaxis indication, microbiome-based and phage-based therapies, immune targeting therapies, anti-biofilm agents and medical devices including in vitro diagnostics.

Christine Årdal

Senior Researcher, Norwegian Institute of Public Health

Christine Årdal MBA PhD has worked for over 25 years on access to medicines through different sectors, including research institutes, governmental development assistance, pharmacy, national health services and insurance. At the Norwegian Institute of Public Health, her research focuses on the policy aspects of antimicrobial access and innovation. Årdal was previously the co-lead of the research and innovation work package for the EU-JAMRAI, which aimed to detail European strategies to implement mechanisms to increase antibiotic and alternative therapeutic innovation. She was also a co-lead in the DRIVE-AB research project which aimed to transform the way policymakers stimulate innovation, the sustainable use, and the equitable availability of novel antibiotics to meet unmet public health needs. She is the co-lead for the Programme Committee of the Oslo Medicines Initiative, aiming to improve access to innovative, high-priced medicines, and an active member of the Norwegian assessment of local production for critical antibiotics and the MIA-research project, examining supply chain solutions to improve access to medicines.

EU-JAMRAI aimed to define European common policies to fight Antimicrobial Resistance and control Healthcare-associated Infections in line with ongoing EU and international policies. The Joint Action identified best practices and facilitated multi-state cooperation to improve national AMR-related policies.

DRIVE-AB (Driving reinvestment in research and development and responsible antibiotic use) is a project funded by the Innovative Medicines Initiative (IMI), a joint undertaking between the EU and the European Pharmaceutical Industry Association (EFPIA). DRIVE-AB was tasked with defining responsible use of antibiotics, identifying the antibiotic-related public health priorities, calculating the societal value of having new antibiotics available for these priorities, developing and costing new economic models to promote the desired antibiotic innovation, and sustainable use of the resulting, novel antibiotics. The purpose was to transform the way policymakers stimulate antibiotic innovation and to ensure that these new antibiotics are used sustainably and are available equitably.

The Norwegian Institute of Public Health (NIPH) is a government agency under the Norwegian Ministry of Health and Care Services. Its Antibiotic Resistance and Infection Prevention department contributes to the prevention of infections and antibiotic resistance, as well as the correct use of antibiotics nationally and internationally through health analyses, research and knowledge-based advice.

Kerstin Åkerfeldt

Policy Expert, ReAct Europe

As a Policy Expert, **Kerstin Åkerfeldt** supports the development of ReAct's policy positions, recommendations and advocacy strategies towards relevant stakeholders and provides input to debates at global, regional and national level on antibiotics resistance. Her work focuses on Research & Development and access to medicines, global governance, sustainable financing for health and strengthening of health systems. Before joining ReAct, she worked 20 years in different capacities for MSF including as a Health Policy- and Advocacy Advisor and a liaison officer towards the Global Fund to fight AIDS, Tuberculosis and Malaria. She also has experience from health policy and advocacy work in low resource settings. Kerstin holds a Master's degree in International Studies from Uppsala University.

ReAct is one of the first international independent networks to articulate the complex nature of antibiotic resistance and its drivers. ReAct was initiated with the goal to be a global catalyst, advocating and stimulating for global engagement on antibiotic resistance by collaborating with a broad range of organisations, individuals and stakeholders. ReAct is present across five continents (with nodes located in Sweden, India, Ecuador, Kenya and the US). Its multi-professional teams gather and disseminate evidence and best practices, develop training and education for implementation of antibiotic policies and promote innovative approaches for sustainable, equitable and affordable access to antibiotics. ReAct's core funding comes from the Swedish International Development Cooperation Agency (Sida).

These proceedings summarise the presentations and discussions before the European Parliament's Health Working Group as part of the workshop on 'New incentives to improve the accessibility and availability of antimicrobial medicinal products', held on 26 October 2022. The five presentations touched, inter alia, upon the burden of AMR, the current research on development of antimicrobials, and incentive models.

These workshop proceedings were provided by the Policy Department for Economic, Scientific and Quality of Life Policies for the European Parliament Committee on the Environment, Public Health and Food Safety (ENVI).

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