Institution: Newcastle University		
Unit of Assessment: 12		
Title of case study: Reducing Waterborne Superbug Dissemination Around the World		
Period when the underpinning research was undertaken: 2001 - 2020		
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:**
Prof David Graham	Professor of Ecosystems Engineering	2006 - present
Prof David Werner	Professor Environmental Systems Modelling	2004 - present
Dr Shaikh (Zia) Ahammad	Research Associate	2010 - 2013
Dr Clare McCann	PhD student & Research Associate	2010 - 2019
Dr Marcos Quintela-Baluja	PhD student & Research Associate	2013 - present
Dr Joshua Bunce	PhD student	2015 - 2019
Dr Myra Giesen	Research Associate	2017 - present
Period when the claimed impact occurred: 2013-2020		
Is this case study continued from a case study submitted in 2014? N		

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

Antibiotics have revolutionised the treatment of infectious disease. However, gains have been compromised by increasing antimicrobial resistance (AMR), including increased multi-resistant “superbug” pathogens in global healthcare systems. In 2014, we changed perceptions of the drivers of AMR by showing environmental pathways dominate AMR spread in the emerging world. We found superbug levels drastically increased in the Ganges where urban pilgrims visited pristine sites on the river, work that supports recommendations from the World Health Organisation (WHO). Our tiered sociotechnical cost-benefit approach underpins three of the six WHO Action Areas to reduce AMR through improved water, sanitation, and hygiene (WASH) guidance.

2. Underpinning research (indicative maximum 500 words)

Original work demonstrating environmental pathways as key to AMR spread was performed by Graham and Werner studying the influence of agricultural, human, pharmaceutical and industrial waste releases on AMR spread in Latin America [P1]. These studies showed imprudent antibiotic use and-or waste management in agriculture and industry increased environmental AMR, but the study locations were often so polluted it was impossible to assess how human waste releases versus clinical factors most impact AMR spread.

Core work in this case study started in 2012 when Graham and Ahammad commenced sampling the Ganges River near human pilgrimage sites in the Himalayas. This site was a game-changer for AMR research because no local agriculture or industry exists, upstream waters were nearly pristine, and the main influence on river water quality was seasonal pilgrim visits because limited waste management exists. Sampling showed that “superbug” genes in the river increased by 20 to 60 times per resident during the pilgrimage season [P2]. Given most pilgrims come from polluted cities [G1], the work showed that superbugs and other AMR can significantly spread across the environment solely due to untreated human faecal releases.

Prior to this work, confusion existed over the main cause of AMR spread, but we showed AMR from the clinic and environment were interlinked [P3], and one needed to simultaneously reduce antibiotic reliance in human and veterinary medicine and pollution to reduce global AMR. However, we wanted more proof and extended the breadth of our global studies, including soils in Denmark [P3], landscapes across the UK [G2], solid waste landfills in China [G3], estuaries in Malaysia [G4], and elsewhere in the world [G5].

This work showed environmental AMR was critical to global AMR spread, but the main driver of AMR spread differed from place to place, although there was a common thread. Where wastes are not treated adequately, AMR spreads locally, exposing humans and wildlife to AMR genes and bacteria. However, more concerning, Graham and McCann found AMR “superbug” genes in highly remote locations, including the High Arctic [P4]. Specifically, we found the NDM-1 gene,

which originated in India and Pakistan and confers multidrug resistance in many pathogens, at levels 100 times background in bird nesting areas in Svalbard, research which received global acclaim.

These studies culminated in strategic work by Graham, Bunce and Giesen that showed AMR mitigation solutions must be incremental, and each local place will have its own "optimal" solutions based on existing infrastructure and cost-benefits [P5]. This work underpins three of the six WASH and AMR mitigation Action Areas recommended by the World Health Organization (WHO), Food and Agriculture Organization (FAO), and the World Organisation for Animal Health (OIE) in 2020.

AMR fieldwork inspired Werner to develop a suitcase laboratory to bring molecular microbiology tools within reach of stakeholders in low-income countries [P6]. Work on AMR also enabled our rapid response to the demand in the UK for SARS-CoV-2 monitoring in wastewater during the current pandemic as an early warning system for predicting COVID-19 cases.

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

[P1]. Graham DW, Olivares-Rieumont S, Knapp CW, Lima L, Werner D, Bowen E. 2011. Antibiotic resistance gene abundances associated with waste discharges to the Almendares River near Havana, Cuba. *Environ Sci Technol*, 45(2):418-24. DOI: 10.1021/es102473z

[P2]. Ahammad ZS; Sreekrishnan TR; Hands CL; Knapp CW; Graham DW. 2014. Increased waterborne blaNDM-1 resistance gene abundances associated with seasonal human pilgrimages to the Upper Ganges River. *Environ Sci Technol*, 48(5):3014-20. DOI: 10.1021/es405348h

[P3]. Graham, DW, Knapp CW, Christensen BT, McCluskey S, Dolfing J. 2016. Appearance of β-lactam resistance genes in agricultural soils and clinical isolates over the 20th Century. *Sci Rep*, 6:21550. DOI: 10.1038/srep21550

[P4]. McCann CM, Christgen B, Roberts, JA, Su JQ, Arnold KE … Graham DW. 2019. Understanding drivers of antibiotic resistance genes in High Arctic soil ecosystems. *Environ Int*, 125:497-504. DOI: 10.1016/j.envint.2019.01.034

[P5]. Graham DW, Giesen MJ, Bunce JT. 2019. Strategic approach for prioritising local and regional sanitation interventions for reducing global antibiotic resistance. *Water*, 11(1):27. DOI: 10.3390/w11010027

[P6]. Acharya K, Blackburn A, Mohammed J, Haile AT, Hiruy AM, Werner D. 2020. Metagenomic water quality monitoring with a portable laboratory. *Water Res*,184:116112. DOI: 10.1016/j.watres.2020.116112

<u>Grants</u>

[G1]. Expanding the impact of environmental antibiotic resistance research in India. EPSRC IAA. £13.7K. 01.05.2014 to 25.09.2015.

[G2]. Quantifying spatial AMR patterns across urban and rural landscapes. NERC (AMR in the Real World). £199K. 2016-2018.

[G3]. Expanding the reach of multi-disciplinary environment and health research in SE Asia. EPSRC IAA. £49.6K. 2017 to 2018.

[G4]. Innovate UK/Newton Fund. Improving community health in Malaysia using sustainable decentralised wastewater treatment. £79.800. 2018 to 2020.

[G5]. DARWIN: Dynamics of antimicrobial resistance in the urban water cycle in Europe. JPI-AMR (MRC). £1.8M. 01.04.2017 to 30.06.2020.

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

Changing global policy, enabling impact

Antimicrobial resistance (AMR) is a threat to public health and has become a policy priority across the globe. Our work has shown the breadth of AMR spread through the environment and

its negative impact to global human and veterinary health. Importantly, our research highlights environmental AMR is everywhere, but the primary driver of AMR spread differs from place to place. These findings are critical to ensure effective local mitigation strategies to combat a global threat. The research detailed above demonstrated that water and environmental pollution were major causes of AMR spread in the developing world. By proving this, Newcastle's research is allowing low-income countries to prioritise small-scale, low-cost, yet high impact solutions that benefit local populations and facilitate AMR reductions globally.

Newcastle researchers have led and continue to lead efforts to push these findings into policy globally, changing perceptions at the UN, WHO and major global organisations, persuading them to expand recommended interventions away from just the clinic, but also away from large-scale expensive infrastructure investments and towards low-cost, easily deployed, yet higher impact solutions. Incorporation of the research is included in the International Environmental AMR Forum white paper "Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges", hosted by the U.S. Centers for Disease Control and Prevention (CDC), the UK Science & Innovation Network, and the Wellcome Trust in April 2018 [E1]. The report acts as a guide for stakeholders, to improve national and international understanding on how to best evaluate and address antimicrobial-resistant microbes in the environment. Specifically, Graham contributed two major chapters on the need for tiered waste management strategies for reducing AMR and a primer for AMR in hospital wastes [E2].

Graham co-authored the 2020 WHO/FAO/OIE Technical brief on water, sanitation, hygiene (WASH) and wastewater management to prevent infections and reduce the spread of antimicrobial resistance [E3]. This brief emphatically states that WASH and wastewater considerations must be included in multi-sectoral AMR national action plans. It includes a summary of evidence and the co-benefits rationale for action in each sector. In parallel to identifying the different global AMR pathways, NCL has produced the toolkits and cost-benefit analyses that are utilised by developing countries to address AMR in a country specific context. These methodologies are embedded within the WHO and UN.

"Graham personally finished drafting the brief for the WHO, contributing 60% of its core content. Importantly three of the six recommended Action Areas incorporated Newcastle University research (i.e., community waste management, addressing hospital wastes and future priorities for AMR research). The Newcastle incremental intervention approach to AMR mitigation was promoted, which nicely paralleled costing work by the World Bank on the value of WASH implementation to prevent infectious disease." [E2]

The global shift in AMR policy options is already having a tangible real-world affect. Specific projects include the monitoring of water quality and environmental AMR in the Akaki River catchment in Addis Ababa, Ethiopia, home to 5 million people. Here NCL research has underpinned local staff training in the Addis Ababa Water and Sewerage Authority (AAWSA), and the collaboration resulted in an affordable suitcase laboratory for molecular water microbiology in low-income countries. A co-authored publication attests to the co-creation of this research impact [P6 above]. This has then led to World Bank investment into AAWSA facilities for further analysis of wastewater in the region [E4]. Equally local staff training in Thailand enabled surveyance in Bangkok's periurban aquaculture region and showed how inadequately managed urban wastewater is the main local driver for environmental AMR.

The WHO, evidenced by Prof Peter Collignon (WHO Advisory Group on Food Safety), highlights the importance of both policy and resulting action driven by NCL research:

"My work in medicine and at the WHO has convinced me that a major proportion of the antibiotic resistance in emerging and developing countries is due to exposure to poor quality water. Work at Newcastle University has not only been fundamental in confirming this realization, but their research is now providing the tools and mitigation strategies that will help us achieve global solutions"

He further recognised the importance of NCL work:

"his [Graham's] research on quantifying environmental links between water- and food-borne resistance sources and potential health consequences has been indispensable, especially if we want to reduce superbug spread across the global community." [E5].

Highlighting the global threat and driver action

NCL's research on waterborne AMR in India was "headline news" around the world, receiving international coverage on BBC World News and across media [E6]. In 2014, Graham was invited to meet with Dame Sally Davies (Chief Medical Officer; 07/07/14) to report on Indian findings, as they impact both UK policy and role in curbing international AMR. Based on the work in India, Graham was acted as an Advisor to the US Presidential Council on Antibiotic Resistant Bacteria, including presenting to the Council in Washington DC in 2016 on how the drivers of environmental AMR spread differ in developed versus developing countries.

Beyond wider policy influence, a "popular science" book was published in October 2017 on the Ganges entitled "River of Life, River of Death: The Ganges and India's Future", written by Victor Mallet. This book includes a chapter on NCL's work on the river, including superbug spread due to limited waste management. At the time, Victor Mallet was Asia News Editor for The Financial Times. Graham worked closely with Mallet on revisions in the chapter and is a highlighted contributor [E7].

Graham has actively engaged with a variety of stakeholders ensuring widespread global communication of the NCL research and methodologies. Graham was a key member of the "Integrated Discussion Group on the Use of Antibiotics in Animal Food Production" convened by the New York Academy of Sciences. The Group published a series of reviews on the problem of AMR, including complexity of problem – a review on which Graham was lead author [E8]. From this, Graham was invited to be a Keynote Speaker at the 55th National Meeting on Poultry Health, Processing and Live Production in 2019 in the USA. Dr Donald Ritter then acting Chairman of the Poultry Health & Welfare for the US-based Demarva Chicken Association notes:

"he [Graham] provided understandable invaluable presentation that placed antibiotic resistance within my industry into a global context, which strongly influenced members of my organisation. Research at Newcastle University is clearly world-leading on an academic level, but it also has practical value at the "coal face" in different discipline among practitioners like myself." [E8]

Research recognition, COVID-19 wastewater-based epidemiology (WBE)

Our research on understanding and mitigating the global spread of AMR was short-listed in the STEM (Science, Technology, Engineering and Mathematics) Research of the Year category in the UK THE (Times Higher Education) Awards 2020 [E9]. This and other recognition led us to be called upon by the UK Strategic Advisory Group for Emergencies (SAGE) to join WBE efforts on SARS-CoV-2 (the COVID-19 virus) detection, spread, and epidemiology, performing core WBE research and government advisory work in the UK and around the world [E10]. Our work on WBE related to the Covid-19 pandemic has been highly influential, including work with Northumbrian Water, the Joint Biosecurity Centre (JBC), and Defra. Quintela-Baluja and Graham are now UK "methods experts" and both are on multiple government advisory teams.

Through this period, Graham co-authored "Monitoring the presence and infection risk of SARS-CoV-2 in the environment: approaches, limitations and interpretation" for SAGE, as a member of the Expert Team on the Transmission of Covid-19 in the Wider Environment Group (TWEG). Graham had been invited to join TWEG to provide guidance on the risk of SAR-CoV-2 spread via water and wastewater systems, Graham and Quintela-Baluja continue to formally advise the JBC on SARS-CoV-2 detection methods in wastewater samples and WBE modelling. Finally, Graham and Quintela-Baluja are the Scientific Advisors for NE England on the massive Core

Cities project, which is quantifying relationships between sewage SARS-CoV-2 levels and Covid-19 cases major UK cities.

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

[E1] CDC International Environmental AMR Forum white paper: Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges. 2018. https://wellcome.org/sites/default/files/antimicrobial-resistance-environment-report.pdf. specifically see pps 76 ref 12,13,16,84,146

[E2] Written Affidavit: Astrid Wester, former Environmental AMR Point for the WHO detailing importance of NCL research in WHO report.

[E3] WHO/FAO/OIE Technical Brief: Technical brief on water, sanitation, hygiene and wastewater management to prevent infections and reduce the spread of antimicrobial resistance. ISBN: 978-92-4-000641-6. https://apps.who.int/iris/bitstream/handle/10665/332243/9789240006416-eng.pdf.

[E4] Written Affidavit: Jemila Mohammed; Head, Wastewater Quality Control, Addis Ababa, Ethiopia; also see [P6] for co-authored publication.

[E5] Written Affidavit: Prof Peter Collignon, MD, is a Member of the Advisory Group to the WHO on Integrated Surveillance of Antimicrobial Resistance for Food Safety, 2014-2019, (http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/agisar_members/en/). His full comments will be provided in a REF Case Impact Study.

[E6] Combined Media Evidence (inc. BBC global, The Financial Times, The Times of India)

[E7] Reference to NCL Research: River of Life, River of Death: The Ganges and India's Future, 2017 [ISBN 13: 978-0198786177], https://victormallet.org see pps 97 and 102-8.

[E8] Written Affidavit: Dr G Donald Ritter, Chairman of the Poultry Health and Wellbeing Delmarva Chicken Association

[E9] THE Awards 2020 shortlist for Research Project of the Year: STEM: Engineering a halt to the 'superbug', https://the-awards.co.uk/2020/en/page/shortlist

[E10] SARS-CoV-2 government advisory work.
Evidence of Wider Environmental Transmission of SARS-CoV-2: Assessing risk of transmission through outdoor air, water, outdoor surfaces, and food and Monitoring the presence and infection risk of SARS-CoV-2 in the environment: approaches, limitations and interpretation TWEG reporting to SAGE.
Monitoring wastewater for COVID-19 Prepared for The Parliamentary Office of Science and Technology (POST).