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One Health in action:

Pharmaceuticals including antimicrobials and their environmental impact

Policy session, 2nd European One Health Conference

Summary report - 21 June, Bucharest

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About the FEAM European Biomedical Policy Forum

The FEAM European Biomedical Policy Forum provides a platform for discussion on key policy issues for the biomedical community.

The Forum is an initiative from the Federation of European Academies of Medicine (FEAM). It aims to bring together representatives from academia, research charities, industry, European and national trade associations and professional bodies, public health bodies, and patient and consumers groups. If you would like further information on the FEAM European Biomedical Policy Forum or becoming a partner, please contact info@feam.eu or elisa.corritore@feam.eu

Disclaimer

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Federation of European Academies of Medicine (FEAM) and their Members.

All web references were accessed in July 2019.

Acknowledgments

FEAM warmly thanks the speakers and Brian Maguire for their contribution to the policy session as well as Dr Elisa Corritore for organising the policy session and Dr Rosa Castro for writing this report. FEAM is very grateful to the Romanian Academy of Medical Sciences and the One Health Comparative Medicine Institute for hosting this policy session within its 2nd European One Health Conference, and to the UK Academy of Medical Sciences that funded this event by using a grant from the UK's Department of Business, Energy & Industrial Strategy (BEIS).

FEAM EUROPEAN BIOMEDICAL POLICY FORUM

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Introduction

As animals and humans share their eco-systems, their health and well-being is intrinsically connected. Thus, efforts to tackle key health-related challenges such as emerging infectious diseases and anti-microbial resistance require a deep understanding of the complex mechanisms affecting the environment, human and animal health. This is the vision behind the "One Health" approach[1], which requires the development of cross-disciplinary research and policy, and is expected to lead to better health outcomes and significant economic benefits[2].

The "One Health" approach has been endorsed by international organisations such as the World Health Organisation (WHO), the World Organisation for Animal Health (OIE) and the Food and Agricultural Organisation (FAO)[3]. At the EU level, it is at the core of several policy initiatives including the One Health Action Plan against antimicrobial resistance (AMR) launched in 2017[4] and emergency preparedness efforts[5].

In spite of progress, further cross-sectorial collaboration and responses are needed to address current challenges such as the effects of climate change on health or rising antimicrobial resistance. For instance, significant gaps persist on the implementation of National Action Plans (NAPs) against AMR[6]. Additionally, the environmental side of the One Health triad (i.e. animals, humans and the environment) has often been neglected[7].

The "European Union Strategic Approach to Pharmaceuticals in the Environment" focuses on the effects of rising volumes of pharmaceuticals in the environment. Sustained efforts are needed to promote the prudent use of pharmaceuticals, develop "green pharmaceuticals", and fill current knowledge gaps. Against this background, the FEAM European Biomedical Policy Forum convened a policy session and roundtable to discuss the effects of pharmaceuticals in the environment, including on AMR. The session was organised in collaboration with the Romanian Academy and the Romanian One Health Institute and preceded scientific presentations within the 2nd European One Health Conference[8].

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[1] See the WHO definition of One Health as "an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes", and has identified the control of zoonotic diseases, food safety, and antibiotic resistance as some of the areas for which this approach could be particularly beneficial, available at: https://www.who.int/features/qa/one-health/en/

[2] World Bank. (2012). People, Pathogens and Our Planet: The Economics of One Health.

[3] FAO–OIE–WHO Tripartite Concept Note (2010), The FAO–OIE–WHO Collaboration – Sharing responsibilities and coordinating global activities to address health risks at the animal–human–ecosystems interfaces.

[4] European Commission, A European One Health Action Plan against Antimicrobial Resistance, 2017, available at: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

[5] See European Centre for Disease Prevention and Control. Towards One Health preparedness. Stockholm: ECDC; 2018.

[6] European Public Health Alliance, Translating Political Commitments into Action: The development and implementation of National Action Plans on antimicrobial resistance in Europe, December 2018, https://epha.org/wp-content/uploads/2019/03/amr-nap-study.pdf

[7] Essack, S.Y., 2018. Environment: the neglected component of the One Health triad. The Lancet Planetary Health, 2(6), pp.e238-e239.

[8] https://onehealthevents.eu/

Summary

Pharmaceutical products may enter into the environment via manufacturing processes, or through their inappropriate disposal or consumption - and subsequent excretion - by humans and animals. An ageing population, the development of new pharmaceuticals, and the intensification of agriculture, are all contributing factors. Climate change and population dynamics could further exacerbate potential health impacts, especially with regard to the use of antibiotics and the rising threat of antimicrobial resistance (AMR). While knowledge gaps exist about the effects of human exposure to pharmaceuticals via the environment, the World Health Organisation (WHO) has recommended monitoring this problem. A recent study by the OECD found that current policy approaches are too reactive, substance-specific and resource intensive[9]. The study offers policy recommendations ranging from measures directed at the sources to those related to the use of pharmaceuticals and end of pipe measures.

Within the EU, an environmental risk assessment (ERA) for human medicinal products has been required only since 2006 -this leaves out more than 80% of drugs currently on the market. While only a few drugs have been found in quantities considered above dangerous levels, current studies face methodological limitations (e.g. their scope being limited to one substance at a time).

The EU has responded to these concerns with its "Strategic approach to Pharmaceuticals in the Environment", which address the whole production cycle of pharmaceuticals using a preventive approach. Along with the EU's pharmaceutical legislation and the EU One Health Action Plan on AMR, this strategy uses an integrated One Health approach to address a multisectoral issue.

Of special concern are the potential effects that traces of antibiotics in the environment may have on AMR. The main drivers of AMR are the use, misuse and abuse of antimicrobials, as well as their release in the environment. Resistance can spread very easily with devastating consequences for the treatment of patients. While AMR is an ancient and naturally occurring phenomenon, rising AMR has been linked to corruption and overall governance. Significant differences -both in terms of the burden of AMR and the implementation of plans to combat AMR- persist across European countries.

In some countries (e.g. India), this phenomenon is exacerbated by pharmaceutical manufacturing, which is less spread but can lead to higher volumes and serious effects for the local population. With over 60% of the world production of vaccines and antiretroviral drugs originating from India, it was noticed that the implementation of more stringent manufacturing regulations poses very complex questions. The adoption of voluntary commitments by the pharmaceutical industry, the reform of Good Manufacturing Practice (GMP) rules, and the use of green public procurement were discussed as possible solutions. The discussion highlighted existing knowledge gaps as well as complex challenges faced by multiple stakeholders -these include governments, citizens, NGO's, industry and insurance companies.

[9] OECD, Pharmaceutical residues in freshwater: Hazards and policy responses, forthcoming August 2019.

Report of the event

Policy session: Pharmaceuticals including antimicrobials and their environmental impact

Welcome and introduction

Prof *George Griffin* (President of FEAM) opened this session by mentioning several studies associating a high concentration of contraceptives[10] and cocaine[11] in water with troubling or unknown effects for wildlife. These studies and their media coverage have contributed to raise awareness about the effects of pharmaceuticals in the environment. Next, *Prof Griffin* gave the floor to speakers to reflect on the environmental impact of pharmaceuticals, including antimicrobials.

EC Strategic approach on Pharmaceuticals in the environment

Hans Stielstra, DG Environment, European Commission (through a video recorded message)

Mr Stielstra started by explaining that the EU Strategic approach to Pharmaceuticals in the Environment[12] aims to give visibility to this problem among EU actors and stakeholders. The Strategy responds to evidence about the increasing volume of pharmaceutical (e.g. traces of antibiotics, antidepressants and contraceptives) found in water bodies such as lakes and rivers. While studies have found that human exposure to pharmaceuticals via the environment seems to be low, the World Health Organisation has recommended to monitor this problem over time.

Next, *Mr Stielstra* referred that manufacturing is an important source of pharmaceuticals in the environment for some non-EU countries. While this is not the case for the EU, problems caused by the rising presence of pharmaceuticals in the environment –such as rising antimicrobial resistance—can spread both locally and globally.

Within the EU, the Environmental Quality Standards Directive[13] required the EU Commission to propose a strategy to deal with water pollution by pharmaceutical products[14]. While this obligation stems from EU's water legislation, EU pharmaceutical legislation has also followed a similar

[10] Andrea Sella and Lorna Stewart, How drugs are entering UK water systems through urine, BBC News, 12 September 2014, https://www.bbc.com/news/health-29108330

[11] BBC newsbeat, Cocaine contaminates drinking water, report suggests, 12 May 2014, http://www.bbc.co.uk/newsbeat/article/27375178/cocaine-contaminates-drinking-water-report-suggests

[12] European Commission, European Union Strategic Approach to Pharmaceuticals in the Environment, Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee, COM (2019) 128 final, http://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF

[13] Directive 2008/105/EC as amended by Directive 2013/39/EU.

[14] Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy.

approach[15]. In addition to this, the One Health Action Plan on AMR also called for an integrated strategy to support the fight against AMR[16].

Current developments in this area include the ongoing evaluation of the EU's Water Legislation[17]. While it could be tempting to put all emphasis on the need for (better) water treatment, this approach would be very costly and could also lead to higher prices.

Therefore, the proposed strategy is broader in scope and addresses the whole production cycle of pharmaceuticals, using a preventive approach. It proposes solutions over 6 different areas:

1. **Increase awareness and promote the prudent use of pharmaceuticals.** This includes incorporating environmental concerns within medical training, decreasing the preventive use of antibiotics, exchanging best practices that take into account environmental aspects, and fostering cooperation between organisations, including the WHO and other organisations.
2. **Developing better and greener pharmaceuticals.** Activities under this area will include the use of research funds to support the development of greener pharmaceuticals, the revision of the list of substances of concern (under the Water Framework Directive), and the use of green public procurement as a mechanism to provide incentives for producing greener pharmaceuticals.
3. **Risk assessment.** Improving the process of risk assessment in collaboration with all the involved institutions (e.g. EMA and Member States) as well as setting up a review system for pharmaceutical veterinary products (as mandated by the new Regulation on veterinary medicinal products) are among the activities that will be pursued.
4. **Reduce waste and improve management of waste.** This will include collaborating to identify mechanisms to reduce waste, and exchanging best practices for the safe disposal of waste and the collection of pharmaceutical residues.
5. **Expand environmental monitoring.** Finding out additional substances that might be of concern, as well as using the watch list mechanism (under the Water Framework Directive), supporting research to better understand the impact of substances, and gathering data and information through the Information Platform for Chemical Monitoring, are among the activities that will lead to more knowledge and therefore better measures to address the problems.
6. **Filling knowledge gaps.** Finally, issues such as the eco-toxicity of pharmaceuticals (especially those not covered by risk assessment), the causal links between pharmaceutical residues in the environment and the emergence of AMR will need to be addressed through better knowledge about the mechanisms underlying these processes.

Some stakeholders have expressed concern about the lack of legislative solutions proposed in the Strategy. However, the EU Commission wishes to foster broad cooperation among different sectors while so far, the main involved actors at the level of the European Commission have been the

[15] See among others, Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products.

[16] European Commission, A European One Health Action Plan against Antimicrobial Resistance, https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

[17] See information about the fitness check of EU Water Legislation, including the results of a public consultation: https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-5128184_en

Directorate General for Health and Food Safety and for Environment. *Mr Stielstra* pointed out that this issue should not be perceived as an exclusively environmental or health-related problem. He finished his presentation by recommending that more debate across sectors and stakeholders (including health professionals and academies) should be fostered.

Pharmaceutical residues in freshwater: Policy responses from OECD countries

Hannah Leckie, Policy Analyst, Water Team, Climate, Biodiversity and Water Division, Environment Directorate, OECD

Ms Leckie presented the key messages of a forthcoming OECD report[18]. Firstly, she illustrated the complex interactions between different sources of pharmaceutical residues in the environment. Traces of pharmaceuticals in the environment can originate from pharmaceutical manufacturers, individuals and households via wastewater treatment plants and inappropriate disposal of pharmaceuticals, agriculture and aquaculture, and hospitals and elderly care homes[19]. The direct discharge of untreated wastewater can also be a major source of pharmaceuticals in the environment, particularly in developing economies where wastewater collection and treatment facilities may not yet be established. In OECD countries, the consumption stage of the life cycle of pharmaceuticals is considered the greatest contributor to the environmental load of pharmaceutical residues in water. 30 to 90% of oral doses administrated to humans or animals are excreted as active substances.

The effects of pharmaceutical residues in human health and the ecosystems have received increasing attention and media coverage during the past years[20]. There are several reasons why the presence of pharmaceuticals in the environment is a growing concern. First, the use of pharmaceuticals is increasing due to the combined effects of an ageing population, increasing life-spans and economic growth, the development of new pharmaceuticals, and the intensification of activities related to livestock production and aquaculture. On top of these factors, climate change is exacerbating the potential impact of pathogens, for instance by causing the global spread of vector-borne diseases[21]. Finally, population dynamics such as population growth, urbanisation and easier transportation around the globe, are contributing to the threat of rising antimicrobial resistance (AMR).

Ms Leckie described several shortcomings of current policy approaches, which are mostly reactive, substance-by-substance and resource intensive; most established policies focus on monitoring and end-of-pipe measures. On top of this, environmental risks are not part of the risk benefit analysis of human pharmaceutical authorisation.

[18] OECD, Pharmaceutical residues in freshwater: Policy responses from OECD countries, forthcoming August 2019.
[19] Boxall, A. B. A. 2004. The environmental side effects of medication - How are human and veterinary medicines in soils and water bodies affecting human and environmental health? Embo Reports, 1110-1116.
[20] See for instance, Devlin Hannah, Antibiotic resistant superbugs 'will kill 90,000 Britons by 2050', The Guardian, 12 November 2018; Marriage Madison, Pollution puts pharmaceutical supply chains under the spotlight, Financial Times, 9 October, 2016; The Economist, Antidepressants are finding their way into fish brains, The Economist print edition, 8 February 2018; and Agence France-Press, Drug waste clogs rivers around the world, scientists say, The Guardian, 11 April 2018.
[21] Cavicchioli et al. 2019, Scientists' warning to humanity: microorganisms and climate change, Nature Reviews Microbiology.

Current approaches to deal with pharmaceuticals in the environment are problematic for the following reasons: 1) an increasing number of pharmaceuticals and their consumption; 2) knowledge gaps (e.g. on the long-term, mixture and additive effects, and the effects of metabolites and transformation products); 3) diffuse pollution being largely unregulated; 4) wastewater treatment plants (WWTP) upgrades being costly and limited by removal efficiencies; and 5) the fact that there are multiple stakeholders and sources at different stages of the pharmaceutical life cycle – no one policy approach will solve the problem.

A questionnaire by the OECD identified the following barriers to government action on mitigating pharmaceuticals in the environment[22]:

- Cost and lack of available resources;
- Knowledge related barriers, including lack of evidence and poor understanding, as well as the lack of a systematic approach for risk assessment;
- Legislative barriers, including the absence of a framework to develop further legislation, the fact that legislation is not flexible enough, the lack of control over internet purchases, and the existing boundaries and reluctance to apply the precautionary and polluter pays principles; and
- Resistance from industry.

An efficient abatement strategy combines policy options at various stages of the pharmaceutical life cycle, involving all stakeholders, including government agencies (involving environmental and health policy and marketing authorisation), pharmaceutical companies and manufacturers, distributors, physicians, veterinarians, pharmacists, hospitals, individual users (both patients and farmers), and wastewater treatment utilities.

Next, *Ms Leckie* offered a number of OECD preliminary policy recommendations:

1. **Source directed measures**, including the consideration of environmental risks in risk-benefit analysis for pharmaceutical authorisation, regulations on good manufacturing processes, prioritising substances and water bodies of highest concern, and incentivising the development of green pharmaceuticals.
2. **Use-oriented measures.** These measures include promoting sustainability through restrictions on environmentally harmful pharmaceuticals, improved diagnostics, livestock vaccinations, eco-labelling, and education campaigns on hygiene and correct disposal of pharmaceuticals.
3. **End of pipe measures**, as a complementary measure to source-directed and use-orientated measures. These include upgrades in wastewater treatment plants, and public take-back schemes of unused drugs.

As an illustrative example of the positive effects of a combined policy approach, *Ms Leckie* referred to an OECD study[23], which models the cost-effectiveness of policy approaches to tackle AMR. A mixed intervention package of stewardship programmes to promote the prudent use of antibiotics, enhanced hygiene in hospitals, mass media campaigns to educate the public, and rapid diagnostic testing could

[22] See OECD, op. cit. (forthcoming report).
[23] OECD, Stemming the Superbug Tide just a few dollars more, OECD Health Policy Studies, 2018.

save up to 47,000 lives saved per year in the OECD and EU alone, and decrease healthcare expenditure by an average of 3 USD/Capita/Year.

To close her presentation, *Ms Leckie* mentioned some key next steps within the OECD programme of work. These include: the launch forthcoming OECD report "Pharmaceutical residues in freshwater: Hazards and policy responses" in August; a detailed economic study on the management of pharmaceutical household waste, looking at drug-take back schemes and extended producer responsibility; and an evaluation of the indirect costs produced by AMR and progress with the One-Health framework.

Discussion

Prof *Jos Van Der Meer* (past President of the European Academies Science Advisory Council, EASAC) compared the EU comprehensive approach to pharmaceuticals[24] in the environment with the OECD approach, which seems to focus on more specific aspects of this problem. Ms Leckie supported the EU life-cycle approach to pharmaceuticals in the environment, but highlighted the need for prioritising action, including targeting high-risk pharmaceuticals and pollution hotspots, and ensuring value for money and cost recovery for wastewater treatment plant upgrades.

When asked by a participant from the audience about the lack of cooperation from the industry as a barrier to address this problem, *Ms Leckie* mentioned that in spite of being a barrier, there are some examples of voluntary action by the industry in this area. Lastly, when asked what could be the role of technology to predict or address this problem, *Ms Leckie* answered that innovative monitoring techniques, modelling and decision-support tools could indeed support better management and understanding of the risks of pharmaceuticals in the environment. Increasing access to data and information, and institutional coordination, will also be necessary to reduce knowledge gaps.

Multi-drug resistance as a growing global problem and its clinical impact

Dr Christoph Lübbert, Professor of Medicine, Head of the Division of Infectious Diseases and Tropical Medicine, Leipzig University Hospital, Germany

Dr Lübbert, started by saying that, as a clinical practitioner he would be sharing his experience on how the problem of antimicrobial resistance (AMR) is affecting everyone at a global level. He started by explaining that antibiotic resistance is an ancient phenomenon; bacteria have always been fighting antibiotics in naturally occurring systems (e.g. antibiotics found in fungi)[25]. Metagenomic data from permafrost materials dating from around 30,000 years ago shows that the same processes have occurred since ancient times. Also, there is evidence that only a few years after the discovery of penicillin, resistance started to emerge[26].

[24] https://ec.europa.eu/commission/news/pharmaceuticals-environment-2019-mar-11_en

[25] D'Costa, V. M., King, C. E., Kalan, L., Morar, M., Sung, W. W., Schwarz, C., ... & Golding, G. B. (2011). Antibiotic resistance is ancient. Nature, 477(7365), 457.

[26] Iredell, J., Brown, J., & Tagg, K. (2016). Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications. Bmj, 352, h6420.

However, rising AMR has also been linked to bad governance, corruption and overall governance in a country[27]. Significant differences persist even between countries across Europe. For instance, the burden of antibiotic resistant bacteria in terms of number of yearly deaths due to infections has been estimated to be around 10,700 for Italy, 200 for the Netherlands and 15 for Estonia[28]. While the current global number of deaths due to AMR is around 700,000 per year, the 2016 O'Neill report estimated that by 2050, AMR could be causing 10 million extra deaths per year[29].

Among the main drivers of AMR are the use, misuse and abuse of antimicrobials, as well as their release in the environment. Resistance genes can spread very easily in a globalised world. This was the case with the New Delhi Metallo-β-lactamase, which presumably originated in India and has now spread around the world[30].

Dr Lübbert reflected on the meaning of these trends for clinical practice. Firstly, he pointed out that many antibiotics are no longer useful for treating some conditions. He showed figures that illustrated the prevalence of multidrug resistant bacteria in patients that were hospitalised abroad. In the Leipzig University Hospital, where Dr Lübbert leads the Division of Infectious Diseases and Tropical Medicine, between 2010 and 2013 105 patients were infected with a Klebsiella pneumoniae Carbapenemase (KPC)-producing strain due to a single patient that had been hospitalised in Rhodes, Greece.

Next, *Dr Lübbert* discussed the presence of pharmaceuticals in the environment. He mentioned the case of India, where a major problem exists with regard to the concentration of pharmaceuticals in waters nearby pharmaceutical manufacturing plants. At the same time, it is important to notice that over 60% of the world production of vaccines and antiretroviral drugs comes from India.

Production conditions in India –mainly on the Hyderabad region—are poor, for instance, high levels of fluroquinolones have been found in rivers across the area due to effluent discharges from bulk drug manufacturers. This is leading to the spread of antibiotic resistance via the environment and has affected people living in the area[31]. For instance, the high concentration of pharmaceutical residues has led to the poisoning of several million fish. While the pharmaceutical industry has compensated affected fishers after 2017, a general solution to this problem has yet to be found. To aggravate the situation, access to antibiotics is very easy and this increases the frequency of self-medication among the population.

Dr Lübbert finished his presentation by sharing some personal conclusions with the audience:

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[27] Collignon, P., Athukorala, P. C., Senanayake, S., & Khan, F. (2015). Antimicrobial resistance: the major contribution of poor governance and corruption to this growing problem. PLoS One, 10(3), e0116746.

[28] Cassini A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., ... & Ouakrim, D. A. (2019). Burden of AMR Collaborative Group. 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, 19(1), 56-66.

[29] Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations http://amr-review.org (2016).

[30] Holmes, A. H., Moore, L. S., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., ... & Piddock, L. J. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet, 387(10014), 176-187.

[31] Lübbert, C., Baars, C., Dayakar, A., Lippmann, N., Rodloff, A. C., Kinzig, M., & Sörgel, F. (2017). Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. Infection, 45(4), 479-491.

- First he explained that outsourcing dirty antibiotic manufacturing processes to very fast emerging countries that already have the biggest resistance problems worldwide cannot be considered fair and the industry should transparently disclose its supply chain.
- Secondly, he appealed to the European Commission to ensure transparency disclosure by the pharmaceutical industry about its supply chains and to strictly prevent the release of antibiotics into the environment
- Finally, in Dr Lübbert's opinion, this can only be achieved through a redefinition of the good manufacturing practices (GMP) criteria under the auspices of the WHO as well as through globally harmonized environmental standards that are included within regulatory controls for pharmaceuticals, especially antibiotics and chemotherapeutics.

Discussion

Prof André Parodi (Honorary President of both the French National Academy of Medicine and the Veterinary Academy of France) mentioned the use of antibiotics as growth promoters. *Dr Lübbert* commented that while this is regulated within the EU, the same does not apply to other countries, including China and India. He also mentioned, that even if antibiotics are not used as growth promotion factors, the use of antibiotics in veterinary medicine is still very large. Studies from the Netherlands suggest that around 20-25% of resistance genes in Gram-negative bacteria important to human medicine origin from this (veterinary) use. So this is a persistent problem that should be addressed as part of meat production and politicians need to communicate these issues to the population and perhaps discuss if and why controlling measures could lead to higher meat prices.

When asked why is there a higher rate of deaths for Italy due to antibiotic resistance, *Dr Lübbert* explained that a significant north-south gap exists, with Scandinavian countries and the Netherlands having the lowest amounts, Germany and other countries being in the middle, and southern countries of Europe lagging behind. This is linked both to use of antibiotics but also to strict hygiene measures, and therefore both aspects should be addressed.

Prof Jos Van der Meer reflected about the fact that the uncritical use of drugs should be addressed as shown by the cases discussed during the presentation. Next, a participant asked whether the migrating population over the past years has also contributed to the distribution of AMR. To this, *Dr Lübbert* replied that it is mostly the percentage of patients colonized with resistant bacteria that have contributed to this problem, including those traveling abroad.

Prof *Jean Michel Foidart* (Permanent Secretary, Royal Belgian Academy of Medicine and member of the FEAM Board) commented on the plans by the US administration to use massive amounts of oxytetracycline and streptomycin[32]. He mentioned that this announcement was very worrisome in the light of what was discussed during the presentation and the experience of the Indian case.

Asked whether the proposed solutions in this area were viable from a political point of view, *Dr Lübbert* suggested that this question could perhaps be addressed later by other speakers.

[32] Jacobs Andrew, Deadly germs, lost cures, Citrus Farmers Facing Deadly Bacteria Turn to Antibiotics, Alarming Health Officials, The New York Times, May 17, 2019, https://www.nytimes.com/2019/05/17/health/antibiotics-oranges-florida.html

The environmental dimensions of AMR: Industry perspective

Prof Jason Snape, Global Safety, Health and Environment Director and Senior Principal Environmental Scientist, AstraZeneca

Prof Snape began his presentation by reminding the audience about the multiple routes by which pharmaceuticals may enter the environment. He also referred to the phenomenon of pseudo-persistence –the persistence of pharmaceutical products on the environment due to their continuous and growing use. Improvements on analytical detection methods have contributed to better measurement and more awareness about the presence of pharmaceuticals in the environment.

Next, *Prof Snape* explained that many drug targets are conserved across taxa and how this translates into potential environmental impacts due to the effects of human medicines on wildlife species[33]. In the EU, an environmental risk assessment (ERA) for human medicinal products has been required since 2006. The first step for this assessment (Phase I) is an estimation of exposure with the assumption that each product will be used for treating 1% of the population –which is an overestimation of their actual use in >95% of cases. Phase II of the ERA is required when certain parameters of phase I are met (for instance the Predicted Environmental Concentration in surface water is over 10 ng/l). Applications for the approval of new drugs need to include this information since 2006. However, this means that over 80% of drugs currently on the market –those authorised before 2006—lack long-term chronic environmental toxicity data. Therefore, there are data gaps in the public domain that are a cause for concern with some stakeholders.

Prof Snape then commented on existing knowledge about environmental risks. A recent study found that most pharmaceuticals pose low or insignificant risks to the environment. Very few drugs were found in quantities that could be considered above dangerous levels. This was the case for instance of some contraceptives and drugs used to treat prostate cancer. While the same exposure scenario applies for antibiotics, in this case we should not lose sight of the effects of livestock use[34]. When conducting an ERA for antibiotics only the tests conducted on cyanobacterial species[35] drive the environmental protection goals; the drugs targets are not present in the daphnia and fish that are tested. Studies have showed the need to use a wider range of different bacterial species and to consider other possible end-points for ecotoxicity beyond those currently used to improve the reliability and relevance of ERA for antibiotics.

With regard to the environmental exposure for antibiotics, studies in 22 EU countries using worst-case exposure predictions have found that most antibiotics (around 84% of them) have a consumption-based predicted environment concentration below the threshold of 100 ng/l; the minimum selective concentration for resistance development for ciprofloxacin. In general, for these types of studies, the

[33] Gunnarsson, L., Snape, J. R., Verbruggen, B., Owen, S. F., Kristiansson, E., Margiotta-Casaluci, L., ... & Tyler, C. R. (2019). Pharmacology beyond the patient–The environmental risks of human drugs. Environment international, 129, 320-332. See also Verbruggen, B., Gunnarsson, L., Kristiansson, E., Österlund, T., Owen, S. F., Snape, J. R., & Tyler, C. R. (2017). ECOdrug: a database connecting drugs and conservation of their targets across species. Nucleic acids research, 46(D1), D930-D936.

[34] Ashbolt, N. J., Amézquita, A., Backhaus, T., Borriello, P., Brandt, K. K., Collignon, P., ... & Lawrence, J. R. (2013). Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. Environmental health perspectives, 121(9), 993-1001.

[35] Le Page, G., Gunnarsson, L., Snape, J., & Tyler, C. R. (2017). Integrating human and environmental health in antibiotic risk assessment: a critical analysis of protection goals, species sensitivity and antimicrobial resistance. Environment international, 109, 155-169.

data covers only one-substance at a time and does not assess potentially additive or synergistic effects. This could also lead to some uncertainty following a drug-by-drug regulatory approach.

The situation is different with regard to exposure related to pharmaceutical manufacturing[36]. While pollution due to drug manufacturing is less spread, the concentration of drugs related to manufacturing processes tends to be higher and more localised.

The current situation with regard to the environmental effects of pharmaceuticals is also affected by the complex interactions and challenges faced by multiple stakeholders. These include NGO's and investors exercising pressure, governments initiating action, and insurance companies interested in addressing the potential costs and societal health risks of AMR.

Prof Snape finished his presentation by referring to AstraZeneca's approach to pharmaceuticals in the environment which is available online[37]. The wider pharmaceutical industry has responded also by developing an AMR roadmap, participating in discussions at the UN General Assembly, and leading voluntary efforts to address this problem. In his conclusive remarks, *Prof Snape* referred to a previous comment about the need to address this problem through Good Manufacturing Practice (GMP) rules. *Prof Snape* mentioned that changes in GMP regulatory may not be the right approach and it might be difficult to realise; he suggested that procurement standards should be reformed. He suggested that using cost as the sole or main criterion for public buying could undermine efforts to combat AMR and drive poor production practices, and that in this sense, green procurement was as important as other types of regulation to combat AMR.

Discussion

A representative of Active Immunity asked the speaker to comment on the use of other alternatives including biologic products as solutions. *Prof Snape* commented that while many innovations are ongoing, vaccine- and phage- based treatment are only limited to some bacteria. He also added that it was very important to take into account the economic model (e.g. sales and size of the market), and to consider the incentives needed from discovery and development, as well as questions regarding payment and the value placed by society on antibiotics. In other words, he suggested that it was important to consider which types of antibiotics should be valued by society and how.

Round table discussion: Pharmaceuticals including antimicrobials and their environmental impact

Speakers from the previous session (Ms. Hannah Leckie, Dr Christoph Lübbert, and Prof Jason Snape) were joined by the following speakers for a roundtable discussion:

- *Alexandru Muntean*, Assistant Professor, Carol Davila University of Medicine and Pharmacy
- *Bogdan Miron Alexandru*, Professor, Carol Davila University of Medicine and Pharmacy

[36] Larsson, D. J. (2014). Pollution from drug manufacturing: review and perspectives. Philosophical Transactions of the Royal Society B: Biological Sciences, 369(1656), 20130571.

[37] https://www.astrazeneca.com/content/dam/az/PDF/2018/A2E303_Pharmaceutical%20in%20the%20environment_A4_Final_V4.pdf

- *Carmen Cristina Diaconu*, Senior Scientist and Director of the Stefan S. Nicolau Institute of Virology of the Romanian Academy

The moderator started the discussion with a reference to the 2016 O'Neill report, which predicted that by 2050 more people will be dying from AMR than from cancer. When asked whether they thought that science could reverse this trend, the audience was divided. The moderator then asked panellists to reflect on the most important actions needed to address this problem. The key messages that emerged from this discussion are summarized below:

- AMR is an urgent and global issue requiring political will as well as citizen engagement.
- More education is needed to communicate the urgency and entity of rising AMR. Everyone – including physicians and patients- needs to be aware about the footprint caused by the use of antibiotics. It was also mentioned that due to adaptation processes, AMR would be hard to defeat only through education.
- Complex changes in behaviour are needed. The example of Uganda was mentioned to exemplify the impact of small changes adopted by hospitals. The importance of hygiene to achieve meaningful changes was also highlighted. It was acknowledged that tackling cultural habits and complex behavioural changes is complex and requires significant time and resources.
- Investments are needed to tackle rising AMR and to address the issue of pharmaceuticals in the environment. Since these problems should be addressed holistically and globally, investments should go beyond research and development, including for instance water and sanitation.
- While positive steps have been taken by governments and industry, continuous and integrated policies are needed. Complex factors such as the ageing of the population and climate change need to be effectively integrated into policy design.
- The role of scientists in tackling AMR was discussed. Scientists need to develop new AMR strategies, including on the use of new antimicrobials. More research to understand and develop better options is also needed.

Concluding remarks

Prof George Griffin summarised the key messages of the policy session. He started by highlighting the importance of bringing together the effects of pharmaceuticals in the environment and rising threats of AMR as part of an integrated discussion. While reflecting on some aspects that were not covered during the debate, he mentioned how bacteria are often described to medical students as organisms that produce enzymes to fight against antibiotics. However, bacteria can be better defined as a sort of machine that recognises environmental threats and switches DNA on and off in order to survive. Acting as a sort of artificial intelligence (AI) system, bacteria spreads its resistance genes through conjugation—which explains why bacterial conjugation is a key tool to fight AMR.

Next, *Prof Griffin* provided a summary of the policy session, which covered the following issues:

- The 2016 O' Neill report provides a good starting point as it predicted that the burden of AMR would surpass cancer in terms of annual deaths by 2050. As a practitioner, *Prof Griffin* mentioned that seeing and treating patients with highly resistant bacteria helps people understand the entity of the problem. As AMR spreads, more people are expected to face this reality.

- Industry seems to be taking this problem seriously. This is consistent with the One Health approach, which seeks to be multidimensional and encompass all interested stakeholders. However, the entity of the problem is serious, as shown by the case of India. The question is then, what can (and should) be done about pollution. This essential issue must be addressed.
- Another interesting aspect that emerged during the panel discussion was the role of the insurance sector, and the fact that higher (insurance) premiums due to the threat of AMR will play an important role in future debates.
- This leads to the economics of AMR. Investments needed to tackle this issue are high. For industry, it does not make sense from an economic point of view to invest in developing new antibiotics only to be faced with growing AMR.
- The global nature of these problems is another important consideration. Even for countries that are progressing fast, globalisation places a big threat for all.
- Antibiotic use is important and changes in behaviour are needed. Spain had an important problem of overuse of antibiotics until recently, which has now been controlled. However, this is still a problem in other countries within and outside Europe. Education at all levels is needed to address this, possibly starting early at the school level. Rapid diagnostics is an advancement that needs to be accepted by practitioners. Only in the UK, many kids die because they are sent home without a diagnosis of (bacterial) meningococcal disease.
- The use of antibiotics for growth promotion and their massive preventive veterinary use in many countries remains problematic.
- There is no time to waste. While changes in behaviour take long time, AMR is rapidly evolving and needs to be addressed now.
- A key question is how this issue should be addressed. While the WHO is certainly a key actor, its own budget has been decreasing lately. Therefore, a combined, multi-disciplinary and global approach is needed. *Prof Griffin* mentioned the example of a committee on dangerous pathogens he chaired in the UK. The committee brought together different governmental agencies and stakeholders, including animal and human health, industry and food and agriculture departments; this multisectoral and integrated approach worked very well at the national level.

Prof Griffin closed the policy session by thanking speakers, panellists and the audience for a very fruitful debate.

Many other important topics were discussed during the 2nd European One Health Conference[38], including the following:

- Comparative oncology in translational medicine;
- Antimicrobial resistance in respiratory centers in Romania;
- Antibiotic resistance in a global perspective (experience from Vietnam);
- Antimicrobial susceptibility of equine clinicals isolates (experience from France);
- European Union-funded research projects on Zoonoses;
- Identification of unknown zoonotic viruses by exploring animal reservoirs-human interfaces;
- Malaria as a risk factor for invasive bacterial disease;
- Vaccination of dairy goats against Q-fever to protect the general human population (evidence from the Netherlands);
- Foodstuff safety in relation with animal treatments.

[38] https://onehealthevents.eu/

Annex I - Agenda

21 June 2019 (10:00 – 13:00)
Spiru Haret University - Berceni Sos., no. 24, District 4, Bucharest – Romania

10:00-10:20	**Registration and coffee**
10:20-12:00	**Plenary session: Pharmaceuticals including microbials and their environmental impact**
10:20-10:45	Hans Stielstra – EC Strategic approach on Pharmaceuticals in the environment
10:45-11:10	Hannah Leckie – OECD strategy on pharmaceutical in the environment and AMR
11:10-11:35	Christoph Lübbert – Multi-drug resistance as a growing global problem and its clinical impact
11:35-12:00	Jason Snape – The environmental dimensions of AMR -industry perspective
12:00-12:50	**Cross-sectoral roundtable discussion – FEAM European Biomedical Policy Forum** *Moderator:* Brian Maguire, Brussels-based journalist **Panellists:** • Alexandru Muntean (MD Assistant Professor at the Carol Davila University of Medicine and Pharmacy - UMF CD) • Bogdan Miron Alexandru (MD, PhD, Professor at the Carol Davila University of Medicine and Pharmacy - UMF CD) • Carmen Cristina Diaconu (PhD, Senior Scientist and Director of the Stefan S. Nicolau Institute of Virology of the Romanian Academy, Bucharest) • Christoph Lübbert • Cristian Busoi (MEP - Committee on Industry, Research and Energy | Committee on the Environment, Public Health and Food Safety) • Hannah Leckie • Hans Stielstra • Jacqueline Alvarez (United Nations Environment Programme – UNEP) • Jason Snape • Pavel Poc (MEP, tbc) • Vasile Cepoi (Former Minister of Health, Government of Romania) *The panel discussion included a Q&A with the audience*
12:50-13:00	**Conclusions - The way forward** Prof. George Griffin, President, Federation of European Academies of Medicine (FEAM)

Annex II - Speakers' biographies

Brian Maguire

Moderator

Brussels-based journalist, producer and broadcaster, Brian Maguire, specialises in European politics and business; producing short documentary films exploring Europe's competing policy dimensions. He hosts live radio and television debates with European Commissioners, Members of the European Parliament and independent experts, and was co-anchor for one of the live European Presidential debates during the 2014 elections. His new Euractiv interview series with Europe's leading policy makers launched at the beginning of October. A graduate in Government and Law, he has worked across a broad range of publications, especially within the business-to-business sector. A specialist in corporate and political communications, his clients have included start-ups, SMEs, blue chip companies, and NGOs.

George Griffin

President, Federation of European Academies of Medicine (FEAM)

Prof. George Griffin gained BSc in Pharmacology and Molecular Biology at King's College London Sciences, where he was awarded the Delegacy Prize for Excellence in Preclinical Science. He was awarded PhD in Cell Biology/Biochemistry, University of Hull, and returned to clinical studies at St George, University of London, where he was awarded the MBBS. Professor Griffin's postgraduate training paralleled basic and clinical science. During this time, he was awarded a Harkness Fellowship of the Commonwealth Fund of New York at Harvard Medical School. On return to the UK, he continued clinical training at Royal Postgraduate Medical School where he was tutor in Medicine, and the National Hospital for Nervous Diseases. He then returned to St George's as lecturer and was awarded a Wellcome Trust Senior Lectureship and became consultant physician on the Clinical Infection Unit where he was instrumental in developing an internationally renowned research unit twinned to the Clinical Unit. He held prestigious research fellowships in the University of Michigan and National Institutes of Health.

He has chaired scientific advisory boards in major pharmaceutical industry in the USA and UK. He has been chair and member of major Wellcome, Medical Research Council and Gates Foundation committees. He was censor at the Royal College of Physicians and was made a member of the Academy of Medical Sciences in which he has been elected to become foreign secretary and council member. He was appointed to the board of Public Health England where he will help shape strategy for research and clinical development. Professor Griffin was awarded the distinction of CBE in 2018 (Commander of the British Empire) for his research and its contribution to Public Health.

His research has focussed on the host response to infection at cell, molecular and whole body level. Such work involves immune and metabolic responses in vivo in humans. Furthermore, cell and molecular studies include culture of human mucosal explants and definition of macrophage activation in vitro by microbial agents. A macrophage is a cell which ingests particles (microorganisms or host cells) for destruction and immune presentation. It is important in intracellular infection and also produces cytokines (a category of signaling molecules) as part of the immune response.

Professor Griffin's principal clinical contributions to knowledge have been in the characterisation of intestinal disease in HIV infection, mechanism of weight loss in HIV and definition of loss of mucosal immune response in advanced HIV infection. The dominant cell and molecular achievements have been the characterisation of NF-kb, a crucial factor maintaining macrophage differentiation and the role this transcription factor plays during tuberculosis infection of the macrophage and the mechanism of enhanced HIV transcription in such cells. More recently he has characterised the role of co-infection of HIV infected cells with herpes virus in enhanced HIV transcription in the genital epithelium.

Hans Stielstra

Deputy Head of Unit - European Commission. Directorate General Environment, Unit ENV.C.1 Clean Water

Hans Stielstra is Deputy Head of Unit C1 (Clean Water) at the European Commission (DG Environment). He has worked for the Commission's directorate general environment since 1998 in a range of different posts including international environment issues and trade. Mr. Stielstra has a background in political science and administration.

Hannah Leckie

Policy Analyst, Water Team Climate, Biodiversity and Water Division Environment Directorate, OECD

Hannah Leckie is a Policy Analyst in the Water Team of the OECD Environment Directorate. She leads the OECD's work on water quality. Recent work includes strategies to control pharmaceutical residues in water, emerging policies to manage diffuse (non-point) pollution and bridging the financing gap for investment in water supply and sanitation infrastructure. She is particularly interested in water pollution and the cost of inaction, the water-food-energy-environment nexus, and innovative solutions utilising the value of nature. Hannah holds a Master of Science in Water Science, Policy and Management from the

University of Oxford, UK, and a Bachelor's degree with Honours in Soil Science from Lincoln University, New Zealand.

Christoph Lübbert

University of Leipzig, University Hospital

Born on 6 January 1971 in Ratzeburg (Germany). Medical studies at the Universities of Kiel, Zurich (Switzerland) and Durban (South Africa). Doctorate (Dr. med.) with an experimental work on cytomegalovirus infections in 1999. Clinical training in internal medicine, gastroenterology, infectious diseases and tropical medicine (including a DTM&H at the Liverpool School of Hygiene and Tropical Medicine, UK) from 2000-2008 at various locations. 2008-2012 senior physician at the University Hospital Halle (Saale) in Germany, specializing in gastrointestinal endoscopy and infectious diseases. 2012 takeover as head of the Division of Infectious Diseases and Tropical Medicine within the Department of Gastroenterology and Rheumatology of the University Hospital Leipzig, Germany. 2015 habilitation and receipt of the venia legendi for internal medicine at the University of Leipzig. In the same year election to the scientific advisory board of the German Society of Infectious Diseases (DGI). 2016 winner of the prevention award for internal medicine of the German Society of Internal Medicine (DGIM). In the same year also winner of the Theodor Litt award for special commitment in teaching by the University of Leipzig. In 2017 call for a full professorship at the University of Lübeck (rejected). Early appointment as professor for internal medicine and infectious diseases by the University of Leipzig. Elected to the board of the German Society of Infectious Diseases (DGI) in 2017.

Jason Snape

Global Safety, Health and Environment Director and Senior Principal Environmental Scientist, AstraZeneca

Jason Snape joined AstraZeneca in 1995 as an experimental scientist to study the environmental fate, behaviour and degradation of pharmaceuticals as they enter the environment after patient use. As this area of study has grown in understanding and visibility, his role has developed and progressed and he is now the Senior Principal Environmental Scientist responsible for leading the Safety, Health and Environment foresight and research programmes.

Jason Snape has always been passionate about science-based advocacy and his PhD in environmental microbiology and biochemistry from Cardiff University, which investigated the bacterial metabolism of nitrate esters that are used as active ingredients in cardiovascular drugs and explosives, set him up for his current role. Being at the science-policy interface helps to ensure regulations are based on sound science and that all stakeholders work together to ensure that patients can access medicines without compromising the health of our natural environment.

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