Institution: King's College London (KCL)

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Successful and cost-effective methods of controlling the spread of MRSA (methicillin-resistant *Staphylococcus aureus*) in hospitals

1. Summary of the impact

Two significant impacts have resulted from King's College London (KCL) research on preventing infections of the so-called antibiotic-resistant MRSA 'superbug' associated with hospital treatment. KCL's research exemplifies NIHR's stated "end-to-end" strategy for translating discoveries made in individual infections to population benefit through treatment and prevention.

First, KCL research contributed to Department of Health guidelines. Following the publication of those guidelines, NHS Trusts set out stronger procedures for screening patients for MRSA and for routine 'decolonisation' - involving the use of antibacterial shampoo, bodywash and nasal cream by patients. This made a major contribution to the dramatic 75% fall in MRSA cases reported by Public Health England between 2008/09 and 20012/13.

Second, KCL research showed that some MRSA strains are more easily transmitted and more virulent than others. Specifically, we identified a molecule produced by one such strain of bacteria that enabled it to adhere to and colonise a host. We patented this molecule as a rational vaccine component to prevent MRSA infection, and the Novartis pharmaceutical company took up this patent in 2009.

2. Underpinning research

KCL's multidisciplinary approach to research

In 2002, Dr Jonathan Edgeworth (Consultant Microbiologist & Reader in Clinical Infectious Diseases, KCL 2002-present) and Professor Gary French (KCL 1994-2012) brought together a multi-disciplinary group of scientists, clinicians, geneticists, mathematicians and epidemiologists, and established an embedded centre of clinical-academic excellence within St Thomas' Hospital called the Centre for Clinical Infection and Diagnostics Research (CIDR) that has gone on to forge vital relationships with leading organisations such as the Wellcome Trust Sanger Institute and Novartis. The creation of this centre was co-ordinated by the KCL Department of Infectious Diseases. The goals of CIDR were (i) to identify factors explaining the spread of healthcare-associated MRSA, including its virulence mechanisms, and (ii) to apply this research promptly to improve the prevention of MRSA infections. These objectives continue to resonate closely with the Department of Health's 5-year Antimicrobial Resistance Strategy, announced in September 2013.

KCL research on screening and decolonisation strategies: clinical impact and cost-effectiveness

The KCL team first created large clinical databases and stores of MRSA samples. These were taken from 4500 patients admitted to the intensive care unit (ICU) at St Thomas' Hospital between 2002 and 2006, of which over 20% were colonised with MRSA, and from 850 patients with blood-borne MRSA (bacteraemia) between 1999 and 2009.

KCL research has focused on assessing the effectiveness of different MRSA screening methods, including use of polymerase chain reaction (PCR), a fast but relatively expensive technique [1]. The group also collaborated with Public Health England to determine the cost effectiveness of various combinations of control measures (screening method, isolation and decolonisation) in order to provide economic evidence to policy makers [2]. This involved mathematical models (Bayesian, longitudinal and multi-state modelling) of data on ICU patients. Decolonisation was shown to improve patients' health outcomes and reduce costs in all scenarios [2].

Studies on the behaviour of MRSA strains: novel results that have had significant impact

The KCL team provided the first evidence that:

- a single strain of MRSA can differ in its transmissibility – which has improved our understanding of how pathogens adapt to hospital environments [3];

- MRSA strains can differ in their response to infection control methods, especially with regard to becoming resistant to chlorhexidine (one of the antimicrobials most often used for MRSA decolonisation) – which has implications for the tailoring of treatments [4]; and
- MRSA strains can differ in their ability to cause bacterial infections of the blood [5] and heart lining [6] – which has improved our understanding of the causes of disease.

Unique characteristics found for MRSA strain ST239-TW
Strain ST239-TW (which was most likely imported into the St Thomas' ICU from South-East Asia) caused a protracted 2-year MRSA outbreak [7,8]. It was unique in being highly transmissible, causing four times more catheter-related bloodstream infections than local strains, and being resistant to decolonisation using chlorhexidine. Through whole-genome DNA sequencing of ST239-TW, the KCL team identified ***sasX****:* a novel molecule, or adhesin, on the bacterium's surface. These findings indicate that *sasX* was responsible for ST239-TW's increased binding to catheters inserted into blood vessels and the bloodstream infections associated with this.

The new MRSA strain ST239-TW was found to carry an antiseptic resistance gene, *qacA*
qacA had not previously been suspected of any clinically significant activity when using chlorhexidine for decolonisation. However, epidemic analysis showed that the transmission of ST239-TW actually increased after chlorhexidine-based decolonisation [3]. We also found that the presence of *qacA* in ST239-TW was associated with a significant reduction in chlorhexidine susceptibility that was also seen in some but not all MRSA lineages carrying *qacA* [9]. These findings indicated that the decolonisation strategy may need to be different for different MRSA strains.

3. References to the research

1. Clinical application of real-time PCR to screening critically-ill and emergency-care surgical patients for methicillin-resistant *Staphylococcus aureus*: a quantitative analytical study. **Herdman MT**, **Wyncoll D**, **Halligan E**, **Cliff PR**, **French G**, **Edgeworth JD**. *J Clin Microbiol*. 2009;47:4102-8.

2. Screening, isolation and decolonisation strategies in the control of methicillin-resistant *Staphylococcus aureus* in intensive care units: cost-effectiveness evaluation. Robotham JV, Graves N, Cookson BD, Barnett AG, Wilson JA, **Edgeworth JD**, **Batra R**, Cuthbertson BH, Cooper BS. *BMJ*. 2011;343:d5694. doi: 10.1136/bmj.d5694.

3. Quantifying type-specific reproduction numbers for nosocomial pathogens: evidence for heightened transmission of an Asian sequence type 239 MRSA clone. Cooper BS, Kypraios T, **Batra R**, **Wyncoll D**, **Tosas O**, **Edgeworth JD**. *PLOS Computational Biol.* 2012; 8(4):e1002454. doi: 10.1371/journal.pcbi.1002454.

4. Efficacy and limitation of a chlorhexidine-based decolonization strategy in preventing transmission of methicillin-resistant *Staphylococcus aureus* in an intensive care unit. **Batra R**, Cooper BS, **Whiteley C**, **Patel AK**, **Wyncoll D**, **Edgeworth JD.** *Clin Infect Dis*. 2010;50:210-7.

5. An outbreak in an intensive care unit of a strain of methicillin-resistant *Staphylococcus aureus* sequence type 239 associated with an increased rate of vascular access device-related bacteremia. **Edgeworth JD**, Yadegarfar G, **Pathak S**, **Batra R**, Cockfield JD, **Wyncoll D**, **Beale R**, Lindsay JA. *Clin Infect Dis*. 2007;44:493-501.

6. An association between bacterial genotype combined with a high vancomycin minimum inhibitory concentration and risk of endocarditis in methicillin-resistant *Staphylococcus aureus* blood stream infection. **Miller CE**, **Batra R**, Cooper BS, **Patel A**, **Klein J**, **Otter JA**, Kypraios T, **French GL**, **Tosas O**, **Edgeworth JD**. *Clin Infect Dis*. 2012;54:591-600.

7. Genome sequence of a recently emerged, highly transmissible, multi-antibiotic- and antiseptic-

resistant variant of methicillin-resistant *Staphylococcus aureus*, sequence type 239 (TW). Holden MT, Lindsay JA, Corton C, Quail MA, Cockfield JD, **Pathak S**, **Batra R**, Parkhill J, Bentley SD, **Edgeworth JD**. *J Bacteriol*. 2010;192:888-92.

8. Evolution of MRSA during hospital transmission and intercontinental spread. Harris SR, Feil EJ, Holden MT, Quail MA, Nickerson EK, Chantratita N, Gardete S, Tavares A, Day N, Lindsay JA, **Edgeworth JD**, de Lencastre H, Parkhill J, Peacock SJ, Bentley SD. *Science*. 2010;327:469-74.

9. Selection for *qacA* carriage in CC22 but not CC30 MRSA bloodstream infection isolates during a successful institutional infection control programme. **Otter JA**, **Patel A**, **Cliff P**, **Halligan E**, **Tosas O**, **Edgeworth JD**. *J Antimicrob Chemother*. 2013, 68:992-9.

4. Details of the impact

Impact 1: Recommendations adopted for chlorhexidine-based decolonisation in preventing MRSA transmission [References 2, 3, 4, 7, 8 and 9].

KCL work on the importance of decolonisation in preventing MRSA transmission, particularly in critical care areas, had a very considerable impact in the preparation of the Department of Health's Saving Lives – High Impact Interventions care bundles 'Screening for MRSA colonisation' that recommend pre-emptive decolonisation as an integral part of MRSA control for high-risk patients in all NHS Trusts [10]. Professor Gary French was a member of the Department of Health committee preparing these guidelines, and the findings from KCL were instrumental in their development. Guy's and St Thomas' Trust is therefore cited in these guidelines, which links our research to this advice and impact (see p.6). Subsequent guidance from the Department of Health [11, p.3] reiterates the previous guidance [10] on the importance of decolonisation for patients who test positive for MRSA after screening.

From April 2009, all NHS Trusts were expected to screen all elective admissions for MSRA in line with Department of Health guidance [11]. In response, many Trusts published and implemented their own guidelines and procedures for MRSA screening and decolonisation [12]. A clear pathway can therefore be seen from the KCL work to the following major impact: a dramatic fall of 75% in MRSA bacteraemia cases reported by NHS Trusts between 2008/09 and 20012/13, according to Public Health England (Trust apportioned cases) [13] (p.1). Recent data from the Shelford group of 10 leading UK academic healthcare organisations shows a continuing decrease in incidence of MRSA rates [14].

KCL work showing that some MRSA strains carrying *qacA* can be clinically resistant to chlorhexidine has raised concerns and has led to considerable impact across the infection control community [15-17]. Locally, a 4-fold increase in the presence of *qacA* in MRSA bacteraemia cases has been seen at Guys and St Thomas' Hospital, which has prompted a change from the use of chlorhexidine to an alternative antiseptic, octenisan. Octenisan is now being increasingly introduced for decolonisation in acute NHS Trusts [18].

Impact 2: Identifying that *sasX* is associated with MRSA strains that are more transmissible and virulent [References 3, 4, 5, 7 and 8].

KCL researchers filed an EU-wide patent identifying *sasX* as a potential diagnostic and vaccine target in 2009 (PCT/GB2010002056; [19]). On the basis of the clinical and scientific data described in Section 2, this patent/finding has had considerable impact and the patent has now been extended to Europe, Japan, the USA and China. Novartis Vaccines took an option to exploit *sasX* as a component of a multivalent *S. aureus* vaccine under a three-year licensing agreement (Nov 2009-Nov 2012) which has now been extended for a further year. Studies have been taking place at Novartis Vaccines, Siena, Italy.
The KCL discovery of sasX has had a significant impact on the management of MRSA in

China. In a follow-up paper published in Nature Medicine in May 2012 [20], a US group took up the KCL findings and investigated the epidemiology of *sasX* in MRSA strains in Chinese hospitals. They found that *sasX*-containing ST239 clones had spread rapidly over the past five years to become the dominant healthcare-associated MRSA clones in Chinese hospitals and that *sasX* had spread to other MRSA clones. They also found that *sasX* was highly virulent in animal models. They called for "vaccine efforts aimed at *sasX* to prevent MRSA colonisation and disease". The identification of these highly transmissible strains as the major MRSA clones stems directly from the KCL discovery of sasX, impacts on the most populous country in the world, and further substantiates the strategy of using sasX for vaccination.

5. Sources to corroborate the impact

10. Saving Lives – High Impact Interventions. Screening for Methicillin-resistant *Staphylococcus aureus* (MRSA) Colonisation. A Strategy for NHS Trusts: A Summary of Best Practice. Department of Health, 2007. http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_078128.pdf (see page 6)

11. MRSA Screening – Operational Guidance 2. Department of Health, 2008. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1232094401893

12. Examples of local Trust guidelines include: http://www.cuh.org.uk/resources/pdf/cuh/profile/publications/selected_policies/mrsa_guidelines.pdf http://www.royalberkshire.nhs.uk/pdf/MRSA_screening_policy_v3_october_2010%20_CG179.pdf http://www.uhcw.nhs.uk/clientfiles/File/MRSA_Policy__Dec_2007.pdf

13. Public Health England, July 2013. Summary Points on Methicillin Resistant *Staphylococcus aureus* (MRSA) Bacteraemia http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1233906819629).

14. http://www.shelfordgroup.org/ Data derived from http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1233906819629

15. Jarvis WR. What increases the risk for persistent MRSA after decolonization? **Medscape Infectious Diseases** Mar06 2012, Video and transcript discussing our findings of an increase in chlorhexidine resistance [4] (http://www.medscape.com/viewarticle/759246)

16. Horner C, Mawer D, Wilcox M. Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter? *J Antimicrob Chemother.* 2012;67:2547-59. (Cites ref [4], p. 2555)

17. Meyer B and Cookson B. Does microbial resistance or adaptation to biocides create a hazard in infection prevention and control? *J Hosp Infect.* 2010;76:200-5. (Cites ref [4], p.203)

18. Evidence for use of octenisan in hospitals: Papworth Hospital NHS Foundation Trust DN339 MRSA Procedure. http://www.papworthhospital.nhs.uk/docs/policy/DN339_MRSA_Procedure.pdf

19. Patents: Bacteremia-associated antigen from Staphylococcus aureus; https://www.google.com/patents/WO2011058302A1?dq=edgeworth+J+2009&ei=OrcMUoSNOfDv0gXzgoHgCg&cl=en

20. Li M, Du X, Villaruz AE, et al. MRSA epidemic linked to a quickly spreading colonization and virulence determinant. *Nat Med.* 2012;18:816–19. (Cites refs [7,8] p.816).