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EASAC and FEAM
Joint Statement from the Presidents

FEAM
Federation of European Academies of Medicine

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On 19 May 2016, the final report of the Independent Review on Antimicrobial Resistance, 'Tackling drug-resistant infections globally', chaired by Jim O'Neill was issued. This report, which analyses the global antimicrobial resistance crisis mainly from an economic perspective, gives several important recommendations. A first set of recommendations aims to reduce the demand for antibiotics. To this end the report recommends the following:

1. A massive global public awareness campaign.
2. Improvement of hygiene and prevention of spread of infection.
3. Reduction of unnecessary use of antimicrobials in agriculture and their environmental spread.
4. Improvement of global surveillance of antimicrobial resistance and use in humans and animals.
5. Promotion of new rapid diagnostics for infectious diseases.
6. Promotion of development and use of vaccines and alternatives.
7. Improvement of the numbers, pay and recognition of people working in infectious diseases.

A second set of recommendations deals with development of new drugs:

8. Establishment of a Global Innovation Fund for early stage and non-commercial research.
9. Better incentives to promote investment for new drugs and improvement of existing drugs.

The tenth and final recommendation regards the building of a global coalition for action on antimicrobial resistance via G20 and the United Nations.

The O'Neill Commission has done a formidable job, but in fact these recommendations come as no surprise. Previous reports, from us[1] and others[2] came to similar recommendations, and, in line with *O'Neill recommendation 10*, significant international coalitions have been initiated already, especially the European Union (EU) Action Plan and the World Health Organization Global Action Plan.

However, the economic approach by the O'Neill committee gives the recommendations added flavour. The European Academies' Science Advisory Council (EASAC; www.easac.eu) and the Federation of European Academies of Medicine (FEAM; www.feam-site.eu) endorse these recommendations, highlight the scientific and clinical perspective, and translate and prioritise the recommendations for the EU and its Member States. In this context, the conclusions of the Ministerial One Health Conference on antimicrobial resistance[3] under the Dutch EU presidency will also be taken into account, as they emphasise the European political focus.

First of all, EASAC and FEAM have always stressed that solutions to the antimicrobial crisis should primarily come from science, i.e. the development of new antimicrobials, new vaccines and other innovative treatment modalities.

The Ministerial One Health Conference concludes that there is a need for a new research and development policy involving Ministers of Health and Agriculture.

Elsewhere, EASAC has pointed out that there are substantial obstacles in place for antimicrobial drug discovery and development in Europe[4]. The recommendations in this EASAC statement are still very valid for Europe (Box 1).

What is not so evident from the O'Neill report and from the ministerial conclusions is that public sector research will have to play a key role in antimicrobial drug discovery. It is not just a matter of investment, important though that is: it also requires a strategic change for academia, as was pointed out by EASAC.

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1 EASAC (2007) Tackling antibacterial resistance in Europe. EASAC (2011) European public health and innovation policy for infectious diseases: the view from EASAC. EASAC (2014) Antimicrobial drug discovery: greater steps ahead.

2 German National Academy of Sciences Leopoldina and Academy of Sciences Hamburg (2013) Antibiotics research: problems and prospects. G8 Science academies with other science academies (2013) Drug resistance in infectious agents – global threat to humanity. Inter Academy Panel and InterAcademy Medical Panel (2013) Antimicrobial resistance – a call for action.

3 On 10 February 2016 in Amsterdam (http://www.eu2016.nl/documenten/publicaties/2016/03/11/conclusions-and-findings-as-presented-during-the-eu-ministerial-one-health-conference-on-amr-on-the-10th-of-february-2016-amsterdam).

4 EASAC (2014) Antimicrobial drug discovery: greater steps ahead.

Box 1 Recommendations from the EASAC Statement 2014

1. Support for basic research
   - Invest in novel ideas and sources of natural products;
   - Stimulate neglected disciplines, for example medicinal chemistry;
   - Make field more attractive for (young) researchers.
2. Install and promote EU platforms
   - Ensure systematic approaches to compound identification, lead optimisation and characterisation, for example rejuvenate rules for understanding antibiotic penetration into cells.
3. 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.
4. Optimise EU partnerships
   - The Innovative Medicines Initiative is vital and so is the Joint Programme Initiative on Antimicrobial Resistance but underfunding has to be addressed;
   - Stimulate multiple engagement – researchers, funders, regulators and others – needed to tackle challenges in translating research.
5. Rethink regulatory frameworks
   - More flexibility required, for example simpler framework for narrow spectrum drugs;
   - There may be important general lessons for accelerating drug development to be learnt from the Ebola outbreak.
6. 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.

Still, the business models presented in the O'Neill report (*O'Neill recommendation 9*) are very important, and should be considered for implementation as soon as possible. The plea of the Ministerial One Health Conference for better alignment of national investments in antibiotic research, as well as delinking investment costs from sales (volume) of antibiotics, fits very well with this recommendation. It is also relevant for the EU to take account of the challenges for ensuring access to effective antibiotics for all who need them worldwide when addressing the priorities for pathogen targets and business models. The EU has pioneered some great collaborations between academia and industry in the Innovative Medicines Initiative, but it is vital that pharmaceutical partners are encouraged to contribute their best assets to these pre-competitive consortia, which must also be given the flexibility to explore emerging findings[4]. Moreover, it is highly desirable that EU publicly funded innovation partnerships serve as a basis for wider international collaboration, for example to ensure strategic complementarity with the USA and to share limited infrastructure, such as pathogen-handling facilities.

From a clinical point of view, the O'Neill report pays little attention to antibiotic stewardship and efforts to change behaviour of prescribing physicians. Here, the input of social sciences is urgently needed, as is giving enough attention to increasing the knowledge and skills of medical students, and young doctors in antimicrobial prescribing. Awarding a 'license to prescribe antibiotics' after a mandatory course on antimicrobial stewardship for residents would be a step forward to enhance prudent prescribing. In the EU, the Union of European Medical Specialties (UEMS) and the European Society for Microbiology and Infectious Diseases (ESCMID)[5] could take the lead here. The important differences in prescribing behaviour across Europe should be taken into account in such a programme[6]. Another important measure that can be taken at the national level is the instalment of antibiotic teams in hospitals (consisting of an infectious disease physician, a medical microbiologist and a pharmacist) to implement stewardship.[7] The O'Neill report points out that there are too few specialists in infectious diseases and medical microbiology in the world and that pay and esteem are less than for other medical specialties (*O'Neill recommendation 7*). To combat the current crisis we need a strong workforce, which implies that Member States should invest here.

[5] Especially through the ESCMID Study Group on Antimicrobial Policy, ESGAP.

[6] Hulscher ME, Grol RP, van der Meer JW (2010) Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *Lancet Infectious Diseases* **10** (3): 167–175.

[7] Such antibiotic teams have been installed in hospitals in the Netherlands.

In addition to development of new drugs, we agree that new diagnostics are also urgently needed to allow precision medicine with antibiotics (*O'Neill recommendation 5*). From the clinical side, we feel that the difficulties in implementing new rapid diagnostics are an underestimated issue in the report. Lessons can be learned, for instance, from the procalcitonin test, which would allow for less and shorter antibiotic prescribing[8], but has not found general acceptance for a variety of reasons.

Rapid diagnostic methods are not a solution for all problems: physicians often still prescribe antibiotics for bronchitis ('cough'), sinusitis, uncomplicated otitis media and enteritis, infections that are easy to diagnose and for which antibiotics are not indicated. Such practice can only be stopped by training doctors and raising public awareness (*O'Neill recommendation 1*).

The O'Neill report rightly stresses the need for infection prevention (*O'Neill recommendation 2*). There is quite a difference among the EU Member States in the amount of money spent on antibiotics compared with that spent on hospital hygiene[9]. These kinds of inequality need to be addressed, and it is good to see that the Ministerial One Health Conference agreed to establish twinning mechanisms and country-to-country peer review. Nonetheless, there is no excuse for the poor compliance of health-care workers with hand hygiene and other infection-prevention measures. Implementation of the use of hand alcohol[10] and behavioural change should be mandatory and health authorities at the level of the EU Member States should act now.

The report also addresses the restriction of use of antibiotics in agriculture (*O'Neill recommendation 3*). We stress that there is very little, if any, science base for the prophylactic use of antibiotics in agriculture, either for prevention of infections or for growth promotion. From human medicine we know that prolonged use of prophylactic regimens will unavoidably meet with a decreasing efficacy, a point that is rarely realised by the users. Hence, stopping prophylactic use of antibiotics will not suddenly lead to outbreaks of infections, and the time frame for reducting such use as proposed by the O'Neill report (2018–2028) is unnecessarily long.

The European Commission should be praised for taking the lead in stopping antibiotics for growth promotion, and there is a continuing prospect of the EC doing more, for example the EC Guideline for Prudent Use of Antimicrobials in Animals[11]. In addition, a ban on the preventive use of antibiotics in animals was also a prominent item in the Ministerial One Health Conference.

A recommendation from the report which should be explored at the EU level is the special labelling of food if it contains antibiotics (*part of O'Neill recommendation 1*).

Antibiotics in hospital effluents (as well as in manufacturing waste) are a problem, the magnitude of which is not fully clear (mentioned under *O'Neill recommendation 3*). Some antibiotics will probably be rapidly degraded (such as penicillin) whereas others (such as quinolones and aminoglycosides) probably remain intact. The selection pressure exerted by these antibiotics needs to be investigated further.

The report rightly mentions the over-the-counter and internet sales of antibiotics (under *O'Neill recommendation 1*). The former might be as high as 30% in parts of southern and eastern Europe, and no doubt lead to inappropriate use. Authorities in Member States and pharmaceutical companies should both take measures to control these sales. As proposed in the report, a coordinated global effort is required by domestic regulators and international bodies like Interpol to limit unregulated online sales. EU should act here.

Not mentioned by the O'Neill group is the effect of sales promotion for antibiotics by the pharmaceutical industry. Although the effect size of this activity is unknown, it would probably be wise to stop this promotion. This does not preclude the industry from providing factual and scientific information about their antimicrobial products.

Regarding surveillance (*O'Neill recommendation 4*), the European Centre for Disease Prevention and Control (ECDC) has mechanisms in place to monitor antibiotic use (ESAC-net) and antimicrobial resistance (EARS-net) in the EU Member States. However, these activities need to be intensified to enable the Centre to provide more real-time information.

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[8] Christ-Crain M, Stolz D, Bingisser R, et al. (2006) Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *American Journal of Respiratory and Critical Care Medicine* **174** (1): 84–93.
Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J (2008) Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *American Journal of Respiratory and Critical Care Medicine* **177** (5): 498–505.

[9] Beaujean DJ, Weersink AJ, Troelstra A, Verhoef J (2000) A pilot study on infection control in 10 randomly selected European hospitals: results of a questionnaire survey. *Infection Control & Hospital Epidemiology* **21** (8): 531–534.

[10] Hansen S, Schwab F, Gastmeier P; PROHIBIT study group, et al. (2015) Provision and consumption of alcohol-based hand rubs in European hospitals. *Clinical Microbiology and Infection* **21** (12): 1047–1051.

[11] (2015/c/299.04).

On the basis of the considerations above – and incorporating the O'Neill report as well as the Ministerial One Health Conference – EASAC and FEAM propose a series of priority actions for the EU (Box 2). We emphasise that these are a mix of EU institutional and Member State activities, but even where responsibility lies primarily at national level, there is value in sharing good practice and lessons for implementation.

Box 2 Recommendations from EASAC and FEAM for EU priority action

1. Enhance public awareness.
2. Promote the development of new drugs, take away the obstacles (including those for market entry), and promote the development of new vaccines.
3. Reduce unnecessary agricultural use of antimicrobials and prohibit prophylactic use of antibiotics in agriculture.
4. Invest in antibiotic stewardship and antibiotic teams, train students and physicians, and increase the workforce for infectious disease and microbiology.
5. Stimulate the development of rapid diagnostics and implement these.
6. Make hygiene a priority and implement strict rules of hand hygiene for health-care workers.
7. Stop over the counter selling of antibiotics in Europe and regulate internet sales. Stop sales promotion of antibiotics.
   Intensify the surveillance activities (antimicrobial resistance and antibiotic use) of the European Centre for Disease Prevention and Control.

FEAM

FEAM's mission is to promote cooperation between national Academies of Medicine and Medical Sections of Academies of Sciences in Europe; to provide them with a platform to formulate their collective voice on matters concerning human and animal medicine, biomedical research, education, and health with a European dimension; and to extend to the European authorities the advisory role that they exercise in their own countries on those matters.

EASAC

EASAC – the European Academies' Science Advisory Council – is formed by the national science academies of the EU Member States, Norway and Switzerland, to enable them to collaborate with each other in providing independent science advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.

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