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Incidence and Characterisation of Methicillin-Resistant *Staphylococcus aureus* (MRSA) from Nasal Colonisation in Participants Attending a Cattle Veterinary Conference in the UK

Gavin K. Paterson¹, Ewan M. Harrison¹, Emily F. Craven¹, Andreas Petersen², Anders Rhod Larsen², Matthew J. Ellington³, M. Estée Török³,⁴,⁵, Sharon J. Peacock³,⁴,⁵, Julian Parkhill⁶, Ruth N. Zadoks⁷, Mark A. Holmes¹

¹ Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge, United Kingdom, ² Department of Microbiological Surveillance and Research, Statens Serum Institut, Copenhagen, Denmark, ³ Health Protection Agency, Microbiology Services Division Cambridge, Level 6 Addenbrookes Hospital, Cambridge, United Kingdom, ⁴ Department of Medicine, University of Cambridge, Addenbrooke’s Hospital, Cambridge, United Kingdom, ⁵ Cambridge University Hospitals National Health Service Foundation Trust, Cambridge, Cambridge, United Kingdom, ⁶ The Wellcome Trust Sanger Institute, Wellcome Trust, Genome Campus, Cambridge, United Kingdom, ⁷ Moredun Research Institute, Bush Loan, Penicuik, United Kingdom

Abstract

We sought to determine the prevalence of nasal colonisation with methicillin-resistant *Staphylococcus aureus* among cattle veterinarians in the UK. There was particular interest in examining the frequency of colonisation with MRSA harbouring mecC, as strains with this mecA homologue were originally identified in bovine milk and may represent a zoonotic risk to those in contact with dairy livestock. Three hundred and seven delegates at the British Cattle Veterinarian Association (BCVA) Congress 2011 in Southport, UK were screening for nasal colonisation with MRSA. Isolates were characterised by whole genome sequencing and antimicrobial susceptibility testing. Eight out of three hundred and seven delegates (2.6%) were positive for nasal colonisation with MRSA. All strains were positive for mecA and none possessed mecC. The time since a delegate’s last visit to a farm was significantly shorter in the MRSA-positive group than in MRSA-negative counterparts. BCVA delegates have an increased risk of MRSA colonisation compared to the general population but their frequency of colonisation is lower than that reported from other types of veterinarian conference, and from that seen in human healthcare workers. The results indicate that recent visitation to a farm is a risk factor for MRSA colonisation and that mecC-MRSA are rare among BCVA delegates (<1% based on sample size). Contact with livestock, including dairy cattle, may still be a risk factor for human colonisation with mecC-MRSA but occurs at a rate below the lower limit of detection available in this study.

Introduction

*Staphylococcus aureus* is an important opportunistic pathogen associated with nosocomial and community-acquired infections in people, and is responsible for disease in animals where it is most economically significant as a cause of bovine mastitis [1,2].

Methicillin-resistant *S. aureus* (MRSA) have acquired one of a number of staphylococcal cassette chromosome mec elements (SCCmec) [3], carrying a gene (mec) encoding a penicillin binding protein (PBP 2a) with low affinity for β-lactam antibiotics [4]. Since 2005 there have been a number of reports suggesting that the rate of carriage of MRSA is higher in people living or working on pig farms than in the wider community due to zoonotic acquisition of MRSA, primarily belonging to the clonal complex (CC) 398 lineage. Although initially associated with pigs, subsequent reports indicate that other domestic animal species are also affected includingveal calves [5], dairy cattle [6], poultry [7] and horses [8].

In 2011 we described a previously unreported divergent mecA homologue [9]. Genome sequencing revealed a mecA homologue (mecAALGA251, now designated mecC [10]) within a new SCCmec element (type XI). A search of human and bovine isolates, suggesting transmission between the two host populations. Strengthening this supposition of interspecies transmission, work in Denmark has identified mecC MRSA human isolates from two different farms that are identical by sequence.
Between host species [12]. Little is known of the epidemiology of genome, substantiating that transmission events had occurred by only a few single nucleotide polymorphisms across the core sequencing revealed that these human and animal isolates differed cattle or sheep on those farms [11]. Subsequent genome Sample Collection and Processing Study Setting and Participants Antimicrobial Resistance Testing

Antimicrobial susceptibility testing was performed by disc diffusion (Oxoid, Basingstoke, UK) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology (www.eucast.org, (v 2.1, 7 Feb 2012)) for 12 antimicrobial agents: penicillin, cefoxitin, norfloxacin, erythromycin, clindamycin, kanamycin, tetracycline, linezolid, fusidic acid, rifampicin, trimethoprim/sulfamethoxazole and mupirocin. All susceptibility results were interpreted according to EUCAST guidelines with the exception of trimethoprim/sulfamethoxazole, for which interpretation was made according to CLSI guidelines. In addition the MIC was determined for cephalixin and oxacillin by microbroth dilution performed as described by EUCAST using Mueller Hinton BBL II broth (Becton Dickinson, Heidelberg, Germany) and a final inoculum of 5×10^5 CFU. S. aureus ATCC 29213 was used for quality control.

Genome Sequencing and Analysis

Genomic DNA was extracted from overnight cultures by MasterPure™ Gram Positive DNA Purification Kit (Cambio, Dry Drayton, UK) and sequenced by HiSeq 2000 (Illumina Inc., Little Chesterfield, UK). Multi-locus sequence types and SCCmec types were derived from the genome sequences and antimicrobial resistance determinants identified by BLAST analysis [24].

Ethics Study protocol was submitted for consideration for ethical review to the National Research Ethics Service (East of England), which reported that formal ethical approval was not required for this study because the subjects were healthy individuals in a non-healthcare environment, non-invasive sampling was used, and no human tissues were being collected. Delegates who volunteered to be swabbed were provided with an information sheet about the study and provided written informed consent for participation in the study.

Statistics Statistical analysis was performed using SPSS v20 (IBM Corporation). The threshold for statistical significance was an alpha error of 0.05. The Mann-Whitney U Test was used to compare the time since subjects were last on a farm for MRSA positive and negative subjects as this data was not normally distributed.

Results and Discussion MRSA Carriage Amongst Study Participants From the 307 swabs taken, eight produced growth characteristic of MRSA on MRSA Brilliance 2 plates, giving an overall carriage prevalence of 2.6% (95% CI 1.1–4.1%). The approximate geographical location of the primary work address reported by UK subjects is shown in Figure 1. Unsurprisingly, these locations reflect the general distribution of dairy farming in the UK (cattle farms in the UK are concentrated in western regions). The primary place of work of nine participants was outside the UK. The MRSA carriage rate in the general population has been reported to be in the range of 0.8–1.3% [25,26,27,28]. The observed MRSA colonisation rate in delegates at the BCVA 2011 conference of 2.6% was higher than the rate expected in the general population, but lower than the 4.6% observed in human healthcare workers [29] as well as the carriage rates obtained from screening attendees at other veterinary conferences, Table 1. For instance, a survey of Dutch veterinarians and veterinary students found an overall carriage rate of 4% [30], and a survey of British
small animal veterinarians found a rate of 17.9% [31]. Participants at veterinary conferences provide a convenient sample of veterinary practitioners. Although a proportion of people attending these conferences may have little direct contact with animals (e.g. company sales representatives, students or academics, industry and government veterinarians), the majority of participants are likely to have frequent, direct interactions with animals under their care. The median time between swabbing and last visit to a farm was shorter in the MRSA-positive group (median = 1 day, range 1–14 days) than in the MRSA-negative group (median = 3 days, range 0.1–365 days) although not statistically significant using a Mann-Whitney U Test (p = 0.08). The Australian study of a number of different conferences provides a useful comparison of veterinarians working with different species, and reported a 4.7% MRSA carriage rate in veterinarians working with cattle, although this figure has wide confidence intervals (0.57–15.81) due to the small denominator (n = 45) [32]. The carriage rate in small animal veterinarians was comparable (4.9%, n = 430), while the carriage rate in equine veterinarians was considerably greater (11.9%, n = 202) [33]. There are however differences in methodology between studies which may affect rates of isolation and it should be noted that the lack of a broth enrichment step may have reduced the sensitivity of MRSA detection in this survey.

The occupational nature of the risk association with MRSA carriage suggested in this study is strengthened by the association between a subject’s recent presence on a farm and them testing positive for MRSA. It is reasonable to suggest that participants at the congress who had recently visited a farm were more likely to be actively engaged in clinical work on farms and therefore have increased exposure to livestock, and/or, that colonisation by MRSA is rapidly lost after occupational exposure. In support of these suggestions, there is evidence that carriage rates of livestock-associated CC398 MRSA in veal calf farmers are associated with intensity of animal contact and rapidly decrease in the absence of contact with livestock [34]. While the increased rate of MRSA carriage in human health workers might be explained by greater exposure to MRSA through close contact with patients with MRSA and associated fomites. This is less likely to be the situation in veterinary medicine as there is no evidence of high carriage rates of MRSA in UK livestock. The occupational risk of MRSA acquisition and carriage by veterinarians may be associated with working in environments where antibiotics are present, which might offer a selection advantage to colonising bacteria that are resistant. In this regard even low, sub-inhibitory concentrations may be sufficient to provide a selective advantage to resistant strains [35]. Alternatively or additionally, many SCCmec elements contain genes that provide resistance to other bactericidal agents (e.g. the arsenical resistance gene in type XI SCCmec) [36]) and these could explain an increased survival of MRSA in veterinary environments.

**Characterisation of Methicillin-resistant Staphylococci from Study Participants**

All eight MRSA isolates where femB and mecA gene positive by PCR but negative for mecC. Genome sequencing confirmed each isolate as being mecA-positive MRSA, and selected genotypic and phenotypic characteristics are shown in Table 2. Antimicrobial susceptibilities were compared with the presence/absence of known resistance determinants or mutations (the so-called ‘resistome’) [37]. As described previously for ST22 MRSA [37], antimicrobial phenotypes and genotypes in our study show concordance, further supporting that whole-genome sequencing may in future have a role in informing therapy and represents a powerful tool for the discovery of new drug-resistance mechanisms [9].

There were three methicillin-resistant non-S. aureus isolates that grew on MRSA Brilliance 2 agar, which were identified as *Staphylococcus haemolyticus* by MALDI-TOF. By PCR these were negative for femB and mecC but positive for conventional mecC and each showed resistance to several other antibiotics, Table 3. These displayed relatively high MICs to oxacillin and cephalxin and resistance to multiple other antibiotics. Little data are available on carriage rates of *S. haemolyticus* but it is a nosocomial pathogen characterised by resistance to multiple antimicrobial agents [38,39].

The ST398 MRSA isolated in this study came from a delegate from continental Europe where ST398 is the predominant lineage of LA-MRSA. In the UK MRSA ST398 is apparently rare with only two published reports to date [40] [41], including our recent description of MRSA ST398 isolated from bulk tank milk from five dispersed UK dairy farms which may represent an emerging problem in the UK [41]. Heterogeneity is seen within the ST398 population with human and livestock-associated lineages differentiated by the presence or absence of specific virulence factors and resistance genes [42,43]. The absence of the *sak*, *cph*, and *acr* genes and the presence of *tet(M)* in BCVA198 indicates that it belongs to the livestock-associated lineage.

Four of the eight MRSA isolates belonged to CC22. BCVA7, 182 and 191 were ST22 while BCVA16 was a novel single locus variant in *arcC*, ST2274. CC22 is a diverse and widespread lineage common in many countries [44,45], including in England where it was responsible for >75% of MRSA bacteraemia between 2001–7 [46]. In addition to its importance in human, this lineage has also been isolated from a range of animals: cats, dogs, horses, bats, turtles, pet birds, pigs and goats [31,47,48,49,50,51]. While it has yet to be

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**Table 1. A summary of the results from previous MRSA carriage surveys undertaken at veterinary or animal health conferences.**

| Conference            | Country   | Year | MRSA rate | No. of subjects | Reference |
|-----------------------|-----------|------|-----------|-----------------|-----------|
| Cattle                | UK        | 2011 | 2.6%      | 308             | This study |
| Pig Health            | Denmark   | 2006/7 | 12.5%     | 272             | [64]      |
| Multiple              | Denmark   | 2006/7 | 1.9%      | 574             | [65]      |
| ACVIM                 | USA       | 2005 | 6.5%      | 417             | [66]      |
| AAEP                  | USA       | 2006 | 10.1%     | 257             | [67]      |
| ACVS                  | USA       | 2008 | 17.3%     | 341             | [68]      |
| Multiple              | Australia | 2009 | 5.8%      | 771             | [33]      |
| Dermatology           | Italy     | 2010 | 1.6%      | 128             | [69]      |

ACVIM, The American College of Veterinary Internal Medicine; AAEP, American Association of Equine practitioners; ACVS, American College of Veterinary Surgeons.

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Table 2. Characteristics of the eight MRSA isolates found in the survey of conference participants.

| Strain          | Region of workplace of subject | Clonal Cluster | spa type | SCC type | mec type | Resistant to antibiotic | Additional resistance 1 | Resistance determinates 2 |
|-----------------|--------------------------------|----------------|----------|----------|----------|-------------------------|--------------------------|---------------------------|
| BCVA7 ST22 CC22| Somerset, England              | CC22 type IVa  | t032     | SCC t032 | mecA     | 128/128                 | NOR, ERY, CLI            | GyrA S84L,ermC,ermT       |
| BCVA16 ST22 CC22| Cornwall, England              | CC22 type IVa  | t032     | SCC t032 | mecA     | 128/128                 | NOR, ERY, CLI            | GyrA S84L,ermC,ermT       |
| BCVA42 ST2014 CC22| Continental Europe              | CC22 type IVa  | t032     | SCC t032 | mecA     | 128/128                 | NOR, ERY, CLI            | GyrA S84L,ermC,ermT       |
| BCVA14 ST22 CC22| Devon, England                 | CC22 type IVa  | t032     | SCC t032 | mecA     | 128/128                 | NOR, ERY, CLI            | GyrA S84L,ermC,ermT       |
| BCVA296 ST59   | Gloucestershire, England       | CC59 type IVa  | t032     | SCC t032 | mecA     | 128/128                 | NOR, ERY, CLI            | GyrA S84L,ermC,ermT       |

1 Susceptibilities tested: linezolid, rifampicin, kanamycin, tetracycline, trimethoprim, mupirocin, fusidic acid, tetracycline, trimethoprim/sulfamethoxazole and mupirocin.  
2 Genome screened for M21136, tetM, ermC, ermT, SCCmec-IVa, Panton-Valentine leukocidin (PVL)-positive, arginine catabolic mobile element-positive, and having more than six AT repeats within the SACOL005 locus (a feature used in combination with PVL for PCR identification of USA300 strains).  

The aim of this study was to look for evidence of transmission between cow and humans of MRSA harbouring the newly described mecA homologue mecC. The failure to detect any mecC MRSA isolates provides evidence to indicate that the carriage rate of these MRSA strains in UK cattle veterinarians is likely to be less than 1%. A calculation of the binomial exact confidence intervals reveals that our sample size of 307 would have had a 95% probability of finding at least 1 positive result if the prevalence had been 1%. However, the prevalence of MRSA among UK cattle, both mecA and mecC MRSA, is not yet known so it is unclear how likely occupation exposure is for cattle veterinarians. The origins and epidemiology of MRSA mecC, including the risk factors associated with its acquisition remain unclear. Prevalence studies in the general population and in dairy cattle are currently underway in the UK. Recent contact with dairy cattle may yet be an important risk factor for human colonisation with mecC-MRSA but occurs at rates below the lower limit of detection in this study.
Table 3. Characteristics of the three S. haemolyticus isolates found in the survey of conference participants.

| Strain     | Oxacillin MIC (mg/l) | Cefoxitin MIC (mg/l) | Additional resistances† |
|------------|----------------------|----------------------|-------------------------|
| BCA70      | >128                 | 64                   | KAN, NOR, ERY, CLI, TET, |
| BCA233     | >128                 | >256                 | KAN, NOR, ERY, CLI, FUS, TET, SXT |
| BCA257     | >128                 | 256                  | KAN, NOR, ERY, CLI, FUS, TET, SXT |

†Susceptibility tested: linezolid, rifampicin, kanamycin, norfloxacin, erythromycin, clindamycin, fusidic acid, tetracycline, trimethoprim/sulfamethoxazole and mupirocin.

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