Institution: University of Salford

Unit of Assessment: 3

Title of case study: Improving healthcare systems to tackle antimicrobial resistant infections in Uganda

Period when the underpinning research was undertaken: December 2013 – December 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:
Dr Chloë James	Senior Lecturer in Medical Microbiology	November 2012 – Present
Dr Ian Goodhead	Reader in Microbial Genomics	September 2015 – Present
Prof. Richard Birtles	Chair in Biomedical Science	January 2011 – Present
Prof. (Helen) Louise Ackers	Chair in Global Social Justice	December 2013 – Present

Period when the claimed impact occurred: July 2017 – December 2020

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

1. Summary of the impact

Antimicrobial resistance (AMR) is a major global challenge, the impact of which is felt most acutely in Low- and Middle-Income Countries (LMICs). Salford's unique social science-led, multi-disciplinary approach demonstrates how holistic systems change can be applied to tackle AMR in LMICs such as Uganda. Salford's work has directly led to sustained improvements in antimicrobial stewardship amongst health workers in Uganda, changing behaviour in the following areas: infection prevention and control (IPC); wound management; culture-and-sensitivity testing; antibiotic use; and rational prescribing. Our basic molecular microbiology research has created an evidence base to improve procurement of antibiotics for both treatment and AMR surveillance. Overall, these changes have reduced the number of deaths associated with maternal sepsis, significantly shortened patient stays and lowered readmission rates to hospital, along with reducing the costs associated with treatment.

2. Underpinning research

There is a critical need for multidisciplinary approaches to tackle antimicrobial resistance (AMR), both at global and local levels. Basic molecular microbiology and epidemiology research at Salford, led by James, Goodhead and Birtles, has applied cutting-edge technologies to reveal insights into the biology of AMR including: how bacteria become resistant to antibiotics **[3.1]**; the genetic determinants of AMR **[3.2]**; and the spread of AMR in populations **[3.3]**. This impact case study describes how we have combined our research expertise in this area with action-research in social science (Ackers – UoA20) to tackle AMR in a Low- and Middle-Income Country (LMIC) setting. The research focuses on the local level at Fort Portal Regional Referral Hospital (FPRRH) and other health centres that serve the rural region of Kabarole in Western Uganda. Kabarole is an area where maternal mortality due to sepsis has been disproportionately high. Antibiotics supplies are poorly regulated and little data on AMR have hitherto been published. Our research findings highlight the importance of a local focus, adopted as policy at national level.

2.1. Molecular mechanisms of AMR development and spread in FPRRH

The Ugandan National Action Plan (UNAP) has identified multidrug resistant (MDR) strains of *Staphylococcus aureus* as a major threat to human and animal health. Current national guidelines for managing such infections are based on a relatively small number of studies

centred on urban areas. With a focus on *S. aureus* from surgical site wounds and urinary tract infections, our research combined genome sequencing with clinical profiling (2017 – 2019). This revealed that the majority of *S. aureus* from FPRRH belonged to a common clonal complex of strains found across Africa, normally associated with asymptomatic nasopharyngeal carriage. 73% of the bacteria were resistant to one or more antibiotics and 29% were MDR, explained by the presence of common antibiotic resistance genes. We found evidence of likely development of resistance should the bacteria be exposed to certain antibiotics, indicating the need for close control of antibiotic prescription of "at-risk" antibiotics and an improved antibiogram **[see 2.2]**. Importantly, by including genetic analysis for the first time, we identified previously undiagnosed methicillin-resistant *S. aureus* (MRSA). This highlighted a key point of intervention needed to enable sufficient procurement of appropriate antibiotic disks for culture and sensitivity tests, as well as effective antibiotics for treatment **[3.4]**.

A critical finding was the need for applying local data to inform local AMR policy. Our research suggested that 100% of circulating *S. aureus* were susceptible to clindamycin, an antibiotic on the WHO access list for acceptable use. Nevertheless, including new molecular data alongside existing clinical infrastructure provided evidence of inducible resistance that would likely lead to treatment failure during therapy **[3.4]**.

2.2. Understanding behaviour in public health systems to drive change in antimicrobial stewardship (AMS)

The laboratory research has been combined with social science research to better understand the barriers to Ugandan health systems in tackling AMR and to develop local-level policy towards better AMS for adoption within national guidelines. **The Maternal Sepsis Action-Research Intervention** combined analysis of facility data with ongoing participant observation, qualitative interviews and focus groups. It identified maternity as the dominant source of antibiotic consumption in Ugandan Regional Referral Hospitals and sepsis, arising largely from healthcare acquired infection, as the second most important cause of maternal mortality **[3.5]**.

Salford social science research activities have addressed behavioural change dimensions of AMS in LMICs. Research in community and tertiary facilities identified the critical role that midwives play in antibiotic prescription: although technically illegal, most antibiotics consumed in ante-natal settings are dispensed by midwives in the absence of doctors. Qualitative research showed that midwives had a poor understanding of how antibiotics work and implications of their misuse for AMR. Subsequently, modifications were identified to practice that would improve clinical outcomes. The research showed that task-shifting facilitates collaboration with wider clinical roles: pharmacists, doctors and nurses; and increased utilisation of laboratory facilities, by midwives, for antibiotic sensitivity testing towards generating an antibiogram to improve empirical prescription outcomes **[3.5]**.

These studies laid the foundations for subsequent complex intervention research, funded by the UK government Department of Health & Social Care's Fleming Fund and under the Commonwealth Partnerships for Antimicrobial Stewardship (AMS) for GBP60,000 (grant no. AMSB03), which involved the isolation and characterisation of *S. aureus* from healthcare workers' hands in Kabarole health centres. This work demonstrated the potential for nosocomial spread of infection and created the evidence base to support an intervention of improved access to hand hygiene and infection prevention and control (IPC) **[3.5]**.

3. References to the research

3.1. Molitor A, **James C. E.,** Fanning S, Pagès JM, Davin-Regli A (2018) Ram locus is a key regulator to trigger multidrug resistance in *Enterobacter aerogenes, Journal of Medical Microbiology* (67)2. https://doi.org/10.1099/jmm.0.000667

3.2. Ribiero, C, Rahman, LA, Holmes, LG, Woody, AM, Webster, CM, Monaghan, TI, Robinson, GK, Mühlschlegel, FA, **Goodhead, IB**, and Shepherd, M. (2020) Nitric oxide (NO) elicits

aminoglycoside tolerance in *Escherichia coli* but antibiotic resistance gene carriage and NO sensitivity have not co-evolved, *Archives of Microbiology.* In press 2020: accepted version available at: http://usir.salford.ac.uk/id/eprint/59069

3.3. Clegg SR, Carter SD, **Birtles RJ**, Brown JM, Hart CA, Evans NJ. (2016) Multilocus sequence typing of pathogenic treponemes isolated from cloven-hoofed animals and comparison to treponemes isolated from humans, *Applied and Environmental Microbiology* 2016;82, pp. 4523-4536. https://doi.org/10.1128/AEM.00025-16

3.4. Ackers-Johnson, G., Kibombo, D., Nsubuga, M. L., Kigozi, E., Kateete, D., Kajumbula, H., Walwema, R., **Ackers, H. L.**, **Goodhead, I.**, **Birtles, R.** & **James C.E.** (2020) Antibiotic resistance profiles and population structure of disease-associated *Staphylococcus aureus* infecting patients in Fort Portal Regional Referral Hospital, Western Uganda, *BioRXiv* https://doi.org/10.1101/2020.11.20.371203

3.5. Ackers, H.L., Ackers-Johnson, G., Seekles, M. and Opio, S. (2020) Opportunities and challenges for improving anti-microbial stewardship in low- and middle-income countries; lessons learnt from the maternal sepsis intervention in Western Uganda, *Antibiotics* 9(6), 315. https://doi.org/10.3390/antibiotics9060315

Submitted versions for outputs **3.2** and **3.4** are available as open access preprints in public repositories. All references **3.1 – 3.5** have undergone external peer review.

4. Details of the impact

The resistance of bacteria to antibiotics threatens our ability to treat infections. Approximately 30,000 women die each year as a result of severe infections when giving birth, with sepsis accounting for between 10% and 15% of maternal mortality and most deaths occurring in LMICs **[see 5.1]**. The UK Special Envoy on AMR has praised Salford's partnership with Ugandan health workers in *'driving amazing progress in Uganda and beyond'* in this area and confirmed that low-cost stewardship interventions of this kind can significantly decrease maternal mortality and ultimately reduce the impact of AMR **[5.1]**.

4.1. Improved AMR surveillance and procurement planning for more effective treatment of AMR infections

Salford's research, in collaboration with Ugandan partners, combined molecular and clinical data on antibiotic resistance profiles of bacteria isolated from infections at FPRRH **[3.4]**. This supported a **new and comprehensive FPRRH antibiogram [5.1, Table 5.11, p. 99]**. This is a tool which is well established in high-income countries, whereby collating all hospital Antimicrobial Susceptibility Testing (AST) data allows for evidence-based procurement of effective antibiotics for future empirical prescribing. These research activities and outputs have provided a strong evidence base to inform a **7% increase in procurement budget for antibiotics** at FPRRH **[5.1, Table 6.1, p. 111]**. The 2020/21 Procurement Plan evidences a **shift towards acquiring antibiotics** for which lower levels of resistance have been detected in circulating bacterial strains **[5.1, Table 6.1, p. 111]**.

Similarly, the **FPRRH laboratory procurement policy has been modified in light of the microbiology testing results,** with the Hospital Director noting that *'without the correct access to laboratory supplies, we would be unable to detect undiagnosed MRSA, and are now including our Head of Microbiology in our processes to guide on planning and procurement of lab related supplies such as antibiotic disks'* **[5.2]**. Molecular evidence of inducible resistance to clindamycin **[3.4]** was reported at an infection control meeting at FPRRH; clindamycin is not currently used at the hospital, but any future use will be closely monitored despite clinical evidence of its efficacy **[5.2]**.
Salford's researchers have **improved capacity for molecular AMR testing** by training Ugandan early career researchers in DNA sequencing and bioinformatics analysis at Salford

and repeating and validating the sequencing experiment in Uganda. This work involved collaboration with Makerere University, who had the necessary equipment to undertake state-of-the-art genome sequencing but lacked the training and consumables. Through research exchange visits, the team successfully sequenced the whole genomes of the *S. aureus* culture collection from FPRRH, showcasing this capacity for future sustainable utilisation of molecular methods to type AMR bacteria **[3.4]**. For example, this research has led to follow-up funding to establish a wider Ugandan sequencing infrastructure and associated supply chains towards infectious disease diagnostics and epidemiology (particularly COVID-19; Newton Fund (2020) EP/V029177/1 to Birtles, Goodhead, Ackers and Ugandan partners).

4.2. Sustainable improvements in laboratory, clinical and prescribing behaviours leading to reduced rates of maternal sepsis readmission

The Maternal Sepsis Action-Research Intervention (MSI) has '*generated the evidence base to support a new approach to the management of Maternal Sepsis'* **[5.3]** and led to a **new policy brief** being developed by the Pharmaceutical Society of Uganda, detailing a series of **21 policy changes** arising from this research **[5.4]**. The MSI has resulted in a policy of **midwives undertaking roles with greater responsibility**, such as nurse or doctor roles, leading to closer collaboration with other hospital staff, and **better opportunities for midwives to obtain training** through mentoring and co-working, rather than expensive external opportunities. *'Midwives are now taking the lead in managing patients; they used to wait for doctors to make decisions'* **[5.1, p. 104]**. Adoption of the model has resulted in **midwives having an improved understanding of AMR issues and antibiotic stewardship**. This has led to the **reduction of inappropriate prescribing of antibiotics for non-surgical prophylaxis from 100%** (February 2017) **to just 20%** (August 2018) **[5.4, Table 1]**. FPRRH's Director confirms that *'From an antimicrobial stewardship point of view the intervention and the research underpinning it has transformed Fort Port Regional Referral Hospital into an **example of best practice**'* and the hospital has now set up a Medicines Therapeutic Committee (MTC) to manage AMR as a result **[5.2]**. The establishment of MTCs is seen as critical by the Ugandan Ministry of Health to the operationalisation of the National Action Plan on Anti-Microbial Resistance in Uganda **[5.2]**.

Salford's research **[3.5]** has additionally led to midwives **increasing their rates of wound-swabbing**, and submission to laboratories for bacterial culture and sensitivity testing: FPPRH reported an **increase of laboratory test orders from 0% to 95% in suspected sepsis cases** from 2019 to 2020 **[5.1, Table 5.2, p. 88]**. This is also contributing to a comprehensive FPRRH antibiogram that enables, and provides confidence in, **immediate empirical treatment** whilst patients await test results **[5.1, Table 5.11, p. 99]**: *'The sample size is now very adequate. The antibiogram will be good for the clinicians to guide prescribing and it will be good for the patients'* **[5.1, p. 90]**. The time taken from swabbing to results has led to a **substantial reduction to appropriate antibiotic prescribing from 1 month to 3 days [5.1, p. 84]**.

Engaging midwives (as key actors) with laboratory scientists, pharmacists and doctors has led to significant and sustained improvements in health workers' compliance with hand hygiene guidelines: **compliance with hand-washing guidelines has increased from ~18% in 2019 to ~67% in 2020**, with **hand gel/sanitizer use improving from ~33% to ~79%** over the same period **[5.1, Tables 4.2 and 4.3, pp. 63-64]**.

The Assistant Commissioner at the Ministry of Health in Uganda confirms that: '*The implementation of the Maternal Sepsis Intervention in FPRRH has had a **truly transformative impact on maternal mortality rates** at that hospital'* **[5.5]**. Fewer attending mothers have died from sepsis, **[5.4, Figure 2]**, nor have been re-admitted **[5.2]**. The MSI has **reduced the length of hospital stays for patients with suspected sepsis by an average of 6 days** over an 18-month period **[5.4, Figure 3]**. The combination of reduced lengths of stay, a **reduction of readmissions to zero**, and **fewer surgical referrals** has resulted in ***'major cost savings'*** in hospitals **[5.2]**. The Minister of Health for the Toro Kingdom (Western Uganda) has confirmed plans to **scale up the approach**: '*I am currently identifying ways of applying the Maternal Sepsis Intervention model to other public hospitals across Uganda*' **[5.5]**.

4.3. Other contributions to policy making

Complex intervention research carried out by Salford's researchers in partnership with Ugandan health workers **[3.5]** formed the basis for a policy brief prepared by the Pharmaceutical Society of Uganda in 2020 **[see 4.2]**, which advocated for structural changes in pharmaceutical supply chains and the deployment of pharmacists in public hospitals in Uganda **[5.4]**. The brief was distributed to the Ugandan National Action Planning Group on Anti-Microbial Resistance as well as to the Ministry of Health in Uganda **[5.4]**. This has resulted in further policy change, including improvements in **access to specialist clinical pharmacists,** with specialist knowledge of drug combinations and complex conditions to guide evidence-based prescription of antibiotics **[5.4, informed by the FPRRH hospital antibiogram; Policy Note 4E]**.

Tropical Health Education Trust (THET), a specialist global health organisation that trains and supports health workers through partnerships and enables people in LMICs to access essential healthcare, confirms that, as a result of this research **[3.5]**, it has revised a number of policies attached to its future grants programmes **[5.6].** The Grants Coordinator for THET highlighted the importance of **strong links between the hospital and laboratory** and noted that this is something *'that will be assessed in future AMS programmes*' **[5.6]**. Also informed by Salford's research, THET has revised the importance which needs to be placed on **ensuring that basic levels of IPC are established at implementation sites** before other AMS principles can be put in place **[5.6]**.

5. Sources to corroborate the impact

5.1. Book: Ackers, H.L., Ackers-Johnson, G., Welsh, J., Kibombo, D. and Opio, S. (2020) Anti-Microbial Resistance in Global Perspective, Palgrave. Specifically: Foreword by the UN Special Envoy on AMR; Tables 4.2 and 4.3, pp. 63-64; p. 84 (Source: FPRRH midwife); Table 5.2, p. 88 (Source: FPRRH laboratory); p. 90 (Source: FPRRH Laboratory Scientist); Table 5.11, p. 99 (Source: FPRRH); p. 104; Table 6.1, p. 111 (Source: FPRRH) on improved AMR surveillance and procurement planning (4.1) and use of MSI to reduce maternal sepsis readmission (4.2)
5.2. Testimonial: Fort Portal Regional Referral Hospital, Uganda and Coordinator of Ugandan Regional Referral Hospitals (February 2021), on changes to procurement policy, managing AMR through anti-microbial stewardship (4.1) and maternal sepsis improvements (4.2)
5.3. Testimonial: Pharmaceutical Society of Uganda (January 2021), on maternal sepsis improvements through action-research intervention (4.2)
5.4. Policy Brief: Pharmaceutical Society of Uganda (December 2020), on maternal sepsis intervention and policy recommendations, specifically: Table 1, Figures 2 and 3 (4.2) and Policy Note 4E (4.3)
5.5. Testimonial: Ministry of Health, Uganda (November 2020), on application of the maternal sepsis intervention and resultant maternal sepsis improvements (4.2)
5.6. Testimonial: Tropical Health and Education Trust (January 2021), on changes in policy regarding grants programmes (4.3)