ANTIBIOTIC RESIDUES IN SEWAGE AND AGRICULTURAL RUN-OFF: CAN WE DETERMINE SAFE THRESHOLDS TO COMBAT DEADLY SUPERBUGS?

This is the report of a meeting hosted by the All-Party Parliamentary Group on Antibiotics on Tuesday 24th November 2020
INTRODUCTION

Antibiotic resistance is often described as a “wicked problem” because it involves multiple pathogens and numerous causes.

I suspect that one of the least known, or understood, aspects of this problem (among some politicians and policymakers, anyway) is the relationship between antibiotic resistance and the environment – especially waste water.

From streams and lakes, to rivers and oceans, it’s clear antibiotics are making their way into our waters in ever greater concentrations, where they may exert a selective pressure on the development of resistant bacteria that’s present in our environment. This forms a vicious circle that’s increasing resistance rates and risking a rise in deadly superbugs.

Yet despite the potential implications for human health, current environmental risk assessment guidelines and regulations don’t take account of antibiotic resistance.

It is therefore regrettable that no environment-related recommendations from the UK’s five-year national action plan on AMR (see pp44-48) made it into the Environment Bill 2019-2021 (which is currently making its way through Parliament) – and that the Bill does not refer specifically to antibiotic or antimicrobial resistance.

Against that background, we invited a team of experts from the University of Exeter to tell us about the development of a novel method to establish safe release limits for antibiotics that could, in the near-future, also help to identify highly-contaminated areas through environmental surveillance (you can read more about their work in a short blog post published by the British Society for Antimicrobial Chemotherapy (BSAC)).

We think there is a strong case for considering whether these findings need to be acknowledged and addressed in the Environment Bill, which is scheduled to return to the House of Lords by the end of this year, or the beginning of next. As such, this report contains a number of recommendations that will serve as the basis for draft amendments that the Peers in our Group will endeavour to table in the new year.

We will report back on any progress the Group makes.

Meanwhile, if you have any questions about the nature of our work, I would urge you to get in touch with BSAC, which provides the secretariat for our APPG. You will find contact details on the last page of this document.

With kind regards

Julian Sturdy
Member of Parliament for York Outer
Chair of the APPG on Antibiotics

December 2020
‘Antibiotic residues in sewage and agricultural run-off: can we determine safe thresholds to combat deadly superbugs?’

A meeting of the APPG on Antibiotics
Date: Tuesday 24th November 2020
Time: 1100 to 1200
Location: Microsoft Teams Video Call

1100 Welcome and introduction
Julian Sturdy MP & Dr Nicholas Brown, Consultant Medical Microbiologist, Addenbrooke’s Hospital, Cambridge, & Director of Public & Professional Engagement, BSAC

1105 Antibiotic residues in sewage and agricultural run-off: can we determine safe thresholds to combat deadly superbugs?
Dr Aimee Murray, Prof William Gaze, & Dr Isobel Stanton, University of Exeter

1130 How can these findings be used to inform and influence the Environment Bill?
Baroness Bennett of Manor Castle & Dr Nicholas Brown

1135 Q&A
All speakers

1155 Summary and close
Julian Sturdy MP & Dr Nicholas Brown
ANTIBIOTIC RESIDUES IN SEWAGE AND AGRICULTURAL RUN-OFF: CAN WE DETERMINE SAFE THRESHOLDS TO COMBAT DEADLY SUPERBUGS?

Dr Aimee Murray, Prof William Gaze, Dr Isobel Stanton, University of Exeter

The Environmental Dimension of AMR

William Gaze¹, Anne Leonard¹, Aimee Murray¹, Jason Snape², Isobel Stanton¹, Lihong Zhang¹

¹European Centre for Environment and Human Health, University of Exeter Medical School, Penryn, Cornwall, UK
²AstraZeneca Global Environment, Macclesfield, Cheshire, United Kingdom

Antimicrobial Resistance: Investigating the Environmental Dimension

What is antimicrobial resistance?
Antibiotics, co-selectors and resistant bacteria in the environment
Mitigating the discharge of antimicrobials into the environment
Future research and activities to inform policy

References
Three main issues associated with the environment highlighted in WHO / EU Action plans

- Role of pharmaceuticals in the environment driving emergence of AMR
- Circulation of AMR in the environment
- Environmental transmission of AMR

Antibiotic resistance: an ancient phenomenon

Samples from permafrost before the “Age of Antibiotics”

- Enormous variety of resistance genes against modern antibiotics

O’Coilea et al., 2011, Nature Letters
Mobility of antibiotic resistance genes

- Rare gene transfer events that lead to new genetic combinations – rare but can be extremely important – origin of genes in previously susceptible human pathogens is recognised as the environmental resistome

- Acute transmission events - introduction of human and animal associated AMR bacteria to aquatic and soil systems and human exposure to these bacteria/genes in environmental settings.

One Health AMR
Class 1 integron prevalence in sediments

11 billion litres of wastewater discharged per day in the UK

Chromosomal mutation in single species competition assays

- Streptomycin MSC was $\frac{1}{4}$ of MIC 1 mg / L
- Tetracycline MSC was 1/100 of MIC 15 µg / L
- Ciprofloxacin MSC was between 1/10 and 1/230 of MIC 2.5 µg – 100 ng / L
Exposure to and colonisation by antibiotic-resistant E. coli in UK coastal water users: Environmental surveillance, exposure assessment, and epidemiological study (Beach Bum Survey)

Anne F.C. Aronsen, Lifeng Zhang, Andrew J. Belfour, Ruth Gascide, Peter M. Hawley, Aine O. Murray, Oluola G. Okinnaro, William H. Gean

*European Centre for Environment and Human Health, University of Exeter Medical School, Exeter EX1 2PD, UK

†Exeter Institute for Health Sciences and Care Research, University of Exeter Medical School, Exeter EX1 2PD, UK

‡School of Veterinary Medicine and Science, University of Nottingham, University Park, Nottingham, NG7 2UH, UK

Environmental Risk Assessment and the SELECT method

Dr Aimee Murray
Outline

• Relevance to UK Government Strategies

• Environmental Risk Assessment – current approaches do not consider AMR

• The new SELECT method

UK strategies

“Look to maintain [...] standards set by the Environmental Quality Standards [...] for harmful substances in the aquatic environment which might otherwise contribute to the spread of AMR; and to amend our lists of priority substances [...] (including antimicrobials) and their corresponding standards in future to take account of technical and scientific developments.”

- UK AMR 5 Year Strategy
UK strategies

“Reduce impact of wastewater”

“[…] strengthen the standardisation of methods that assess chemical safety […] and new approaches to risk assessments.”

- A Green Future – 25 Year Plan to Improve the Environment

Environmental Risk Assessment

• Determine the risk a substance poses to the environment

• Considers:
  1. Concentration in the environment
  2. Concentration predicted to have an undesirable effect

• If effect concentration is less than environmental concentration = risk
EMA guidelines for human medicines

Adapted from EMA (2018) EMEA/CHMP/SWP/4447/00 Rev.1

Predicted Environmental Concentration Surface Water, ≥ 0.01µg/L?

Phase I

Phase II

Determine physico-chemical properties, fate and ecotoxicity

Trigger values groundwater, soil, secondary poisoning

No Further Risk Assessment

Are current tests adequate for AMR?

For antibiotics:

Fish toxicity Pre 2018

Daphnia magna Fresh water invertebrate

Green Algae

Cyanobacterial species

NONE consider selective potential
Toxicity ≠ selective potential

Only two on microbes
Water Framework Directive

‘Watch List’ selection process (2020)

Prioritisation exercise (Criteria 1-3)  
Watch List (WL) review and recommendations (Criterion 4)  
Literature search and other sources (emerging pollutants) ( Criterion 5)

Figure 1. Overall process for the selection of candidate substances for the Watch List (WL). SPM+ suspended particulate matter.


AMR Industry Alliance

Integrated Environmental Assessment and Management

Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations

AMR effect concentrations are modelled estimates (Bengtsson-Palme & Larsson, 2016)

- Compared data lowest ecotoxicological to lowest estimated AMR effect concentrations

- 119 antibiotics, 93 cases where estimated AMR effect concentration was lower than the lowest ecotoxicity effect concentration
Determining safe limits of antibiotics experimentally

The novel SELECT method
(SELection Endpoints in Communities of bacTeria)

Murray et al., 2020, EHP
SELECT method validation

* Using intI1 gene as an AMR marker

Comparing methods

<table>
<thead>
<tr>
<th>Previous methods</th>
<th>SELECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>£1000s</td>
<td>£s</td>
</tr>
<tr>
<td>Weeks</td>
<td>&lt;1 day</td>
</tr>
<tr>
<td>Usually 1, more</td>
<td>All</td>
</tr>
<tr>
<td>Greater expense</td>
<td></td>
</tr>
<tr>
<td>May change results</td>
<td>May not change results</td>
</tr>
<tr>
<td>May be less protective</td>
<td>Generally, may be more protective</td>
</tr>
</tbody>
</table>

* Caveat: Single species methods may yield lower effect concentrations but are less environmentally realistic

Rapid risk assessment with SELECT

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Worst Case Scenario</th>
<th>Reasonable Case Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>HIGH</td>
<td>Low</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>HIGH</td>
<td>Low</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>HIGH</td>
<td>HIGH</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>HIGH</td>
<td>Low</td>
</tr>
</tbody>
</table>

Largest dataset with single experimental method
8 antibiotics
6 classes

Based on antibiotic concentrations found in wastewater, using German Environment Agency Database

The need for AMR endpoints

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Which is more protective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>Ecotoxicological</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Ecotoxicological</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td><strong>SELECT</strong></td>
</tr>
<tr>
<td><strong>Chloramphenicol</strong></td>
<td><strong>SELECT</strong></td>
</tr>
<tr>
<td>Clarithromycin</td>
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<td><strong>SELECT</strong></td>
</tr>
</tbody>
</table>
Future SELECT applications?

“Exploring options to consolidate monitoring and horizon-scanning work to develop an early warning system for identifying emerging chemical issues.”

To support the development of new therapeutics, the UK will: Work with international partners to agree a coordinated global system for incentivising new therapeutics.”

- A Green Future - 25 Year Plan to Improve the Environment
- UK AMR 5 Year Strategy

Using SELECT

How can SELECT be used to set safe thresholds?

- OECD Test Guideline
  - EMA guidelines new medicines

And/ Or

- Environmental Quality Standards for antibiotics
  - Water Framework Directive

And/ Or

- British Standard/ISO Test (whole effluent testing)
  - Water quality assessment within UK
Validation next steps

• Further intra-laboratory testing
  • Same results every time?

• UK inter-laboratory testing
  • Same results every time?
  • Same results as other labs?

• International inter-laboratory testing (required: OECD)
  • Same results every time?
  • Same results as other labs?

• Further development for whole effluent testing (required: ISO/BS)
  • Pilot work to commence next year

Relevance to the Environment Bill

• Environmental AMR Surveillance is an emerging issue, a network including many gov departments is developing a strategy for monitoring AMR in the environment (led by Exeter)

• AMR in the environment is now recognised in the EU Water Framework Directive and Urban Wastewater Directive

• Currently no mention of microorganisms, AMR or antimicrobials in the Environment Bill

• The SELECT Assay will play a key role in understanding the relationship between environmental antimicrobials and development of AMR in natural and farmed environments
CONCLUSION

I would like to conclude this report by reemphasising the complex relationship between humans, animals, and the environment, in terms of the transfer of both micro-organisms and antibiotic resistant genes.

The environment acts as a reservoir for antimicrobial resistance, which is fed continuously by our interaction with it, for example through sewage and other faecal contamination. It’s impact is amplified through gene transfer from one bacterial species to another and then transfer back to humans and animals. This relationship is complex and difficult to quantify – and provides the basis for the One Health approach to tackling AMR.

The presentations from the University of Exeter team demonstrated that contamination of the environment by antibiotics and other antimicrobial agents can also have a profound impact and that this is under-recognised. This is in addition to the contamination of the environment by antibiotic resistant bacteria themselves (antibiotics in the environment exert a selective pressure on the development of further resistance).

The current UK AMR strategy 2019-2024 emphasises the importance of the One Health approach and has it as a key area for action.

However, the UK Government One Health report from 2019, which was an update to the previous report from 2015, focused primarily on the use of antimicrobials in animals. There was no specific recommendation relating to the environment.

The Environment Bill that is currently passing through Parliament provides an ideal opportunity to address the impact of AMR on the environment. However, at the time of writing, it does not mention antimicrobial, or antibiotic, resistance at all.

Let us at least try to change that by taking forward some, or all, of the recommendations that follow at the end of this report.

With kind regards

Dr Nicholas Brown
Consultant Medical Microbiologist, Addenbrooke’s Hospital, Cambridge
Director of Public and Professional Engagement, BSAC
The members of the APPG on Antibiotics call for the following recommendations to be accepted as amendments to the Environment Bill 2019-2021 when it returns to the House of Lords by the end of 2020, or the beginning of 2021:

- **Her Majesty’s Government to commit to a definition/acknowledgement of the relationship between the environment and antimicrobial resistance, as outlined in ‘Tackling antimicrobial resistance 2019–2024: The UK’s five-year national action plan’**

- **HMG to commit to establishing routine testing for antibiotic residues in sewage and agricultural run-off**

- **HMG to commit to establishing safe thresholds for antibiotic residues in sewage and agricultural run-off**

- **HMG to commit to trialling the SELECT method, as the means by which safe thresholds might be established through routine, low-cost, testing**
The All-Party Parliamentary Group on Antibiotics exists to raise the profile of antibiotic resistance, the need to preserve antibiotics through education on their appropriate use (including non-human uses), the lack of new treatments for bacterial infections, and to help accelerate efforts to discover, research, and develop, new treatments.

The British Society for Antimicrobial Chemotherapy (BSAC) provides the Secretariat for the APPG, which is chaired by Julian Sturdy MP.

Visit: www.appg-on-antibiotics.com

Follow: @APPGantibiotics

For further information, contact Michael Corley, BSAC’s Head of Policy and Public Affairs (mcorley@bsac.org.uk)