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ON ANTIBIOTICS

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



BRITISH SOCIETY FOR
**ANTIMICROBIAL
CHEMOTHERAPY**



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.

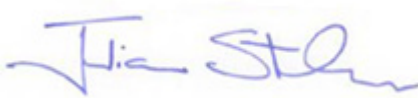
Against that background, we invited a team of experts from the University of Exeter to tell us about the development of a novel method to establish safe release limits for antibiotics that could, in the near-future, also help to identify highly-contaminated areas through environmental surveillance (you 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

AGENDA

‘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

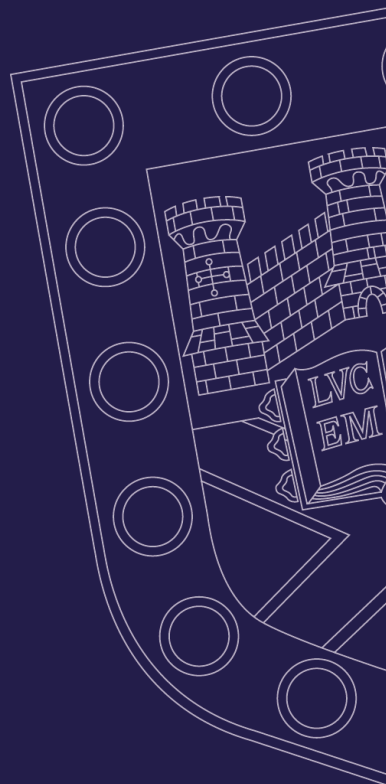


The Environmental Dimension of AMR

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



FRONTIERS 2017

Emerging Issues of Environmental Concern



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

<https://www.unenvironment.org/resources/frontiers-2017-emerging-issues-environmental-concern>

Antimicrobial Resistance: Investigating the Environmental Dimension

Lead Authors

William Gaze, University of Exeter Medical School, Truro, United Kingdom

Michael Depledge, University of Exeter Medical School, Truro, United Kingdom



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

- Role of pharmaceuticals in the environment driving emergence of AMR



WHO, 2015

- Circulation of AMR in the environment
- Environmental transmission of AMR

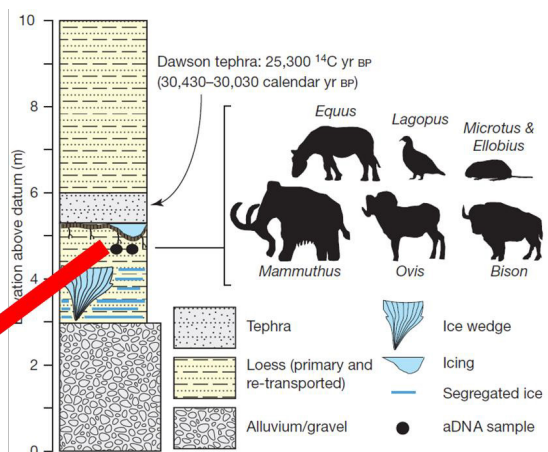
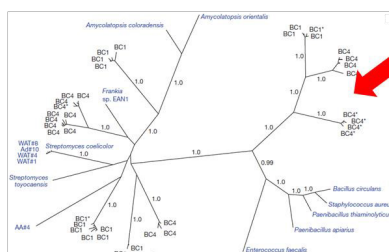


AMR action plan 2017

Antibiotic resistance: an ancient phenomenon

Samples from permafrost before the "Age of Antibiotics"

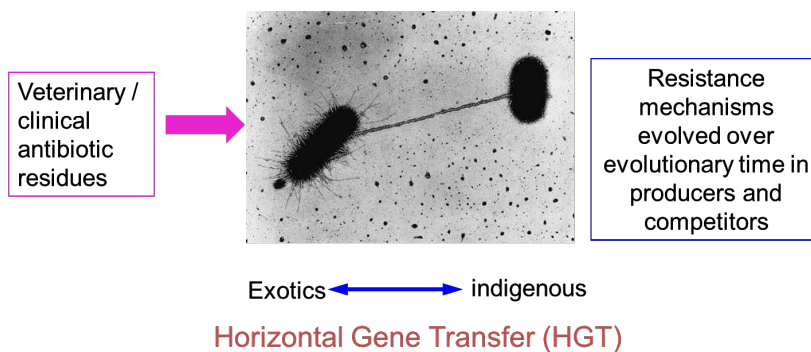
➔ Enormous variety of resistance genes against modern antibiotics



D'Costa et al., 2011, Nature Letters

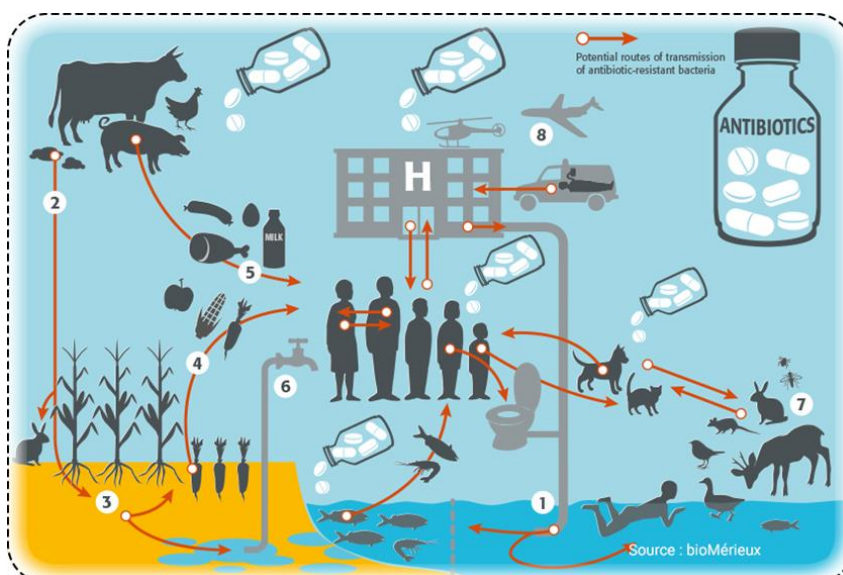
Mobility of antibiotic resistance genes

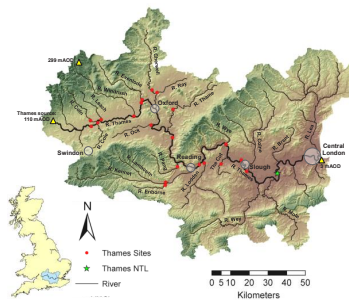
- Rare gene transfer events that lead to new genetic combinations – rare but can be extremely important – origin of genes in previously susceptible human pathogens is recognised as the environmental resistome



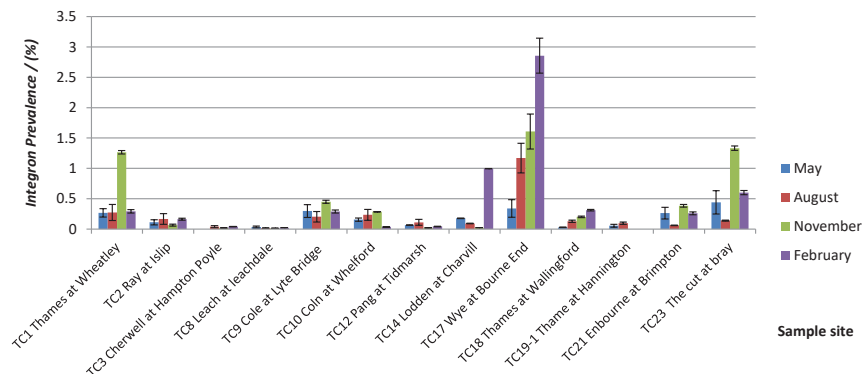
- Acute transmission events - introduction of human and animal associated AMR bacteria to aquatic and soil systems and human exposure to these bacteria/genes in environmental settings.

One Health AMR





11 billion litres of wastewater discharged per day in the UK



OPEN

The ISME Journal (2015) 9, 1467–1476
© 2015 International Society for Microbial Ecology. All rights reserved. 1751-7362/15
www.nature.com/ismej

ORIGINAL ARTICLE

Validated predictive modelling of the environmental resistome

Gregory CA Amos^{1,7}, Emma Gozzard², Charlotte E Carter¹, Andrew Mead^{1,3}, Mike J Bowes², Peter M Hawkey^{4,5}, Lihong Zhang^{1,8}, Andrew C Singer², William H Gaze^{6,9,10} and Elizabeth MH Wellington^{1,9}

Class 1 integron prevalence in sediments

OPEN ACCESS Freely available online

PLOS PATHOGENS

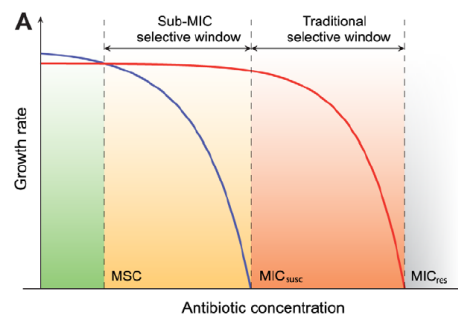
Selection of Resistant Bacteria at Very Low Antibiotic Concentrations

Erik Gullberg^{1*}, Sha Cao^{1*}, Otto G. Berg², Carolina Ilbäck¹, Linus Sandegren¹, Diarmaid Hughes¹, Dan I. Andersson^{1*}

¹ Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden, ² Department of Molecular Evolution, Uppsala University, Uppsala, Sweden

Chromosomal mutation in single species competition assays

- Streptomycin MSC was $\frac{1}{4}$ of MIC
1 mg / L
- Tetracycline MSC was $\frac{1}{100}$ of MIC
15 µg / L
- Ciprofloxacin MSC was between $\frac{1}{10}$ and $\frac{1}{230}$ 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. Leonard^{a,*}, Lihong Zhang^{a,c}, Andrew J. Balfour^a, Ruth Garside^a, Peter M. Hawkey^b, Aimee K. Murray^a, Obioha C. Ukoumunne^c, William H. Gaze^{a,c}

^a European Centre for Environment and Human Health, University of Exeter Medical School, Truro TR1 3HD, UK

^b Institution of Microbiology and Infection, University of Birmingham, B15 2TT, UK

^c National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care South West Peninsula, University of Exeter Medical School, Exeter EX1 2LU, UK

Stanton et al. *Environ Evid* (2020) 9:12
<https://doi.org/10.1186/s13750-020-00197-6>

Environmental Evidence

SYSTEMATIC MAP PROTOCOL

Open Access

What is the research evidence for antibiotic resistance exposure and transmission to humans from the environment? A systematic map protocol



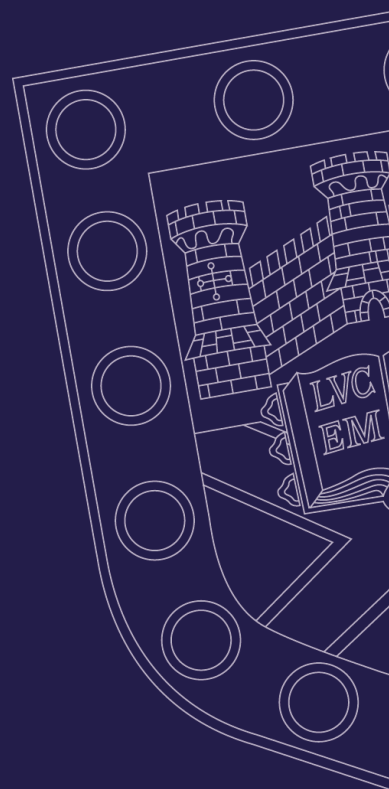
Isobel C. Stanton^{1†}, Alison Bethel^{2†}, Anne F. C. Leonard¹, William H. Gaze¹ and Ruth Garside^{3*}



UNIVERSITY OF
EXETER

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



HM Government

Tackling antimicrobial resistance 2019–2024

The UK's five-year national action plan

Published 24 January 2019

“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



A Green Future: Our 25 Year Plan to
Improve the Environment



“Reduce impact of
wastewater”

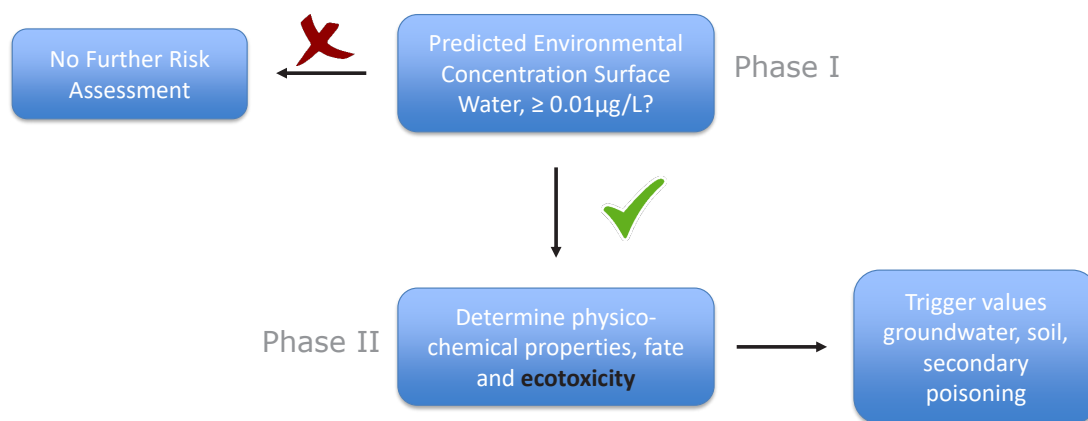
“[...] strengthen the
standardisation of methods
that assess chemical
safety [...] and **new**
approaches to risk
assessments.”

- 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

Are current tests adequate for AMR?

For antibiotics:

Only two on microbes



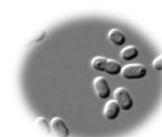
Fish toxicity
Pre 2018



Daphnia magna
Fresh water
invertebrate



Green Algae



Cyanobacterial
species

NONE consider **selective potential**
Toxicity ≠ selective potential

Water Framework Directive



JRC TECHNICAL REPORT

'Watch List' selection process (2020)

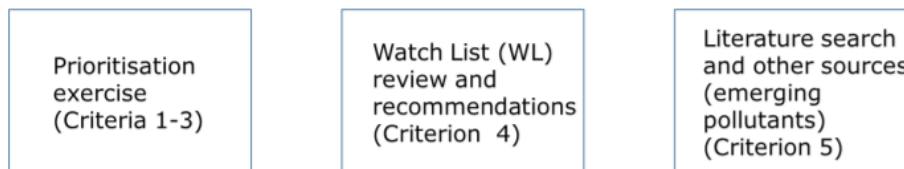


Figure 1. Overall process for the selection of candidate substances for the Watch List (WL). SPM= suspended particulate matter.

Taken from : Livia Gomez Cortes, Dimitar Marinov, Isabella Sanseverino, Anna Navarro Cuenca, Magdalena Niegowska, Elena Porcel Rodriguez and Teresa Lettieri, Selection of substances for the 3rd Watch List under the Water Framework Directive, EUR 30297 EN, Luxembourg: Publications Office of the European Union, 2020, ISBN 978-92-76-19426-2, doi:10.2760/194067, JRC121346.



AMR Industry Alliance



Integrated Environmental Assessment and Management

Brief Communication | Open Access |

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

Joan Tell , Daniel J Caldwell, Andreas Häner, Jutta Hellstern, Birgit Hoeger, Romain Journal, Frank Mastrocco, Jim J Ryan, Jason Snape, Jürg Oliver Straub, Jessica Vestel

First published: 18 March 2019 | <https://doi.org/10.1002/ieam.4141> | Citations: 14

- 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

Selection of Resistant Bacteria at Very Low Antibiotic Concentrations

Erik Gullberg , Sha Cao , Otto G. Berg , ... Diarmaid Hughes, Dan I. Andersson 

Published: July 21, 2011 • <https://doi.org/10.1016/j.cel.2011.06.041>

Mini
tetra
biof

Sara V. L.
Tiranta S.
Larsson P.A.

[Show more](#)

<https://doi.org/10.1016/j.cel.2011.06.041>

Research Article

Novel Insights into Selection for Antibiotic Resistance in Complex Microbial Communities

Aimee K. Murray, Lihong Zhang, Xiaoli Yin, Tong Zhang, Angus Bucking, Jason Snape, William H. Gaze
Joanna B. Goldberg, Editor

DOI: 10.1016/j.cel.2011.06.041 [Check for updates](#)

Research Article

Selection of a Multidrug Resistance Plasmid by Sublethal Levels of Antibiotics and Heavy Metals

Erik Gullberg, Lisa M. Albrecht, Christopher Karpman, ...
Fernando Saenger, Editor

DOI: 10.1016/j.cel.2011.06.041

Sele
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[Show more](#)

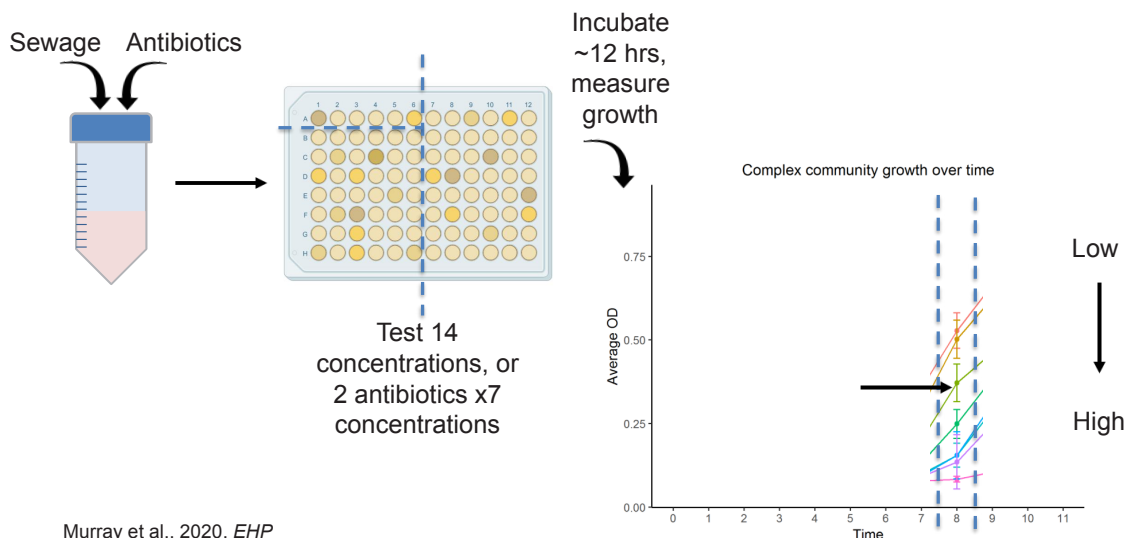
Evolution of antibiotic resistance at low antibiotic concentrations including selection below the minimal selective concentration

Isobel C. Stanton, Aimee K. Murray, Lihong Zhang, Jason Snape & William H. Gaze 

Communications Biology 3, Article number: 467 (2020) | [Cite this article](#)

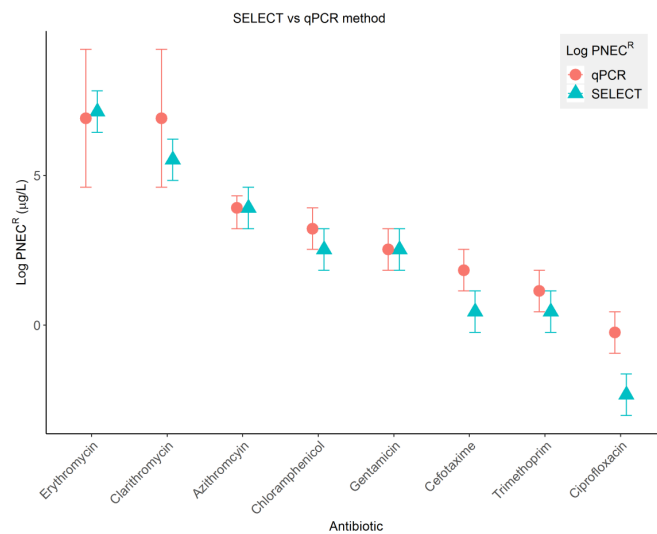
The novel SELECT method

(SELECTION Endpoints in Communities of bacTERia)



Murray et al., 2020. *EHP*

SELECT method validation







* Using *int11* gene as an AMR marker

Murray et al., 2020. *EHP*

Comparing methods

Previous methods

SELECT

£1000s		£s
Weeks		<1 day
Usually 1, more = Greater expense		All
May change results		May not change results
* Caveat: Single species methods may yield lower effect concentrations but are less environmentally realistic		Generally, <i>may be</i> more protective

Murray et al. 2020, *EHP* & Murray et al. Dawning of a new ERA: Environmental Risk assessment of Antibiotics and their potential to select for antimicrobial resistance. Under review, *Environment International*

Rapid risk assessment with SELECT

Antibiotic	Worst Case Scenario	Reasonable Case Scenario
Azithromycin	HIGH	Low
Cefotaxime	HIGH	Low
Ciprofloxacin	HIGH	HIGH
Chloramphenicol	Medium	Low
Clarithromycin	Medium	Low
Erythromycin	Low	Low
Gentamicin	Low	Low
Trimethoprim	HIGH	Low

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

Antibiotic	Which is more protective?
Azithromycin	Ecotoxicological
Cefotaxime	Ecotoxicological
Ciprofloxacin	SELECT
Chloramphenicol	SELECT
Clarithromycin	Ecotoxicological
Erythromycin	Ecotoxicological
Gentamicin	Ecotoxicological
Trimethoprim	SELECT

Future SELECT applications?

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

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



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

- 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



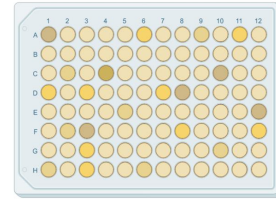
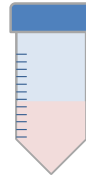
And/ Or

- 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

A handwritten signature in black ink that reads "Nick Brown". The signature is written in a cursive, slightly informal style.

Dr Nicholas Brown

Consultant Medical Microbiologist, Addenbrooke's Hospital, Cambridge

Director of Public and Professional Engagement, BSAC

RECOMMENDATIONS

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



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ON ANTIBIOTICS

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)