

Antimicrobial Drug Discovery

Following publication of the Statement “Antimicrobial drug discovery: greater steps ahead” (<http://www.easac.eu/home/reports-and-statements/detail-view/article/antimicrobia.html>), EASAC organised a discussion in Brussels on 3 December 2014 to raise visibility of the issues with policy-makers and to discuss the EASAC conclusions within the broader context of what is needed to tackle antimicrobial resistance and of how the EU can best contribute to global priorities.

In opening the event Jos van der Meer (EASAC) explained the development of antimicrobial resistance in relation to the use and misuse of antibiotics, particularly the indiscriminate use in some human and animal populations. In terms of mechanisms, resistance occurs because of changes in the antibiotic reaching the target, premature inactivation or pumping out of the bacterium, or the target becomes insensitive.

The public health problems caused by resistance are compounded by stagnation in drug development. This discovery void emerged about 20 years ago and the EASAC Statement draws on work from various scientific disciplines to make a series of recommendations to tackle the challenges (Table 1).

Table 1: Recommendations from the EASAC Statement, 2014

This Statement is based on a meeting organised by EASAC together with academies of science in the Netherlands and Germany and on previous work published by EASAC¹

Recommendation	Examples of action required
Support basic research	Invest in novel ideas and sources of natural products; stimulate neglected disciplines, e.g. medicinal chemistry; make field more attractive for (young) researchers
Install and promote EU platforms	Ensure systematic approaches to compound identification, lead optimisation and characterisation, e.g. rejuvenate rules for understanding antibiotic penetration into cells

¹ Further details are in the EASAC reports from 2007 (Tackling antibacterial resistance in Europe) and 2011 (European public health and innovation policy for infectious diseases: the view from EASAC) as well as the recent Statement (Antimicrobial drug discovery: greater steps ahead) and a paper in Nature Reviews Drug Discovery (van der Meer JWM, Fears R, Davies SC, ter Meulen V, Antimicrobial innovation: combining commitment, creativity and coherence, 2014; 13: 709-10). All material is on <http://www.easac.eu>.

Address bottlenecks in development	Recognise need to provide additional resource on animal models to reach proof-of-principle stage, plus medicinal chemistry, drug metabolism and toxicology, and clinical capabilities; there are various options for supplying new resources but they require new funding and new business models
Optimise EU partnerships	IMI is vital and so is JPI but underfunding has to be addressed; further multiple engagement – researchers, funders, regulators and others – needed to tackle challenges in translating research
Rethink regulatory frameworks	More flexibility required, e.g. simpler framework for narrow spectrum drugs; there may be important general lessons for accelerating drug development to be learnt from the Ebola crisis
Raise public awareness	Global awareness is vital as part of efforts to educate to preserve efficacy of available antibiotics and concomitant need to encourage research and innovation; such effort must emphasise the core importance of animal research and the need to revisit societal expectations of zero drug side-effects

Dame Sally Davies (Chief Medical Officer, UK) addressed the global challenges presented by antimicrobial resistance and the implications for the EU. Resistance has become an increasingly global problem, exemplified by the recent emergence of two strains of Carbapenem-resistant *Klebsiella pneumoniae*, KPC and NDM1: this brings significant problems for surveillance in the developing world and for intergovernmental action. Every year, approximately 25,000 people die of sepsis caused by resistant bacteria in Europe and 23,000 in the USA. One child dies every five minutes in SE Asia of infection caused by resistant bacteria. In the UK, resistant infections have doubled the death rate and doubled the costs of a hospital stay.

Antibiotics are central to modern medicine; for example, the vast majority of surgical procedures use prophylactic antibiotics, yet worldwide 50% of antibiotics are sold without a prescription and 70% of the total volume of antibiotics are used in animals, fish or elsewhere in agriculture. There is need for additional “One Health” research on the links between human and animal use and developing resistance. It is also increasingly important to curtail internet sales of antibiotics and to understand how vaccines can be used in animals so as to reduce antibiotic use.

Evaluating regional variation in use in humans and animals creates opportunities for conserving the efficacy of the antibiotics presently available and there are lessons to be learnt in sharing good practice for reducing overuse in animal husbandry and food production. The EU has demonstrated leadership in outlawing antibiotic use for animal

growth promotion and in reserving critically important antibiotics for human use. In reinforcing and supplementing the EASAC points, Professor Davies emphasised that drug discovery requires more basic, clinical and translational research together with better understanding of the implications of the usage outside of human medicine. In addition, research to develop effective, point-of-care, rapid diagnostic agents is a priority.

The UK recently (re-)launched the national Longitude Prize, to create cheap, accurate, rapid and easy-to-use tests for bacterial infections, representing an important step in public recognition of the importance of the issues. The USA also recently announced a similar prize and the European Commission will do so in 2015. It is important to remember that the goal in better diagnosis is a global one – not just European or American.

There have been several recent achievements worldwide in commitment to tackling the issues of antimicrobial resistance. In particular, the priority at the WHO and elsewhere in the UN has grown and the draft WHO Global Action Plan on antimicrobial resistance is now published². This will facilitate coordinated action with OIE and FAO. There have also been important discussions at the G7 Science Ministers' meeting and the World Health Summit. In the UK, the government has commissioned an independent review³ to examine the economic issues associated with antimicrobial resistance (and the current market failure to encourage industry innovation), which will then inform G20 discussions. In addition, the UK is working with Commonwealth countries to set up laboratory twinning to improve diagnosis and surveillance worldwide.

Much is still needed to be done to build on these achievements, to move from planning to action, to instigate national activity linked to the WHO Global Action Plan, and to make more use of tools to support public education⁴, for example the EU antibiotic awareness day⁵.

Members of the Panel welcomed the EASAC recommendations in helping to inform the way forward and they provided further detail on some of the crucial issues raised by Professors van der Meer and Davies.

² The WHO Global Action Plan on antimicrobial (including antibiotic) resistance will be launched at the World Health Assembly in May 2015. The WHO publication "Antimicrobial resistance: global report on surveillance 2014" is on <http://www.who.int/drugresistance/documents/surveillancereport/en>.

³ <https://www.gov.uk/government/news/prime-minister-warns-of-global-threat-of-antibiotic-resistance>. The Report from this inquiry by O'Neill was published the week after the EASAC event on http://www.his.org.uk/files/4514/1829/6668/AMR_Review_Paper_-_Tackling_a_crisis_for_the_health_and_wealth_of_nations_1.pdf and estimates major public health and economic burdens unless the problems are tackled ("Review on antimicrobial resistance: Tackling a crisis for the health and wealth of nations", December 2014).

⁴ A lay summary of the EASAC Statement, entitled "New antimicrobial drugs: why we need them and how we can get them", was published to coincide with the Brussels discussion event.

⁵ <http://ecdc.europa.eu/en/EAAD/Pages/Home.aspx>

Angela Wittelsberger (Innovative Medicines Initiative, IMI) reviewed how IMI, as a major public-private partnership between the European Commission and pharmaceutical industry, enables pooling of resource and expertise, provides incentive to companies to commit to the therapeutic area and creates a neutral environment that facilitates stakeholders working together. To date, 30% of IMI funding has been invested in the field of infectious disease, variously tackling challenges for clinical development (putting in place clinical trial networks), basic science (especially Gram negative bacteria cell penetration issues), translational science (filling the gaps between the discovery of promising molecules and candidate entry into development) and return on investment (clarifying options for new economic models of antibiotic innovation⁶).

Future IMI work will extend the initiative by bringing in additional partners to address new opportunities to combat infectious disease, for example in diagnosis, information technology and animal health.

Arjon van Hengel (DG Research and Innovation) noted the very large increase in research funding on antimicrobial resistance between Framework Programmes 5 and 7 and highlighted the European Commission's 5 year action plan in place since 2011. This includes significant attention to One Health issues across the human-animal-environment reservoirs of antimicrobial resistance and the possibilities of intervention.

In addition to IMI, the European Commission's strategic actions on research include: (i) coordinating EU-funded research on the European scale for human and veterinary health and nanomaterials (for novel antibiotic delivery systems) to include therapeutics, vaccines and alternative approaches such as phages, with more than 50% of the funding allocated to SMEs; (ii) the Joint Programme Initiative on antimicrobial resistance, to produce effective coordination in Member State research spending, governed by the EU Strategic Research Agenda, now being aligned with the WHO Global Action Plan to generate a global research agenda.

John-Arne Røttingen (Norwegian Institute of Public Health) reiterated the need for a collective international strategy to combat antimicrobial resistance. This must ensure that all who need antibiotics can get them – globally more people still die from lack of antibiotics than from antibiotic resistance. Conservation of the efficacy of the antibiotics presently available must be coupled with support for new research and innovation but this requires incentives throughout the value chain, additional to those supplied by the current public-private partnerships. How could reduced usage from prudent prescribing (and hence weakened market pull) be reconciled with rewarding innovation? That is, what might be new models to decouple incentives for research and high volume use? Significant insights are anticipated both from the IMI DRIVE-AB project (footnote 6) and the UK economic review mentioned previously (footnote 3), and there is continuing need for social sciences research to accompany basic research priorities, in order to understand and inform the economic systems.

⁶ The IMI project DRIVE-AB commenced autumn 2014 and details on this and other IMI infectious disease projects are on <http://www.imi.europa.eu/content/nd4bb>

Brendan Barnes (EFPIA) agreed with previous comments on the potential value to the pharmaceutical sector, companies large and small, of the IMI projects, including the concerted effort for new business models. Companies were also encouraged by the commitment displayed by WHO and in the EU Antibiotic Action Plan, accompanied by sustained cross-sectoral engagement. Action by the regulatory agencies in the EU and USA to review antibiotic guidance and thereby facilitate clinical trials has also been welcome. As recommended by EASAC and the other speakers, it is still vital to accommodate and promote novel science strategies in support of diversity, and to ensure integration of social sciences research. The EU is seen to have a great role in continuing leadership and supporting global efforts.

James Anderson (GSK) provided a perspective from a major pharmaceutical company, which had retained its interest in the antibiotic area despite lack of new product launches, low discovery hit rate and lack of early success in novel approaches based on genomics. This remains a public health priority. Notwithstanding the market failure today, economic returns tomorrow can be anticipated when current initiatives on business models, such as those from IMI, deliver.

GSK regards its participation in public-private partnerships such as IMI and with the US Biomedical Advanced Research and Development Authority⁷ as fundamentally important and is aiming to establish a Centre for Microbiological Innovation to bring together new expertise with new scientific directions. For the regulatory framework, in addition to the advances in EU/US guidelines on antibiotic development described previously, more general trends related to adaptive licensing for patients with high unmet need will be helpful in the anti-infective therapeutic area. It has become clear that antibiotic market failure has had very significant impact on society as well as the pharmaceutical sector. There is need to encompass incentives for future threats (that is, resistance developing to currently effective drugs) and to ensure global access for all patients to antibiotics without wastage.

Keith Spencer (Wellcome Trust) described the ongoing work of the Wellcome Trust relevant to antimicrobial resistance, across human and animal health, funding basic and translational research, surveillance, small molecule drug discovery, public engagement and the current UK economic review (together with the NIHR). The Wellcome Trust is now actively considering options for a new strategic initiative – not only for the issues associated with antibacterials but also antivirals and antifungals - to add value to what is already being achieved and based on understanding of patient needs worldwide.

It may transpire that the Ebola crisis can help to provide a template to design further antimicrobial resistance work – based on the lessons learnt for coordination, data sharing, accelerating new products, and involving collaboration among governments, charities, regulators and companies to enable delivery of innovative products and services.

⁷ <http://www.phe.gov/about/barda/Pages/default.aspx>

In chairing the Panel discussion Anne Glover (European Commission) stimulated further debate in two major areas:

- Is there need for further regulation to manage indiscriminate antibiotic use? Discussants noted that there was good prescribing practice in some Member States, whose lessons should be shared because, even though OTC antibiotic sales are not now allowed in the EU, there is still room for improvement in restricting supply. A problem in developing countries is that the current mechanisms of securing antibiotic access tend to encourage indiscriminate use – there is a need for a new international regimen to balance access with responsible use, perhaps as part of the forthcoming WHO Global Action Plan.
- In developing novel antibiotic drugs, might there be a role for a publicly-funded route – a global institute for drug discovery – with industry helping where appropriate? Discussants observed that there are already several sources of funding for academia to engage in drug discovery but – as identified in the EASAC Statement – not all of the multiple drug development competencies (for example to run GMP facilities or engage with regulatory authorities worldwide) may be available in academia. IMI has shown that partners can learn together and work together and this has helped to share perspectives and experience between companies as well as between sectors.

General discussion pursued various other points raised in the EASAC Statement. For example:

- The potential value of phage therapy, acknowledging previous problems (in particular, narrow selectivity and limited stability) but still a subject of EU research.
- The challenge of building and using chemical compound libraries. IMI has been helpful in developing and maintaining libraries and in offering them for screening against various targets, but there is a continuing problem that conventional libraries do not work well as a source of antibiotics and there is need to collate new libraries (for example, of natural products from maritime sources).

In closing, Professor van der Meer concluded that the meeting had been inspirational in clarifying ways forward – both in the EU setting and the wider global context. Further feedback is welcomed on any of the points raised, together with suggestions for ways whereby EASAC, its member academies and global partners, can help to catalyse further discussion and action.