Institution: University of Exeter

Unit of Assessment: UoA 7 Earth Systems and Environmental Sciences

Title of case study: Research on drug-resistant bacteria in the environment and their impact on human health has shaped policy and practice at a national and international level

Period when the underpinning research was undertaken: 2014 - present

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor William Gaze	Professor of Microbiology	September 2011 – present
Dr Lihong Zhang	Research Fellow	September 2011 - present
Dr Anne Leonard	NERC Fellow	May 2013 - present
Dr Aimee Murray	NERC Fellow	October 2013 - present

Period when the claimed impact occurred: 01/08/2013 – Present

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Antimicrobial resistance (AMR) is predicted to be the leading cause of death globally by 2050, with a predicted cumulative cost of $100 trillion. The University of Exeter's pioneering research has transformed understanding of the evolution, ecology and transmission of drug-resistant microbes in the environment and directly informed and influenced AMR policy and practice.

Our work includes (i) contributing vital parts of the evidence base that underpins UK policy and practice and the government 5-year AMR strategy, (ii) directly informing EU policy on the regulation of antimicrobial pollutants leading to the inclusion of two antimicrobials on the EU Water Framework Directive Priority Hazardous Substances Watch List and, (iii) providing guidance for approaches needed to ensure sustained effective global action to address AMR, adopted by Member States at the third session of the United Nations Environment Assembly.

2. Underpinning research (indicative maximum 500 words)

Antimicrobial resistance (AMR) is predicted to have profound health and economic consequences for the world. It arises when microbes become resistant to medicinal drugs, thereby reducing the effectiveness of antimicrobial therapies and increasing the risk of untreatable infections.

The University of Exeter Medical School AMR research group, led by Prof Gaze, has carried out pioneering research into the evolution and spread of drug-resistant bacteria in the environment, and their impact on human health. The team has demonstrated that environmental pollution plays a significant role in three key aspects of AMR: the evolution of resistant bacteria; the dissemination of resistant bacteria at a landscape scale; and the transmission of resistant bacteria to humans. The research team focuses on bacteria in complex microbial communities, rather than single strains, which brings real-world insights into the evolution and ecology of AMR.

This research provides a unique perspective that fills critical knowledge gaps identified by the World Health Organization (WHO) and helps to tackle the global problem of AMR.

2.1 The evolution of drug resistance

Dr Murray, Prof Gaze and their team have investigated the evolution of drug resistance in bacteria exposed to low concentrations of antimicrobial agents [**3.1**, **3.2**, **3.3**]. These are representative of concentrations typically found in the environment, which are far lower than those found in the clinic. The researchers discovered that even low levels of antimicrobials can drive the natural selection of clinically-important resistance genes in complex microbial communities.

The team has also generated the largest body of data to demonstrate the effects of multiple classes of antimicrobial agents at environmental concentrations, which has enabled them to perform environmental risk assessments on these agents. In addition, the Exeter team showed for the first time that the strength of selection for resistance to antimicrobials may be just as high at these relatively low environmental concentrations, compared to those found in the clinic [**3.1**]. Further novel research revealed that bacteria living in complex microbial communities were less likely to evolve resistance to antimicrobials than those in monocultures, the latter being the traditional method of studying bacteria [**3.4**].

2.2 The distribution of resistant bacteria in the environment

Gaze and colleagues were the first to show that effluent from wastewater treatment plants in the UK is associated with increased prevalence of AMR in the aquatic environment, and that this is a reproducible and predictable phenomenon across entire river catchments [**3.5**]. This research demonstrated that anthropogenic pollution — whether point source or diffuse — is associated with significantly increased prevalence of AMR in the bacterial communities of aquatic sediments. These communities have an increased probability of harbouring clinically important resistance genes and pose an acute transmission risk to humans [**3.5**].

2.3 The environmental transmission of resistant bacteria to humans

Dr Leonard, Prof Gaze and their Exeter colleagues have identified human exposure to AMR bacteria in coastal bathing waters as a significant risk. The 'Beach Bum Survey', a study investigating the association between bathing water exposure and faecal carriage of AMR bacteria, suggested that millions of water sports sessions per year in the UK result in people ingesting *E. coli* bacteria that carry clinically-important resistance genes, which are implicated in the failure to treat human infections with antimicrobials. This was the first study of its kind to link environmental surveillance, human exposure risk assessment and probability of transmission. It demonstrated that frequent water users tended to have increased gut colonisation with resistant bacteria [**3.6**].

3. References to the research (indicative maximum of six references)

3.1. Aimee K. Murray, Lihong Zhang, Xiaole Yin, Tong Zhang, **Angus Buckling**, Jason Snape, **William H. Gaze.** Novel insights into selection for antibiotic resistance in complex microbial communities. MBio. 2018. Jul 24;9 (4). DOI: 10.1128/mBio.00969-18

3.2. Stanton, I.C., Murray, A.K., Zhang, L., Jason Snape, **Gaze, W.H.** Evolution of antibiotic resistance at low antibiotic concentrations including selection below the minimal selective concentration. Commun Biol 3, 467 (2020). https://doi.org/10.1038/s42003-020-01176-w

3.3. Aimee K. Murray, **Isobel C. Stanton**, Jessica Wright, **Lihong Zhang**, Jason Snape, and **William H. Gaze**. The 'SELection End points in Communities of bacTeria' (SELECT) Method: A Novel Experimental Assay to Facilitate Risk Assessment of Selection for Antimicrobial Resistance in the Environment. 2020. Environmental Health Perspectives Vol. 128, No. 10. https://doi.org/10.1289/EHP6635

3.4. U Klümper, M Recker, L Zhang, X Yin, T Zhang, **A Buckling, WH Gaze**. Selection for antimicrobial resistance is reduced when embedded in a natural microbial community. 2019. The ISME journal, 1-11. DOI: 10.1038/s41396-019-0483-z

3.5. Gregory CA Amos, Emma Gozzard, Charlotte E Carter, Andrew Mead, Mike J Bowes, Peter M Hawkey**, Lihong Zhang**, Andrew C Singer, **William H Gaze**† & Elizabeth M H Wellington†. Validated predictive modelling of the environmental resistome. ISME J. 2015. Jun;9(6):1467-76. († Joint final author). DOI: 10.1038/ismej.2014.237

3.6. Anne F. C. Leonard, Lihong Zhang, Andrew J. Balfour, Ruth Garside, Peter M. Hawkey, **Aimee K. Murray, Obioha C. Ukoumunne, William H. Gaze**. 2018. Exposure to and colonisation by antibiotic-resistant E. coli in UK coastal water users: environmental surveillance, exposure assessment, and epidemiological study (Beach Bum Survey). Environment International. May; 114:326-333. DOI: 10.1016/j.envint.2017.11.003

4. Details of the impact (indicative maximum 750 words)

Exeter's research and knowledge exchange activity has transformed the strategies designed to combat AMR, and influenced national and international policy and practice, in organisations including the United Nations, WHO, UK Research and Innovation and the UK government.

4.1 Impact on UK government and industry strategy, policy and practice

Prof Gaze and colleagues have influenced policy and informed strategic thinking about the role of the environment in the development and spread of AMR. This subject was largely ignored in previous strategies — in the government's 2013-2018 AMR Strategy, for example, the word 'environment' was mentioned only 5 times in the 43 page document. In contrast, the current 2019-2024 UK government AMR strategy embeds the environmental dimensions of AMR at the heart of its policies [**5.1**]. According to the Senior Policy Advisor on AMR and Pharmaceuticals at the UK Department for Environment, Food and Rural Affairs (Defra), "*Prof Gaze's research was a primary source in helping us understand the important problem of the environmental dimension of AMR and his activity and research has directly informed government policy development in this area, notably contributing vital parts of the evidence base which underpins the UK government 5-year AMR strategy*" [**5.2**].

The Beach Bum Survey [**3.6**] helped to drive this shift in emphasis. It was the only study on AMR and water cited in the 2019-2024 strategy, out of >1,000 papers published on this theme in the previous 5 years [**5.2**]. Being the only study to integrate environmental AMR surveillance, exposure risk assessment, and evidence of environmental transmission to humans it has gained widespread recognition nationally and internationally. It has been cited by Professor Dame Sally Davies [**5.3**], who was the UK Chief Medical Officer (CMO) from 2010 to 2019 and is currently the UK's Special Envoy on AMR.

Advice provided by Prof Gaze has underpinned national policy at the highest level. In addition to research conducted by Gaze and collaborators, Prof Gaze contributed a summary of scientific evidence of AMR in the environment to inform the CMO's priorities on the environmental dimensions of AMR [**5.4**]. Professor Dame Sally Davies also acknowledged this work as being greatly informative to her [**5.3**]**.** Gaze has also advised the UK's Review on Antimicrobial Resistance, which was commissioned in July 2014 by the UK Prime Minister [**5.5**]. Prof Gaze was one of four academics invited to speak at the Houses of Parliament as part of the UKRI AMR research strategy refresh in 2019 [**5.6**]. He is currently one of four academics, and the only environmental AMR researcher, on the UKRI cross-council AMR steering committee, which is informing future research agendas [**5.6**].

Prof Gaze's contributions to guide policy, regulation and practice in the UK have been facilitated by a Natural Environment Research Council (NERC) Knowledge Exchange Fellowship and a Joint Programming Initiative on AMR (JPIAMR) network grant. By working in partnership with Defra, the Environment Agency (EA), and the water and pharmaceutical industries, these projects facilitated the cross-sectoral knowledge exchange necessary for policy development. The EA Theme Expert said: "*This network leads the way on developing ideas for environmental AMR surveillance and has brought together key individuals from government organisations and Defra agencies including PHE, VMD, APHA and the EA to discuss this issue for the first time*". "*Interactions with WG and his group have played a key part in development of policy and practice in this area* [**5.7**]

Leonard and Gaze are now working with the Environment Agency to trial environmental AMR surveillance methodologies pioneered in the Beach Bum Survey [**3.6**], demonstrating a direct impact on agency surveillance practice [**5.7**] and illustrating the implementation of a key policy objective described in the UK AMR Strategy.

4.2 Impact on EU policy on AMR

The Exeter team has worked with the European Environment Agency (EEA) and European Commission Joint Research Centre (JRC) to inform policy and regulation on AMR and the environment. The team's research [**3.2**, **3.3**] resulted in two antimicrobials (trimethoprim and sulfamethoxazole) being included on the EU Water Framework Directive's Priority Hazardous Substances Watch List (EU) 2020/1161 [**5.8**]. This lists potential aquatic pollutants that should be carefully monitored by EU member states to determine the risk they pose to the aquatic environment, and whether they should be subject to EU Environmental Quality Standards (EQS).

The Water Industries and Pollution Expert at the EEA, who is involved in Water Framework Directive policy formation, said that the research on sulfamethoxazole and trimethoprim "*informed the discussion for the new watch list, as can be seen in the meeting paper acknowledgements and JRC's technical report acknowledgements*" [**5.8**]. This is evidence of Exeter's direct impact on the formulation of EU policy about the regulation of antimicrobial pollutants, based on their ability to drive the evolution of AMR. This will result in changes in environmental surveillance for potentially hazardous chemicals.

4.3 Contributions to global AMR policy via the United Nations

Prof Gaze is either the sole adviser, or one of a handful of advisers globally, on this subject to UNEP, WHO and FAO. He is now a member of the UNEP Expert Group on AMR and Environment; sits on the WHO/FAO pesticides and fertilizers working group, contributing on AMR and environment issues; and is part of the European Food Safety Authority's working group on AMR in livestock production environments.

Prof Gaze and colleagues' research has also informed international AMR policy directly, with several citations in international policy documents such as the WHO / UN Food and Agriculture Organization (FAO) report on AMR in the food chain in 2019 [**5.9**]. Research carried-out by the group has also underpinned WHO recommendations: the Beach Bum Survey [**3.6**], for example, helped guide the WHO recommendations on scientific, analytical and epidemiological developments relevant to the parameters for bathing water quality in the European Bathing Water Directive (2006/7/EC) [**5.10**].

Prof Gaze was the lead co-author of the United Nations Environment Programme (UNEP) Frontiers Report on AMR and the Environment, published in 2017 [**5.11a**]. Gaze presented the UNEP Frontiers Report at the 3rd meeting of the UN Environment Assembly in Nairobi in 2017, at which countries around the world, including the UK, made a commitment to combat antimicrobial resistance from an environmental perspective for the first time [**5.11b**]. This marked the first time that the importance of the environmental dimension of AMR was highlighted at a United Nations Environment Assembly.

The UNEP report [**5.11a]** was one of only two natural environment AMR citations in the UN Interagency Coordination Group's (IACG) final report to the UN secretary general, which is the most significant AMR report produced to date [**5.12**]. Its key conclusion was: "Antimicrobial resistance is a global crisis that threatens a century of progress in health and achievement of the Sustainable Development Goals." The IACG was formed following the 71st Session of the United Nations General Assembly, at which Member States adopted the Political Declaration of the High-level Meeting on Antimicrobial Resistance. This declaration, to which Gaze made a significant contribution highlighting the importance of the natural environment, recognises the magnitude of this global problem and provides a consensus about the actions needed to prevent a post-antimicrobial era.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1. HM Government (2019) Tackling antimicrobial resistance 2019–2024: The UK's five-year national action plan. See citation, p45. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf

5.2. Letter from Senior Policy Advisor at Defra on AMR and Pharmaceuticals citing [**3.6**] and confirming influence on UK AMR strategy document.

5.3. Health Care Without Harm (Europe) online press briefing, 2019. Professor Dame Sally Davies, UK Special Envoy on Antimicrobial Resistance, speaking about Prof Gaze's work on AMR and environment (excerpt from 29 min 35 sec into recording). Available at https://noharm-europe.org/issues/europe/recording-antimicrobial-resistance-major-global-health-threat

5.4. Annual report of the Chief Medical Officer 2017, Summary by Gaze at Chapter 2 page 12 Box 6. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/690846/CMO_Annual_Report_2017_Health_Impacts_of_All_Pollution_what_do_we_know.pdf

5.5. Jim O'Neill (chair) (2016) Tackling drug-resistant infections globally: Final report and recommendations. Dr William Gaze is acknowledged within this report. Available at https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

5.6. Confirmation from UKRI that Prof Gaze is one of four academics, and the only researcher on environment, to speak at the UKRI AMR research strategy refresh at the Houses of Parliament and subsequently to sit on the cross-council AMR call steering committee.

5.7. Letter from Environment Agency Theme Expert, Air, Land and Water Research detailing contribution to policy and practice.

5.8. Letter from Water Industries and Pollution expert at the European Environment Agency on use of data to inform Joint Research Centre Water Framework Directive policy.

5.9. Joint FAO/WHO Expert Meeting in collaboration with OIE on Foodborne Antimicrobial Resistance: Role of the Environment, Crops and Biocides (2019) cites [**3.1**] page 18. Available at http://www.fao.org/3/ca6724en/ca6724en.pdf

5.10. WHO recommendations on scientific, analytical and epidemiological developments relevant to the parameters for bathing water quality in the European Bathing Water Directive (2006/7/EC), final report June 2018, Section E1, page 71, available at: https://circabc.europa.eu/d/d/workspace/SpacesStore/9e89152c-7cfe-4391-9bcf-c173519e8181/WHO%20Recommendations%20on%20EC%20BWD.pdf

5.11a. William H. Gaze (lead co-author). 'Antimicrobial Resistance: Investigating the Environmental Dimension', United Nations Environment Programme (2017) Frontiers 2017: Emerging Issues of Environmental Concern. Available at https://www.unenvironment.org/resources/frontiers-2017-emerging-issues-environmental-concern; **5.11 b**. HM Government (2017) Global commitment at United Nations Assembly to reduce pollution. Available at https://www.gov.uk/government/news/global-commitment-at-united-nations-assembly-to-reduce-pollution

5.12. The UN IACG final report was handed to the Secretary general in 2019 https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/ Prof Gaze's UNEP report [**5.11a**] was one of only two environmental citations, see page 5.