Institution: Aston University

Unit of Assessment: 3 Allied Professions to Health, Dentistry, Nursing and Pharmacy

Title of case study: 2. Antimicrobial resistance (AMR) and the use of antibiotics in healthcare and public settings

Period when the underpinning research was undertaken: 2000 to date

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:
Dr Tony Worthington	Associate Professor in Clinical Microbiology	2004 to date
Prof Anthony C Hilton	Professor of Applied Microbiology	2000 to date
Professor Peter Lambert	Professor of Microbial Chemistry	1980 to date
Dr Eirini Theodosiou	Lecturer in Biochemical Engineering	2015 to date
Dr Amreen Bashir	Lecturer in Biomedical Sciences	2015 to date
Rabia Ahmed	Teaching Fellow in Pharmacy Practice	2013 to date
Dr Jonathan Cox	Lecturer in Microbiology	2017 to date
Professor Andrew Pitt	Professor in Pharmaceutical Chemistry and Chemical Biology	2012 to 2020

Period when the claimed impact occurred: 1 August 2013 to date

Is this case study continued from a case study submitted in 2014? No

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

Antimicrobial resistance (AMR) is predicted to cause 10 million deaths globally, by 2050. Impacts resulting from research into AMR at Aston University are claimed as follows:

1. **Public policy, law and services**: Removal of Triclosan from antiseptic products across the EU and USA.
2. **Practitioners and delivery of professional services**: Development of evidence-based educational tools to inform antibiotic prescribing.
3. **Commerce and the economy**: Development of a patented, licensable germinant for elimination of *Clostridium difficile* spores in healthcare.
4. **Understanding, learning and participation; culture and society**: Raised knowledge and developed sustained understanding of AMR within society, nationally and internationally.

2. Underpinning research

Background: The World Health Organisation identifies AMR as a significant global risk. To date, interventions to improve antibiotic prescribing have had limited impact. Improved public and healthcare-based awareness and engagement in issues relating to AMR are key components of global plans for control.

Underpinning Research: Aston's AMR team has studied both the molecular mechanisms of AMR and approaches to communicate AMR research to a wider audience, since 2000. Major contributions include: 1) discovering links between use of domestic antimicrobial products and emergence of multi-drug resistant microbes; 2) inventing a novel disinfectant to eliminate antimicrobial resistant spores of leading UK healthcare pathogen *Clostridium difficile*; 3) development of evidence-based educational tools to inform antibiotic prescribing behaviour and 4) evaluation of multiple local, national and international public engagement activities designed to raise public awareness/understanding of AMR.

Research Insights/Findings: In early 2000, concern was raised about the escalating use of the antimicrobial triclosan in numerous domestic products regarding the emergence of multi-drug-resistant bacteria. Hilton and co-workers discovered that bacteria subjected to multiple exposures of triclosan demonstrated increased cross-resistance to multiple antibiotics. They went on to prove that the mechanism of antibiotic resistance occurred via efflux pumps (structures in the bacterial membrane that pump multiple molecules out of the cells) (**S3.1**).

AMR also results from inappropriate prescribing. Years of antibiotic awareness campaigns and subsequent, hospital-based antimicrobial stewardship tools had achieved only limited impact on reducing hospital-based antibiotic use. To examine AMR from a prescribers' viewpoint, Bashir, funded by the EPSRC, led the ABMAP (Antibiotic Mapping of Prescribing) study that identified multiple barriers to effective antibiotic prescribing and demonstrated that prescribers are unlikely to change practice based on a single educational tool. Rather, clinicians expressed strong preference for instructions on prescribing antibiotics (**S3.2**).

Meanwhile, healthcare-associated gut infections arising from antimicrobial resistant *C. difficile* were reaching epidemic proportions. Funded by Innovate UK (2008-2011), Worthington and colleagues devised the strategy "germinate to exterminate" (**S3.3**) and invented a product to germinate the spores of *C.difficile* on hard surfaces. The resulting bacteria can be killed readily. Patents have been granted in USA, Europe, China and Japan (**S3.4**).

Public understanding and compliance is also vital in order to combat AMR. The AMR team therefore concurrently investigated how best to disseminate their AMR research beyond the typical academic/medical audience. Funded by the Wellcome Trust & Society for Applied Microbiology (SfAM), they initially developed and presented the *World of Microbiology* (*WoM*) package (2008-2013), to raise awareness/understanding of AMR locally (West Midlands), nationally (London) and internationally (Kenya, Tanzania). Encouraged by positive qualitative feedback and subsequently funded by the EPSRC (2015-2018), they developed '*WoM; Antimicrobial resistance'* a multidisciplinary, interactive roadshow (including interactive sessions on microscopes, ATP-bioluminescence, superbugs, infection control, STIs, food microbiology, molecular applications and career opportunities in microbiology) and 'The Drugs Don't Work', an educational theatre play to raise awareness/understanding of AMR amongst young learners and the general public. Evaluation of the effectiveness of these public engagement strategies has been published recently (**S3.5**, **S3.6**) and accompanying educational videos have been produced/posted on the internet.

3. References to the research

S3.1 Braoudaki, M. & **Hilton, A.C.** (2004) Adaptive Resistance to Biocides in Salmonella enterica and *Escherichia coli* O157 and Cross-Resistance to Antimicrobial Agents. *J. Clin. Microbiol.* **42(1)**, 73-78. https://doi.org/10.1128/JCM.42.1.73-78.2004.

S3.2 **Bashir, A.**, Gray, J., Bashir, S., **Ahmed, R.** and **Theodosiou, E**. (2018). Critical points in the pathway of antibiotic prescribing in a children's hospital: the Antibiotic Mapping of Prescribing (ABMAP) study. *J. Hosp. Infect.* **101(4)**, 461-466. https://doi.org/10.1016/j.jhin.2018.07.038.

S3.3 Wheeldon, L.J., **Worthington, T.** & **Lambert, P.A.** (2011). Histidine acts as a co-germinant with glycine and taurocholate for *Clostridium difficile* spores. *J. App. Microbiol.* **110(4)**, 987-994. https://doi.org/10.1111/j.1365-2672.2011.04953.x.

S3.4 Patents EP2536278B1, US10244758B2 & US9314028B2; **Worthington T.** & Wheeldon L.J. Compositions comprising a germinant and an antimicrobial agent; mirrored patents granted in 2014, 2016 & 2019 respectively.

S3.5 **Ahmed, R.**, **Bashir, A.**, Brown, J.E.P., **Cox, J.A.G.**, **Hilton, A.C.**, Jordan. S., **Theodosiou, E.** & **Worthington, T.** (2020). Aston University's Antimicrobial Resistance (AMR) Roadshow: Raising Awareness and Embedding Knowledge of AMR in Key Stage 4 Learners. *IPIP* **2(2)**, article 100060. https://doi.org/10.1016/j.infpip.2020.100060.

S3.6 **Ahmed, R.**, **Bashir, A.**, Brown J.E.P., **Cox, J.A.G.**, **Hilton, A.C.**, Hilton, C.E., **Lambert, P.A.**,

Theodosiou, E., Tritter J.Q., Watkin, S.J. & **Worthington T.** (2020). The drugs don't work: evaluation of educational theatre to gauge and influence public opinion on antimicrobial resistance. *J. Hosp. Infect.* **104(2)**, 193-197. https://doi.org/10.1016/j.jhin.2019.10.011.

The quality of the research described above is evidenced by S3.1-S3.6, published in international, peer-reviewed journals and the following competitively-awarded research grants: **EPSRC EP/M02735X/1 £729,459,** (UK cross-Research Council Initiative on Antimicrobial Resistance) Bridging the Gaps between Engineering and Physical Sciences in Antimicrobial Resistance (2015-2018); **Society for Applied Microbiology, £6,000** (2011-2014); **Wellcome Trust Society 084905, £49,246** The World of Microbiology: Mastering the Invisible, Invincible, Treatable and Preventable (2008-2011) and **Department of Health / Insight Health Ltd.**, **KTP007110, £164,000** Development of a germination solution for elimination of *C. difficile* spores (2008-2011).

4. Details of the impact

Research detailed above has generated national and international impacts in 4 major categories:

1. Impact on Public Policy, Law and Services: EU and USA Policy change (2017-date)

Hilton's research into the mechanism by which triclosan stimulates antibiotic efflux from bacterial cells (**S3.1**) is the pivotal underpinning evidence in the Florence Statement (**S5.1**, p5, section 9) for the link between triclosan resistance and AMR. His work is also cited in US docket FDA-2015-N-0101 (**S5.2**) which led to the USA-wide ban on adding triclosan to antiseptics. The EU similarly banned such use of triclosan (Biocidal Products Regulations (EU) No 528/2012). Hilton was subsequently invited as a Trustee of the International Scientific Forum on Home Hygiene (IFH) and is a co-author of its consensus white paper (**S5.3**), which calls on international policy makers to recognize a targeted approach to home hygiene. This white paper prompted the Royal Society for Public Health to publish "Too clean or not too clean", (**S5.4**, p4, section 1.1 and subsequent citations); had been downloaded 757 times by December 2020 and was endorsed by the previous UK Chief Medical Officer (**S5.4**).

2. Impact on Practitioners and Delivery of Professional Services: Changes in Antimicrobial Prescribing at Birmingham Children's Hospital (BCH; 2016-date)

As a consequence of Bashir's ABMAP study (**S3.4**), clinical microbiology support has been expanded at BCH to involve direct interaction between infection specialists and antibiotic prescribers (**S5.5, S5.6**). Formal case-based discussions now occur across five specialities, which initially resulted in 40% of patients having their antibiotic treatment amended. The success of this approach is exemplified by a recent review of patients with positive blood cultures which determined that 100% of the target patients are now treated with appropriate antibiotics (**S5.5**). Separately, owing to prescribers' wish for instruction re. antimicrobial prescription (**S3.4**), an algorithm has been developed to guide accurate prescription of meropenem (a broad-spectrum carbapenem antimicrobial) and as a consequence, meropenem usage fell for the first time in 2018-19 by ~5% against a background of continuing rise amongst specialist NHS trusts. Only patients with positive microbiology results justifying its use, now continue on meropenem treatment so reducing AMR risk. Finally, a series of antibiotic education animations have also been developed to educate staff and visitors (**S5.6**). As a consequence of these combined activities, the BCH Consultant Microbiologist states "*We are convinced that our collaboration with Aston University has had a significant and sustained impact on our Antimicrobial Stewardship"* (**S5.5**).

3. Impact on Commerce and the Economy: C. difficile germinant (2019-date)

Worthington's *Clostridium difficile* germination solution was developed at Aston under a KTP agreement. The resulting patent was granted on April 2nd 2019 and covers EU, USA, Japan, China and Hong Kong. The Managing Director of Insight Health Ltd summarises *"we are now partnering with a US-based multinational company to market the resulting products in multiple formats to the food and healthcare industries, with a market estimated to be worth £5 million thus increasing the revenue at Insight Health by 20%"* (**S5.7**).

4. Impact on Understanding, Learning and Participation; Culture and Society: Public educational activities around AMR (impact 2014 - 2018)

Anecdotal evidence of the impact of the WoM roadshow on African IB students in 2014 e.g. **S5.8** "*The overall impact of this inspiring workshop had on our students was more than I could have imagined. It resulted in a significant increase in our students declaring biology as a career track.*" prompted the Aston AMR team to develop and attempt to quantitate the impact of further public interventions concerning AMR. Consequently, *WoM Antimicrobial Resistance* (the Antimicrobial Resistance roadshow) was presented to 159 Midlands-based young learners (years 11-12). In addition to positive qualitative feedback from both staff and students (e.g. **S5.8** "*I really enjoyed the handwashing activity and I still remember the correct way to wash my hands to remove potentially harmful bacteria. … the activities gave me more confidence when I started the A level required practicals*"), questionnaires before and after the roadshow and a 3-month follow-up demonstrated that awareness and knowledge of AMR was increased significantly by the roadshow and still retained 3 months later (**S3.5**). Subsequently, the AMR team's educational theatre event was performed at Birmingham Think Tank and the Cheltenham Science Festival. Its impact on 242 members of the general public (aged 6-94) was analysed via pre- and post-play questionnaires which revealed statistically-significant increases in awareness, knowledge and changes in attitude (**S3.6**). The play was recorded and is available on YouTube (**S5.10**). Collectively, AMR's educational animation and videos (**S5.6**, **S5.9**, **S5.10**) have received 2300+ views on YouTube.

5. Sources to corroborate the impact

The Florence Statement. The statement was first introduced in 2016 at the at the 36th International Symposium on Halogenated Persistent Organic Pollutants (DIOXIN 2016) in Florence, Italy and was subsequently published in 2017 in the journal *Environmental Health Perspectives*. https://doi.org/10.1289/EHP1788.

S5.1 Federal Drug Administration docket **FDA-2015-N-0101.** See references 62&63 on pg 25199 https://www.govinfo.gov/content/pkg/FR-2015-05-01/pdf/2015-10174.pdf

S5.2 **International Forum on Home Hygiene (IFH) White Paper**: Containing the burden of infectious disease is everyone's responsibility: https://www.hygieneforum.nl/files/8915/4089/6863/1810_IFH_White_Paper_on_Hygiene.pdf

S5.3 **Examples of Impacts of the IFH White Paper:** Royal Society for Public Health document "Too clean or not too clean" https://www.rsph.org.uk/static/uploaded/06b37f30-2241-4e98-aba93fc15346e7a5.pdf and related statement from the IFH.

S5.4 Testimonial from **Consultant Microbiologist**, Birmingham Childrens Hospital.

S5.5 **Annual Report** of the Birmingham Women's and Children's NHS Foundation Trust Infection Prevention & Control Team 2018 – 2019, **p15-16** and links to associated animations on YouTube: https://www.youtube.com/watch?v=sucot9DOauw; https://www.youtube.com/watch?v=lo19JnxWYFg; https://www.youtube.com/watch?v=b3dyFGWO1IU

S5.6 Testimonial from **Director, Insight Health Ltd**, London.

S5.7 Exemplar letters from **Senior Biology teachers** in **Africa & UK**.

S5.8 **Antimicrobial Roadshow public videos (YouTube):** https://www.youtube.com/watch?v=eQ0Z1gzhndg; https://www.youtube.com/watch?v=00RvoJSBn1A&feature=youtu.be; https://www.youtube.com/watch?v=qRIR-X7N2VI) https://www.youtube.com/watch?v=zeRmpaCeAmU;

S5.9 The Drugs Don't Work-A tale of Resistance; **explanatory and performance videos of live Educational Theatre** on the understanding of AMR https://youtu.be/qL32XmoqfvU; https://youtu.be/2dMJIm3Qwqg.