Institution: University of Cambridge

Unit of Assessment: 6

Title of case study: Reduction of antibiotic use and methicillin-resistant *Staphylococcus aureus* (MRSA) in livestock agriculture

Period when the underpinning research was undertaken: 2011-2015

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:
Mark Holmes	Professor of Microbial Genomics and Veterinary Science	1991 to date
Duncan Maskell	Marks & Spencer Professor of Farm Animal Health, Food Science & Food Safety	1996 - 2018

Period when the claimed impact occurred: August 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 is one of the biggest challenges of the modern era. The major driver of antibiotic resistance in bacteria is exposure to antibiotics. Therefore, reducing inappropriate antibiotic use is one of the main interventions needed to address the problem of resistance. Research undertaken in the Department of Veterinary Medicine at the University of Cambridge identified a previously unknown MRSA (*mecC*) and generated epidemiological evidence of the burden of livestock-associated MRSA in the UK and internationally. The findings informed policy makers in the UK and Europe, resulting in policies to improve antibiotic stewardship. This contributed to a 45% reduction in antibiotic use in agriculture in the UK, with a 90% reduction in the use of third- and fourth-generation cephalosporins, the antibiotic class to which the *mecC* variant of MRSA is most resistant. UK sampling in 2017, 2018 and 2019 found no occurrence of the resistant strains *mecC* and *mecA* in food-producing animals.

2. Underpinning research (indicative maximum 500 words)

A substantial body of research undertaken in the Department of Veterinary Medicine at the University of Cambridge has identified a previously unknown MRSA and generated epidemiological evidence of the burden of livestock-associated MRSA in the UK.

Discovery of *mecC* MRSA

In 2012, Holmes and Maskell published their discovery of *mecC* MRSA, a novel variant of methicillin-resistant *Staphylococcus aureus* (MRSA) found in both livestock and people (R1). The *mecC* MRSA found in people was found in cases of clinical disease, ranging from skin and soft tissue infections, to bacteraemia and in asymptomatic carriers. Their findings represented a previously unidentified reservoir of infection, which had impact on our understanding of the epidemiology of MRSA and its management (*REF 2014*). Molecular studies of the PBP2a protein product of *mecC* identified a differential resistance to cephalosporins compared to other beta-lactam antibiotics (R2). Cephalosporin antibiotics, including third-generation cephalosporins, are commonly used in the treatment of bovine mastitis and this use is likely to be selecting for *mecC* MRSA.

Measuring the levels of *mecC* MRSA in UK livestock and human populations

Between 2011 and 2012, Holmes led formal epidemiological studies to determine the farm-level prevalence and the human prevalence of *mecC* MRSA in the UK. The farm level prevalence study found that *mecC* MRSA was present in the bulk milk from 10 of 465 dairy farms sampled in England and Wales, i.e. 2.15% (R3). With 8,310 dairy producers in the UK (source: AHDB 2020) this translates to approximately 178 farms with *mecC* MRSA. A study of human MRSA isolates from hospitals revealed that *mecC* MRSA accounted for 1 in 200 of all MRSA, a small but significant proportion, arising from strains that are believed to have originated from farms (R4).

Detection of livestock-associated *(mecA)* MRSA in dairy milk

Most of the MRSA leading to human disease is caused by *mecA* MRSA. Prior to Holmes' investigations it was believed that UK livestock were almost entirely free of this type of MRSA*, livestock-associated MRSA (LA-MRSA also known as ST398 MRSA), which has been a problem in continental Europe. A study undertaken on British dairy farms identified the presence of LA-MRSA in five of the farms surveyed (R5). Although pasteurisation of milk helps to reduce levels of ST398 MRSA entering the food chain, previous studies have shown that individuals with regular contact with infected livestock are likely to have a higher risk of colonisation or infection with LA-MRSA compared to the general population.

Detection of livestock-associated *(mecA)* MRSA in pork meat

In 2015 Holmes undertook a study of retail meat from supermarkets in six different regions of the UK. Over 100 pre-packaged fresh meat products, labelled as being of UK farm origin were analysed, and three pork products were found to contain isolates of ST398 LA MRSA with phylogenetic analysis indicating widespread infection within the UK pig herd (R6).

These formal epidemiological studies have provided baseline prevalence estimates of MRSA that have been used to identify changes in these rates. This body of work has provided objective information about the characteristics and the distribution of antibiotic resistant bacteria, of human medical importance, in livestock, and led to improved antibiotic stewardship in animal farming.

**There are 3 epidemiological patterns of conventional (mecA) MRSA. Hospital-acquired (HA-MRSA), Community-acquired (CA-MRSA) and Livestock-associated (LA-MRSA)*

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

R1 García-Álvarez L, Holden MT, Lindsay H, Webb CR, Brown DF, Curran MD, Walpole E, Brooks K, Pickard DJ, Teale C, Parkhill J, Bentley SD, Edwards GF, Girvan EK, Kearns AM, Pichon B, Hill RL, Larsen AR, Skov RL, Peacock SJ, **Maskell DJ, Holmes MA**. Methicillin-resistant *Staphylococcus aureus* with a novel mecA homologue in human and bovine populations in the UK and Denmark: a descriptive study. *Lancet Infect Dis*. 2011 Aug;11(8):595-603. doi: 10.1016/S1473-3099(11)70126-8. PMID: 21641281; PMCID: PMC3829197.

R2. Kim C, Milheiriço C, Gardete D, **Holmes MA**, Holden MTG, de Lencastre H, and Tomasz A. Properties of a novel PBP2A protein homologue from *Staphylococcus aureus* strain LGA251 and its contribution to the β-lactam resistant phenotype. 2012 *J. Biol. Chem*. Oct 26;287(44):36854-63.

R3. Paterson GK, Morgan FJE, Harrison EM, Peacock SJ, Parkhill J, Zadoks RN and **Holmes MA.** Prevalence and properties of mecC methicillin-resistant *Staphylococcus aureus* (MRSA) in bulk tank milk in Great Britain. *J Antimicrob Chemother*. 2014 Mar;69(3):598-602. doi: 10.1093/jac/dkt417. Epub 2013 Oct 23.

R4. Paterson GK, Morgan FJ, Harrison EM, Cartwright EJ, Török ME, Zadoks RN, Parkhill J, Peacock SJ, **Holmes MA**. Prevalence and characterization of human *mecC* methicillin-resistant *Staphylococcus aureus* isolates in England. *J Antimicrob Chemother*. 2014 Apr;69(4):907-10. doi: 10.1093/jac/dkt462. Epub 2013 Nov 27.

R5. Paterson GK, Larsen J, Harrison EM, Larsen AR, Morgan FJ, Peacock SJ, Parkhill J, Zadoks RN, **Holmes MA**. First detection of livestock-associated methicillin-resistant *Staphylococcus aureus* CC398 in bulk tank milk in the United Kingdom, January to July 2012. *Euro Surveill*. 2012 Dec 13;17(50): 20337.

R6. Hadjirin NF, Lay EM, Paterson GK, Harrison EM, Peacock SJ, Herrtage ME, Parkhill J, **Holmes MA.** Detection of livestock-associated methicillin-resistant *Staphylococcus aureus* CC398 in retail pork, United Kingdom, February 2015. *Euro Surveill*. 2015 Jun 18;20(24) doi: 10.2807/1560-7917.es2015.20.24.21156

Evidence of min 2* research quality: all publications were peer reviewed. Research supported by competitively won grant funding.

Competitively secured funding supporting this research
Medical Research Council (MRC) PI: Mark Holmes; Investigation of LA-MRSA in China and the UK (Jul 2016 - Jun 2019) GBP552,508
MRC PI: Mark Holmes Partnership to investigate the emergence of MRSA clones in cattle and their transmission to man. (Sep 2011 - Dec 2015) GBP1,277,018
MRC PI: Mark Holmes; Determination of the dynamics of antimicrobial resistance genes in the human and animal gut microbiome (Oct 2015 - Jan 2020) GBP1,588,479

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

Antimicrobial resistance is a global human and animal health concern. The Review on Antimicrobial Resistance commissioned by the UK Prime Minister, led by Jim O'Neill, reported in 2016 that approximately 9.3 million additional human deaths a year will be attributable to AMR by 2050 if nothing is done to address this problem, and identified agriculture as an area where intervention was required.

The research undertaken by Holmes and colleagues at the University of Cambridge has informed policy and contributed to improved antibiotic stewardship by a reduction of inappropriate use of antibiotics. This has led to a reduction in antibiotic use in livestock agriculture, and reductions in antibiotic resistance in bacteria.

Raised public awareness and development of new legislation
The discovery of *mecC* MRSA and the presence of LA-MRSA in the UK pig herd was published in articles in national newspapers, leading to public interest and concern [E1]. This publicity led to the submission of a written question in the UK Parliament to the Minister of State for Agriculture, Fisheries and Food by Kerry McCarthy MP (Bristol NE) on 7th October 2016 about the problem (E2); the minister responded that Defra were working with Public Health England to investigate the occurrence of LA-MRSA in veterinarians and farm workers.

Holmes' research was included in a motion discussed at a forum of European politicians, 19-21 November 2015, which contributed to the development of new legislation on the use of antibiotics in farming [E3]. A former UK Member of the European Parliament (MEP), who was part of the Alliance and Democrats for Europe (now Renew Europe) testifies to this: *"The research published by Holmes' group between 2011 and 2015…informed our discussions prior to our 2015 congress… This work helped us develop our response to the issue that was documented in a motion that the ALDE Party then pursued in the European Parliament. As a result of the campaigning new regulations on veterinary medicines (Regulation (EU) 2019/6) and medicated feed (Regulation (EU) 2019/4) were passed by the European Parliament and Council in late 2018."* The new legislation prohibits the prophylactic use of antibiotics other than in exceptional cases (E4, page 6 (schedule 44, page L 4/48)). As a farmer themselves, the former MEP commented that the resolution which was passed avoids undue bureaucracy and cost for farmers [E3].

Improved antibiotic stewardship

Research from Holmes' group has been part of a knowledge exchange relationship with the British Cattle Veterinary Association (BCVA) and British Veterinary Association (BVA) since 2011. An officer who has been Past President of both the BCVA and BVA states that Holmes' research provided evidence that helped inform the BCVA's position on antimicrobial use in cattle practice, which was published in 2016, and also work undertaken by the Responsible Use of Medicines in Agriculture (RUMA) to reduce antibiotic use (details below). The BCVA now runs courses on prescribing practices to better support vets in decision-making. He says that Holmes' "active engagement with the profession…has led to improved antibiotic stewardship, creating a positive impact on the farming sector" [E5].

Prior to the systematic survey of UK retail pork published by Holmes in 2015 (R6) there was only a single case report of ST398 LA-MRSA from Northern Ireland, and the UK pig herd was believed to be free from this MRSA strain. Following the work, Holmes was a named individual contributor to the Food Standards Agency report "Risk Assessment on Methicillin-Resistant Staphylococcus aureus (MRSA), with a focus on Livestock-associated MRSA, in the UK Food Chain", published in February 2017 [E6], which also references earlier research from the University of Cambridge ((R5) cited in points 106/107, page 30/31). This assessment states the high level of uncertainty around the role of agricultural transmission in infection sources and routes of transmission [E6, page 50].

In 2018, Holmes contributed to a workshop organised by the Pig Health and Welfare Council (PHWC) and the Agriculture and Horticulture Development Board (AHDB) which represents farmers, growers and others in the supply chain and have also worked directly with pig companies. He presented his research findings and suggested changes to practice with other experts in the field, and with key implementation stakeholders, i.e. those involved in pig farming and the food supply chain [E7]. Subsequently, in September 2018, the PHWC Antimicrobial Usage subgroup published new guidelines on the responsible use of antibiotics on pig farms. These clearly state that antibiotics should only be used on prescription, should only be used if/until alternative approaches are implemented, and that numbers of pigs receiving antibiotics should be kept to a minimum [E8]. As a key organisation leading professional practice in the sector, this guidance hold considerable influence for stakeholders and has led to reductions in antibiotic usage, detailed below.

Reduction in antibiotic use in livestock in the UK

The heightened awareness of antibiotic-resistant bacteria in animals farmed for food, along with the changes in policy and guidance described above have had significant impact on the use of antibiotics in pig and cattle farming. Official figures published by the Veterinary Medicines Directorate (VMD, an executive agency of Defra) on 18 November 2020 show that from 2014 to 2019, the amount of antibiotics sold for use in food-producing animal species was reduced by 45%. The largest single annual reduction, of 30% was seen between 2015 and 2016, which is after the publication of Holmes' group's paper on the detection of MRSA in pork (R6) [E9, page 13]. The VMD report also documents a reduction in use of all antibiotics in pigs of 60% from 2015 to 2019 [E9, page 32].

These data are from the VMD UK Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS) 2019, which also cites Holmes' research into MRSA in bovine populations [E9, (1) cited on page 32]. Following the stakeholder engagement described above, Holmes' research provided evidence that helped inform the British Cattle Veterinary Association (BCVA)'s position paper on antimicrobial use in cattle practice [E5], published in December 2016. This recommended reducing the overall amount of antibiotics used in cattle practice, with minimal use of third- and fourth-generation cephalosporins (the antibiotic class to which *mecC* MRSA is most resistant), and that that prophylactic use of antibiotics is to be avoided wherever possible [E10]. Holmes' research also informed the Responsible Use of Medicines in Agriculture (RUMA) Alliance Targets Task Force Report 2017, which set focus areas for the sector in order to target reduction of antibiotic usage, the first of these being overall reduction in the use of highest priority critically important antibiotics [E11, pages 14-17, involvement confirmed by E5].

The effect of this influence on change in practice can be seen in the latest figures published in UK-VARSS 2019, which shows that in dairy cows the use of third- and fourth-generation cephalosporins, was reduced by 90% [E9, page 42].

Reduction in prevalence of antibiotic resistance

Following the use of Holmes' research to inform the changes in recommended practice as described above, reduction in levels of antibiotic resistance in livestock pathogens has already been observed. The data in UK-VARSS 2019 on AMR in bovine *S. aureus* isolates reports that no *mecC* or *mecA* MRSA were found in 2017, 2018 or 2019; similarly, no LA-MRSA was found in food-producing animals in England, Scotland and Wales in 2019, with only four occurrences in Northern Ireland [E9, pages 64 and 72].

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

E1. Collated media articles showing public interest in prevalence of MRSA in food products
E2. UK Parliament written question from Kerry McCarthy MP – 47151: Pigs: MRSA
E3. Testimonial from former MEP linking research with development of EU directive
E4. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (published in the Official Journal of the European Union, 07 Jan 2019)
E5. Testimonial from past president of the British Cattle Veterinary Association and the British Veterinary Association.
E6. Risk Assessment on Methicillin-Resistant Staphylococcus aureus (MRSA), with a focus on Livestock-associated MRSA, in the UK Food Chain, Food Standards Agency, February, 2017. Mark Holmes, named contributor to this Report
E7. Pig Health and Welfare Council Biennial Report 2017-18. Page 50. Agreed actions from the LA-MRSA workshop held in Stoneleigh, 4th April, 2018
E8. PHWC Practical Guide to Responsible Use of Antibiotics on Pig Farms
E9. UK Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS 2019), published 18 November 2020
E10. BCVA promotes responsible use of antimicrobials. *Veterinary Record* **180,** 58, 2016
E11. Responsible Use of Medicines in Agriculture (RUMA) Alliance Targets Task Force Report 2017, pages 14-17