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'Feral' and 'wild'-type methicillin-resistant *Staphylococcus aureus* in the United Kingdom

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SUMMARY

Circulation of methicillin-resistant *Staphylococcus aureus* (MRSA) outside hospitals could alter the impact of hospital-based control strategies. We investigated two groups of cases (each matched to controls with MRSA): 61 'community cases' not in acute hospital in the year before MRSA isolation; and 21 cases with ciprofloxacin-sensitive (CipS) MRSA. Multi-locus sequence typing, *spa*-typing and Panton–Valentine leukocidin gene testing were performed and demographics obtained. Additional questionnaires were completed by community case GPs. Community cases comprised 6% of Oxfordshire MRSA. Three community cases had received no regular healthcare or antibiotics: one was infected with CipS. Ninety-one percent of community cases had healthcare-associated sequence type (ST)22/36; CipS MRSA cases had heterogeneous STs but many had recent healthcare exposure. A substantial minority of UK MRSA transmission may occur outside hospitals. Hospital strains are becoming 'feral' or persisting in long-term carriers in the community with regular healthcare contacts; those with recent healthcare exposure may nevertheless acquire non-hospital epidemic MRSA strains in the community.

Key words: Community, MRSA, nosocomial.

INTRODUCTION

Many regions have seen rises in methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitalized patients over the last 15 years with one or two specific lineages dominating per country. For example, the two main UK MRSA lineages, sequence type (ST)22 (EMRSA-15) and ST36 (EMRSA-16), account for nearly all UK invasive disease [1], predominantly occurring in older people with extensive comorbidities and substantial hospital exposure. Major UK policy initiatives, including the introduction of widespread screening and decolonization [2], are currently underway in an effort to contain ongoing MRSA transmission in hospitals. The scientific rationale for focusing on in-hospital transmission comes from mathematical modelling studies demonstrating that hospital-based interventions could effectively eradicate MRSA from the entire population [3, 4], and observations of relatively low community MRSA

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prevalence, mostly relating to very recent hospital exposure. However, as explicitly noted by Cooper *et al.* [3] the degree to which ongoing MRSA transmission within non-hospital compartments could substantially alter the impact of control strategies based on interrupting within-hospital transmission is unknown.

There are two reservoirs which could potentially feed ongoing non-hospital MRSA transmission. The first is nosocomial MRSA lineages which have escaped from hospitals into the community, termed 'feral' MRSA [5] to distinguish them from strains transmitting in hospital. The implication is that such feral strains are being transmitted in the community between individuals without recent hospital exposure. Other distinct MRSA strains may undergo clonal expansion in specific community niches, a recent example being USA300 [multi-locus sequence type (MLST)8] causing major outbreaks of community-acquired staphylococcal infections in North America [6, 7]. These community or 'wild' MRSA lineages, that are unrelated to healthcare, are typically susceptible to most antibiotics including quinolones [8].

Given the relatively low community MRSA prevalence in the UK, directly estimating ongoing community transmission of MRSA would require repeatedly screening large numbers of individuals (mostly non-carriers) over long periods of time. Before embarking on such a wide-scale approach, here, we therefore use two complementary case-control studies to systematically investigate the potential for 'feral' and 'wild' MRSA to be circulating in Oxfordshire in order to inform discussions around the future burden and management of UK MRSA.

METHODS

Case and control selection

We considered two sets of cases selected from all MRSA isolations at the Oxford Radcliffe microbiology laboratories, which include bacteriology services to ~600 000 people and test samples taken inside and outside the Oxford Radcliffe Hospitals (ORH). The first set was designed to identify feral (nosocomial epidemic) strains and wild (non-nosocomial epidemic) strains that could be transmitting in the community. It comprised individuals who had not been in an acute hospital in the year prior to MRSA isolation, i.e. it excluded recent acute hospital exposure which is a clear route for in-hospital MRSA acquisition of epidemic strains. The second set was individuals with ciprofloxacin-sensitive (CipS) MRSA identified from routinely generated resistance profiles as a marker of wild community disease [9].

For the first set of cases, structured questionnaires identifying risk factors for MRSA acquisition were sent to the GPs of all individuals who had MRSA isolated from a clinical or screening sample between 13 February–22 April and 24 July–11 November 2007 (intervening period excluded due to temporary absence) and had not been an in-patient or out-patient in the previous year according to ORH electronic records, other than in the preceding 24 h. Cases were all those without in-patient or out-patient exposure in *any* acute hospital in the last year from electronic records and the questionnaire, denoted *community cases* as they may represent 'community' MRSA acquisition. A hospital-exposed control was identified for each case, namely an individual with MRSA isolated on the same (or consecutive) day who had been an in-patient or out-patient in ORH in the previous year.

The second set of cases were individuals with CipS MRSA isolated from clinical or screening samples (*CipS cases*), from the two time periods above and 1 June 2006–31 January 2007 (the duration of archived samples). CipS MRSA cases were also randomly assigned ciprofloxacin-resistant (CipR) controls from the same time period. To increase the number of CipS strains and allow comparison with another area of the UK, a set of isolates from Brighton and Sussex University Hospitals collected between January and October 2007 was included (without controls).

Data collection

The structured questionnaire sent to the GPs of potential community cases was designed to identify prior hospital exposure outside of ORH and other healthcare-associated risk factors for MRSA acquisition and was therefore not sent to hospital-exposed controls. The questionnaire collected dates, durations and locations of (i) hospital in-patient stay(s) (acute or non-acute), (ii) hospital out-patient visit(s), (iii) nursing-home residence, (iv) regular care from practice nurses (e.g. wound dressing), (v) indwelling catheters or invasive procedures, and (vi) antibiotics during the year preceding MRSA isolation. All but one of the GPs contacted replied. Individuals with no identified or only antibiotic risk factors were investigated further through GP records. For CipS cases and CipR and hospital-exposed controls, previous

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MRSA isolation and basic demographics, including last in-patient or out-patient ORH exposure, were collected from electronic records.

This epidemiological study was covered by Statutory Instrument Regulations 2002 No. 1438, section (iii) 'Communicable disease and other risks to public health (Health Service Control of Patient Information)' of section 60 of the Health and Social Care Act [10] in line with HPA policy; therefore MREC approval was not required.

Microbiology

S. aureus isolates were recovered from glycerol stocks. Identity and sensitivity testing was performed using colonial morphology, tube coagulase, DNAse testing, MRSASelect® chromogenic agar (Bio-Rad, Ireland), and growth on oxacillin plates (E and O Laboratories, UK) following standard methods [11]. Final confirmation of MRSA was through identification of the *mecA* gene by PCR [12]. CipS cases were initially identified through ORH routine testing then susceptibility to ciprofloxacin in community cases, CipS cases and CipR controls was confirmed using E-tests (Bio-stat, UK). DNA was extracted from single colonies and grown overnight in a 5% salt broth (NaCl) (E and O Laboratories) at 37 °C using a DNEasy tissue kit (Qiagen, UK).

PCR

All isolates were tested for 16S rRNA, *lukS/F-PV* and *mecA* using a multiplex PCR [12], modified as previously described [13]. A clinical MRSA isolate from our hospital, isolate 212 (16S rRNA+, *lukS/F-PV*–, *mecA*+) and V7 (16S rRNA+, *lukS/F-PV*+, *mecA*–) (a kind gift of Dr A. Kearns, HPA) were used as positive controls for PCR.

MLST

MLST was performed essentially as previously described [14], noting improved performance using primer pairs that we developed [13]. DNA amplification was performed in a PTC-200 Peltier Thermal Cycler (MJ Research, USA) in a final volume of 25 μl containing 2·5 μl 10 × PCR buffer (Qiagen), 0·125 μl *Taq* DNA polymerase (Qiagen), 0·05 μl forward and reverse primer (Operon Scientific, Germany), 0·0125 μl each dNTP (Invitrogen, UK) and 1 μl DNA. Sequences were read using an ABI 3730xl DNA instrument. Sequence type was determined by comparing the seven alleles with strains of known allele number on the MLST database (http://www.mlst.net).

spa typing

spa typing was performed as previously described [15], modified by the use of primer pairs, developed to increase the amplicon size, thus improving both the yield of DNA from precipitation and the sequence quality at both ends. Primers were as follows:

spa2for: AAMYGAAGAACAACGTAACGGC

and

spa2rev: TAATAACGCTGCACCTAASG.

DNA amplification was performed as for MLST and *spa* types assigned using RidomStaphType software (Ridom GmbH, Germany), modified primers had no adverse effect on assigning *spa* type with Ridom software.

Statistical analysis

The aim was to recruit 60 community cases so that the 95% confidence interval (CI) around an observed prevalence of non-hospital STs of 0% was 0–5%. All CipS cases from archived strains and during the prospective study were to be included. Results were analysed using SPSS version 14.0 (SPSS Inc., USA). Fisher's exact and rank-sum tests were used to compare categorical and continuous variables, respectively, between cases and controls, with logistic regression with backwards elimination (exit $P > 0{\cdot}05$) for multivariable modelling. Time-to-event outcomes were analysed using Kaplan–Meier plots and logrank tests. P values of $< 0{\cdot}05$ were considered statistically significant.

RESULTS

Between 13 February–22 April 2007 and 24 July–11 November 2007, 1015 patients had MRSA isolated by ORH microbiology laboratories (Fig. 1). GPs were contacted for 105/121 individuals with samples taken outside or within 24 h of admission and no electronic record of ORH in-patient or out-patient exposure in the last year (16 had no GP recorded so were conservatively assumed not to be cases). From the GP questionnaire 41/105 had actually been acute hospital in-patients or out-patients in the last year (either in

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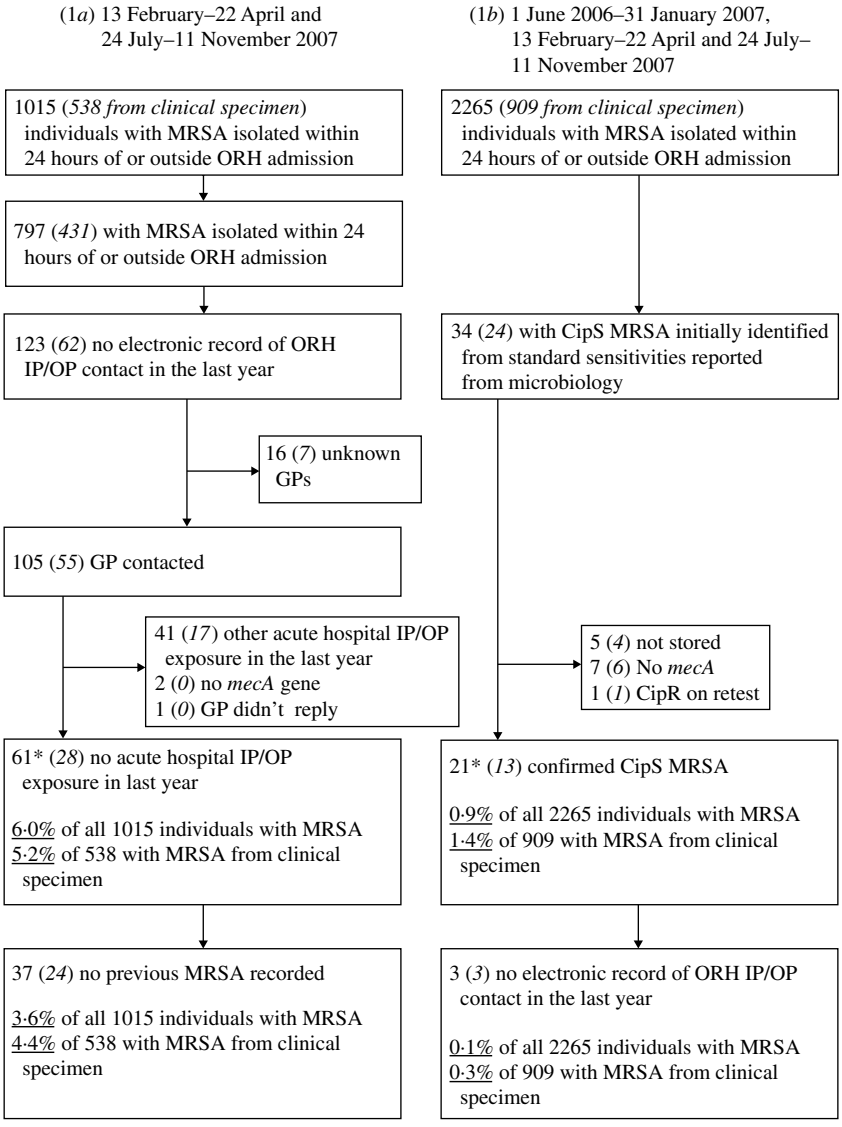

Fig. 1. Case selection. The flow diagram shows selection of community cases (1*a*) and ciprofloxacin-sensitive (CipS) cases (1*b*). Each box gives the total number of individuals fitting that classification. Numbers in parentheses are the number of individuals in that group with clinical samples. ORH, Oxford Radcliffe Hospitals; IP, in-patient; OP, out-patient; CipR, ciprofloxacin-resistant.

ORH not recorded or in another trust), and on confirmatory testing two isolates were not MRSA (no *mecA* gene), and one GP did not reply, leaving 61 confirmed community cases (6·0% of all individuals with MRSA), each with a hospital-exposed control. In these periods 21 confirmed CipS cases were identified (0·9% of individuals with MRSA), each with a CipR control. Between 1 June 2006 and 31 January 2007 eight additional CipS cases were identified retrospectively in Oxford (Fig. 1) and between January and October 2007, 18 CipS strains were obtained from Brighton. All but one community case was ciprofloxacin-resistant.

Community cases were last discharged from hospital a median of 34 months ago (Table 1), and 10 (16%) had no previous ORH in-patient/out-patient visits recorded at all. Although hospital-exposed MRSA controls were chosen to have acute hospital exposure within the last year, most had very recent exposure (median 12 days since last discharged). While, as expected, community cases were predominantly samples sent in from GPs, a substantial minority ($n=12$) came from both admission MRSA and non-acute hospitals. Older age, female gender and fewer hours previously spent as an ORH in-patient were univariably (Table 1) and multivariably

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Table 1. *Characteristics of community cases, hospital-exposed controls, CipS cases and CipR controls at MRSA isolation*

	Community case* (*N*=61) *n* (%) or median (IQR)	Hospital-exposed control*† (*N*=61) *n* (%) or median (IQR)	*P* value community case *vs.* hospital-exposed control	Oxford CipR control† (*N*=21) *n* (%) or median (IQR)	Oxford CipS case (*N*=21) *n* (%) or median (IQR)	*P* value CipS case *vs.* CipR control (Oxford)	Brighton CipS (*N*=18) *n* (%) or median (IQR)
Age (years)	82 (64–90)	72 (55–81)	0·001	74 (65–82)	37 (13–67)	<0·001	56 (21–80)
Sex (male)	19 (31%)	37 (61%)	0·002	9 (43%)	13 (62%)	0·35	10 (56%)
Previous ORH in-patient/out-patient visit recorded in							
Last 3 months	0 (0%)	56 (92%)	—	19 (90%)	14 (67%)	0·13	9 (50%)
Last year	0 (0%)	61 (100%)	—	21 (100%)	18 (86%)	0·23	10 (56%)
Last 3 years	35 (57%)	61 (100%)	<0·001	21 (100%)	18 (86%)	0·23	10 (56%)
Ever	51 (84%)	61 (100%)	0·001	21 (100%)	18 (86%)	0·23	10 (56%)
Days since last in ORH as in-patient or out-patient‡	1020 (626–1835)	12 (0–44)	<0·001	6 (0–28)	28 (3–105)	0·03	84 (0, –)
Hours previously spent in ORH as in-patient‡	41 (0–1162)	698 (47–1716)	0·005	722 (392–1346)	79 (0–318)	<0·005	<0·005
MRSA previously isolated at ORH (any sample)‡	24 (38%)	19 (31%)	0·45	11 (52%)	4 (19%)	0·05	3 (17%)
Antibiotic resistance							
Ciprofloxacin	56/57 (98%)	59/59 (100%)	0·49	21/21 (100%)	0/21 (0%)		0/18 (0%)
Erythromycin	34/60 (57%)	35/59 (69%)	0·85	18/21 (86%)	6/21 (29%)	<0·001	10/18 (56%)
Fusidic acid	2/60 (3%)	1/58 (2%)	1·00	0/15 (0%)	7/15 (7%)	0·006	9/18 (50%)
Gentamicin	0/60 (0%)	2/59 (3%)	0·24	0/21 (0%)	0/18 (0%)	1·00	0/18 (0%)
Mupirocin	2/60 (3%)	3/57 (5%)	0·67	0/20 (0%)	3/20 (15%)	0·23	1/18 (6%)
Netilmicin	0/60 (0%)	0/58 (0%)	1·00	0/20 (0%)	0/21 (0%)	1·00	
Oxacillin	57/60 (95%)	59/59 (100%)	0·24				
Penicillin	60/60 (100%)	59/59 (100%)	1·00	21/21 (100%)	20/21 (95%)	1·00	18/18 (100%)
Rifampicin	3/60 (5%)	0/58 (0%)	0·24	1/20 (5%)	1/21 (5%)	1·00	1/18 (6%)
Tetracycline	2/60 (3%)	6/59 (10%)	0·16	0/21 (0%)	1/21 (5%)	1·00	3/18 (17%)
Vancomycin	0/59 (0%)	0/60 (0%)	1·00	0/21 (0%)	0/21 (0%)	1·00	0/18 (0%)
Number of resistant antibiotics§	3 (2–3)	3 (2–3)	0·74	3 (33)	2 (1–2·5)	<0·001	2 (1–3)
Sample sent from							
GP	47 (77%)	11 (18%)	<0·001	8 (38%)	6 (29%)	0·47	7 (39%)
Acute hospital <24 h	6 (10%)	17 (29%)		4 (19%)	6 (29%)		4 (22%)
Acute hospital >24 h	0 (0%)	27 (44%)		7 (33%)	4 (19%)		4 (22%)
Non-acute/community hospital	6 (10%)	6 (10%)		2 (9%)	5‖ (24%)		3§ (17%)
Nursing home	1 (2%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)
Sample type							
Screening sample	23 (38%)	34 (56%)	0·11	6 (29%)	8 (38%)	0·30	0 (0%)
Surface culture	33 (54%)	20 (33%)		10 (48%)	12 (57%)		11 (61%)
Surface culture & screen	2 (3%)	3 (5%)		0 (0%)	0 (0%)		0 (0%)
Other clinical sample	3 (5%)	2 (3%)		5 (24%)	1 (5%)		7 (39%)

CipS, Ciprofloxacin-sensitive; CipR, ciprofloxacin-resistant; IQR; inter-quartile range; ORH, Oxford Radcliffe Hospitals.

* Community cases had no acute hospital exposure in ORH or another acute trust in the year prior to MRSA isolation, healthcare-exposed controls had MRSA isolated within ±1 day and had ORH hospital exposure in the previous year.

† Hospital-exposed controls and CipR controls did not differ significantly in any categories other than sample type ($P=0{\cdot}009$).

‡ For Brighton strains: details from Brighton and Sussex University Hospital.

§ Excluding oxacillin (i.e. score out of 10) Brighton CipS also excluding netilmicin (i.e. out of 9). Missing susceptibilities to individual antimicrobials classified as sensitive (4 Community caseS, 4 hospital-exposed controlS, 7 CipS, 6 CipR).

‖ One from prison.

P values are rank-sum or two-sided exact tests for continuous and categorical variables respectively, other than for days since last in hospital where Kaplan–Meier medians and quartiles, and log rank test are used.

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associated with being a community case [adjusted odds ratio (aOR) 1·03, 95% CI 1·01–1·05 per year older; 2·44 (95% CI 1·06–5·56) *vs.* males; 0·56 (95% CI 0·39–0·80) per 10-fold longer, respectively]. After adjustment for these factors, community cases were also more likely to have had MRSA previously isolated than healthcare-exposed controls (aOR 2·96, 95% CI 1·15–7·60).

CipS cases and CipR controls univariably (Table 1) and multivariably differed between age (aOR 0·002, 95% CI 0·92–0·98 per year older). One community case and CipS case was in common; a 37-year-old woman with no previous MRSA isolation, last in hospital 20 months previously, with a clinical GP sample.

Of the risk factors investigated in community cases (Table 2), the most common was antibiotics in the past year in 46 (75%) patients, followed by regular care (56%). Community cases had a median of two [inter-quartile range (IQR) 1–3, range 0–5] risk factors excluding previous MRSA isolation, with regular care and antibiotics the most common combination ($n=9$). Of the 18 (30%) community cases meeting the CDC definition for community-acquired MRSA (CA-MRSA) [13], only three had no other risk factors and 10/18 (56%) had received each of regular care and antibiotics. Of the community cases not meeting CDC CA-MRSA definition, those with previous MRSA were significantly less likely to have had a non-acute hospital out-patient appointment in the last year ($P=0·007$) and tended to be more likely to have had a catheter or invasive procedure in the last year ($P=0·06$) (Table 2).

Further investigation of eight community cases with no previous MRSA isolation and no other risk factors ($n=3$) or only antibiotics ($n=5$) showed four had healthcare risk factors unreported on the questionnaire [nursing-home residence ($n=1$), regular GP/nursing care ($n=2$), non-acute out-patient in the last year ($n=1$)], two worked as nurses and one had acute hospital contact 13 months previously; all seven isolates were healthcare-associated ST22. The remaining community case was ST840 and was also the CipS CDC CA-MRSA case (described above). ST840 differs from the globally spread lineage ST5 (EMRSA-3) [16] by just one single nucleotide polymorphism.

Microbiological typing showed that similar proportions of community cases and hospital-exposed controls were ST22 (79%, 81%, respectively) or ST36 (12%, 10%, respectively) (Table 3). Additionally, the STs of two community cases and four hospital-exposed controls differed from ST22 in only one allele. The remaining four community cases and one hospital-exposed control had STs that are not UK epidemic strains. The three non-healthcare associated STs in community cases were all in MLST clonal complex (CC)5, and one was also a CipS case. None of the community cases or hospital-exposed controls had the Panton–Valentine leukocidin (PVL) genes. *Spa* typing supported results found using MLST (Table 3, Fig. 2).

Whereas we found no evidence of a different ST distribution between community cases and healthcare-exposed controls ($P=0·27$), the Oxford CipS strains were more heterogeneous with significantly different STs from CipR and healthcare-exposed controls ($P<0·001$) (Table 3). Only 3/21 (14%) CipS cases were UK epidemic strains ST22 or ST36. Five isolates were ST1 (24%), three were ST526 (CC5) and all other STs had frequencies of two or fewer, although seven (33%) were from CC5. In contrast, CipR controls were much more homogeneous with 20/21 ST22 or ST36, similarly to hospital-exposed controls ($P=0·46$). CipS strains from Brighton were also heterogeneous with no strains from ST22 or ST36, but 8/18 (44%) strains ST1. *Spa* types for CipS cases were similarly more heterogeneous (Table 3, Fig. 2).

The five Oxford and eight Brighton CipS ST1 strains were all *spa* t127 and PVL negative, a distinct strain as neither this ST nor *spa* type can be grouped in a clonal complex with any others found in this study. The five Oxfordshire CipS ST1 t127 strains were isolated from patients of varying ages from 8 to 69 years, four having been in hospital in the last 100 days and one without prior hospital exposure recorded (GP not recorded, therefore not contacted as a community case). Additionally one Oxfordshire and four Brighton CipS strains had the PVL genes (13%) (Table 3, Fig. 2). The Oxfordshire strain with PVL was ST8 *spa* t088 isolated from a surface culture from a 20-year-old male, the same ST as community-associated USA300 [17].

Considering the relationship between *spa* types of all strains studied (see Supplementary Fig., available online), we found most community-case strains clearly grouped with hospital-exposed and CipR controls, even those that fitted the CDC CA-MRSA definition.

DISCUSSION

MRSA in the UK has traditionally been viewed as hospital-acquired [3, 18]. Here we have demonstrated

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Table 2. *Risk factors for MRSA isolation in different categories of MRSA community cases*

	All community cases ($N=61$) *n* (%)	CDC CA-MRSA* community cases ($N=18$) *n* (%)	Non-CDC CA-MRSA* community cases with previous MRSA ($N=24$) *n* (%)	Non-CDC CA-MRSA* community cases with no previous MRSA ($N=19$) *n* (%)	*P* value across three groups [non-CDC CA-previous MRSA] *vs.* [non-CDC CA-no previous MRSA]†
Age [median (IQR)]	82 (64, 90)	79 (52, 87)	82 (64, 90)	84 (64, 95)	0·42
Meets CDC definition*	18 (30%)	18 (100%)	0 (0%)	0 (0%)	—
MRSA previously isolated	24 (38%)	0 (0%)	24 (100%)	0 (0%)	—
Previous in-patient/out-patient visit in ORH ever	51 (84%)	13 (72%)	23 (96%)	15 (79%)	0·08
Risk factors from GP questionnaire					
Non-acute hospital in-patient in the last year	7 (11%)	0 (0%)	2 (8%)	5 (26%)	0·05
Non-acute hospital out-patient in the last year	13 (21%)	0 (0%)	3 (13%)	10 (53%)	<0·0001 [0·007]
Residence in a nursing/residential home in the last year	20 (33%)‡	0 (0%)	10 (42%)	10 (53%)	<0·0001 [0·55]
Regular care in the last year	34 (56%)	10 (56%)	13 (54%)	11 (58%)	1·00
Skin care	23	4	10	9	
Nursing care	5§	2	2	1	
Regular medication	1	1	0	0	
Catheter	1	0		0	
Unspecified care	4	3	0	1	
Catheterized or invasive procedure in the last year	8 (13%)	0 (0%)	7 (29%)	1 (5%)	0·01 [0·06]
Antibiotics in the last year	46 (75%)	10 (56%)	20 (83%)	16 (84%)	0·09
Total number of risk factors [median (IQR)]	2 (1, 3)	1 (1, 2)	2 (1, 3)	3 (2, 3)	0·0001 [0·12]
Risk factors from GP questionnaire					
None	4 (7%)	3 (17%)	1 (4%)	0 (0%)	0·02
Antibiotics only	8 (13%)	5 (28%)	3 (13%)	0 (0%)	
2 or more, or 1 (other than antibiotics) only	49 (80%)	10 (56%)	20 (83%)	19 (100%)	

CA-MRSA, Community-acquired MRSA; IQR; inter-quartile range; ORH, Oxford Radcliffe Hospitals.

* CDC definition of CA-MRSA: (i) MRSA diagnosed in out-patient or within 48 h after admission to hospital, and (ii) no medical history of MRSA infection or colonization, and (iii) no history in the past year of, hospitalization, admission to a nursing home, skilled nursing facility, or hospice, or dialysis or surgery and (iv) no permanent indwelling catheters or medical devices that pass through the skin into the body.

† Where $P<0·05$ comparing across all three groups, pairwise comparison of non-CDC community cases with *vs.* without previous MRSA isolation also performed.

P values are rank-sum or two-sided exact tests for continuous and categorical variables, respectively.

‡ Excluding one case identified through further investigation.

§ Excluding two cases identified through further investigation.

that currently ~6% of individuals with MRSA isolated in Oxfordshire have had no acute hospital contact in the previous year, ~4% have had no acute hospital contact in the previous year *and* no prior MRSA isolation, and ~2% meet the even more stringent CDC definition for CA-MRSA. However, the vast majority in all these sub-populations had CipR MLST ST22/36 MRSA strains indistinguishable from healthcare-exposed (or CipR) controls, suggesting that they are or were once hospital-based strains.

There are two possible explanations. First, individuals may have acquired previously hospital-based

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Table 3. *Bacterial genetics*

	Sequence type (ST)	Community case ($N=61$)	Hospital-exposed control ($N=61$)	CipR control ($N=21$)	CipS case ($N=21$)	Brighton CipS case ($N=18$)
Lost		3	3			
Total known isolates		***58 (100%)***	***58 (100%)***	***21 (100%)***	***21 (100%)***	***18 (100%)***
Clonal complex (CC)5	***All STs***	***3 (5%)***	***0***	***0***	***7 (33%)***	***2 (11%)***
	5	1			1	2†
	105‡	1				
	149‡				2	
	526‡				3	
	840‡	1*			1*	
CC8	***All STs***	***0***	***1 (2%)***	***0***	***3 (14%)***	***0***
	8		1		1†	
	630				2	
CC22	***All STs***	***48 (83%)***	***51 (88%)***	***17 (81%)***	***3 (14%)***	***0***
	22	46	47	16	3	
	927‡	1				
	928‡			1		
	957§	1				
	1080‡		3			
	1138‡		1			
CC30	***All STs***	***7 (12%)***	***6 (10%)***	***4 (19%)***	***1 (5%)***	***1 (6%)***
	30				1	1†
	36‡	7	6	4		
CC45	***All STs***				***1 (5%)***	***2 (11%)***
	45					2
	47‡				1	
CC88	***All STs***				***1 (5%)***	***1 (6%)***
	78				1	
	1140‡					1
CC1	**1**				***5 (24%)***	***8 (44%)***
CC80	**80**					***2***†† ***(11%)***
CC97	**97**					***2 (11%)***

CipR, Ciprofloxacin-resistant; CipS, Ciprofloxacin-sensitive.
Bold italic values are number (%) of known isolates.
* Strain is both community case and CipS case.
†(†) Strain(s) carried the PVL genes.
‡ One single nucleotide polymorphism difference from founder of cluster.
§ One single-base deletion difference from founder of cluster.
Percentages in community cases and hospital-exposed controls calculated excluding lost isolates.
Grouping by clonal complex: community cases *vs.* hospital-exposed controls (exact $P=0{\cdot}27$), hospital-exposed controls *vs.* CipR controls (exact $P=0{\cdot}59$), CipR controls *vs.* CipS cases (exact $P<0{\cdot}001$), Oxford CipS cases *vs.* Brighton CipS cases (exact $P=0{\cdot}06$), community cases *vs.* Oxford CipS cases (exact $P<0{\cdot}001$).

MRSA strains in the community – so-called 'feral' MRSA. This is supported by the observation of substantial 'healthcare at home' exposure in MRSA cases including regular care from GP/nurses, particularly for skin conditions. This could indicate a route of feral community transmission through non-hospital healthcare contacts. Second, these individuals without acute hospital contact in the last year may be persistent carriers of MRSA strains acquired during hospital exposure prior to this. The latter may be less likely given that a substantial minority (16%) of community cases had no previous acute hospital contact recorded at all. Either scenario may have implications for UK policies for MRSA control. Major changes in UK healthcare are planned with increasing transition of care from acute hospitals to non-acute hospitals and the community. If these changes are not accompanied by the rigorous attention to infection

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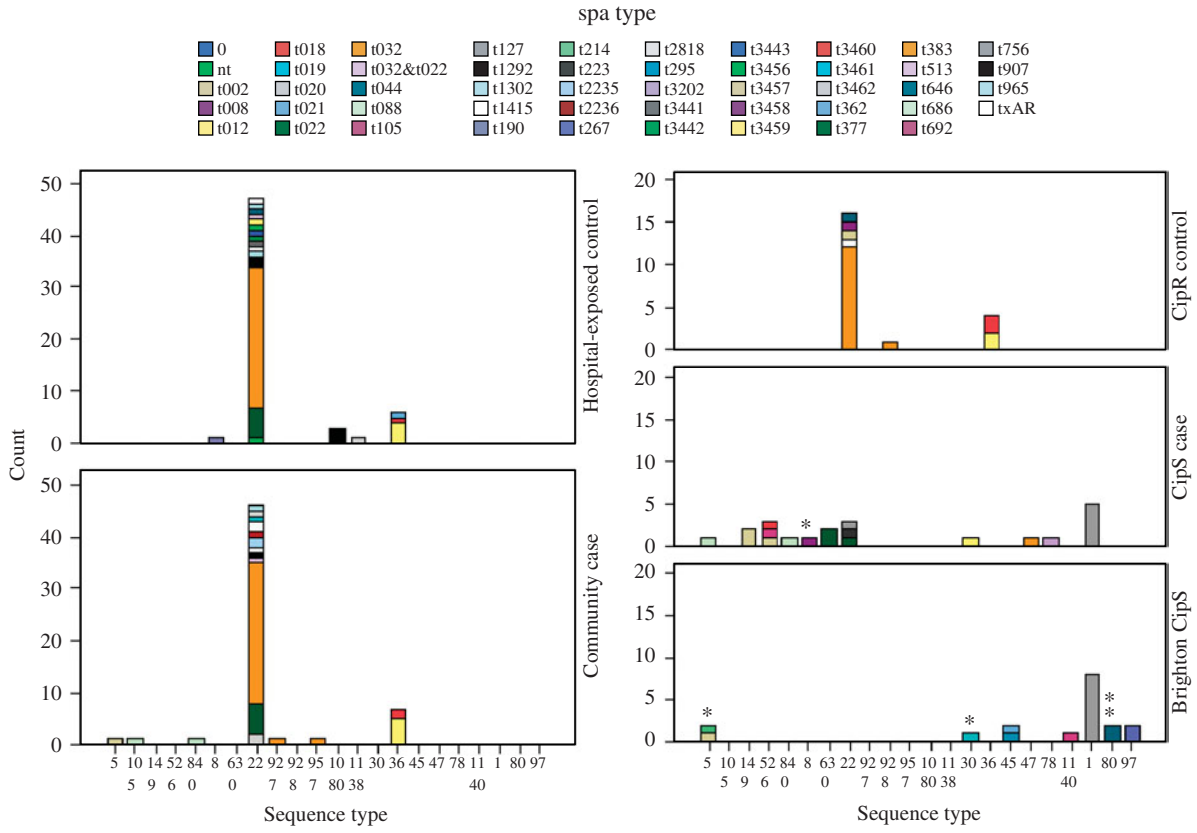

Fig. 2. *spa* typing. Sequence types from each set of cases and controls are further separated by *spa* typing. Isolates with Panton–Valentine leukocidin (PVL) genes are indicated by an asterisk (∗).

control which has become standard in tertiary care over the last 3 years, they have the potential to provide a route for increasing feral MRSA transmission. The ageing UK population is also increasingly affected by multiple comorbidities which may increase the risk of persistent MRSA carriage, particularly in those receiving substantial 'healthcare at home'. More modelling studies are needed to understand the impact of feral MRSA transmission and persistent MRSA carriers in this increasing 'healthcare-at-home' population.

In contrast, we found less evidence of significant spread of MRSA in the wider community with no connection to healthcare as seen in the USA. Only three (0·3%) individuals without acute hospital exposure had non-hospital associated STs. The 39 CipS cases, chosen to most likely represent CA-MRSA, were heterogeneous on MLST typing with clear genetic differences from the UK epidemic strains, and 13% harboured the PVL genes. However, more than half had contact with an acute hospital in the past 3 months. As 5–10% of the Oxfordshire population has been admitted to acute hospital in the last year [19] it is possible that wild strains typically circulating in the community with non-hospital-epidemic STs or PVL could nevertheless be isolated in patients with acute hospital contact in the last year, i.e. that lack of acute hospital contact in the last year has low sensitivity for detecting acquisition of MRSA in the community with no 'healthcare-at-home' contact. For example, the CipS case with ST8 *spa* t088 and PVL visited an acute hospital (unrelated to MRSA isolation) 3 days before GP MRSA isolation, but had not been in hospital for over 1 year before that. Moreover, 4/5 Oxfordshire individuals with CipS ST1 *spa* t127 had been in hospital within the previous 100 days. Of note the ST1 *spa* t127 strain found in CipS isolates in this study was also found in a collection of *S. aureus* isolates from drug users in Brighton 2006–2008 [20].

Although exposure data were collected through a GP-completed questionnaire which could have led to underreporting of risk factors, its structured nature meant that there was nearly always a 'yes/no' answer to each question even if more information was not provided. Additionally, follow-up visits to the GP

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practices of individuals with few risk factors improved risk factor ascertainment. Further, the questionnaire was sent out shortly after MRSA was isolated and was returned in all but one case. As individuals were only identified if a sample was sent into ORH for testing, the number of true CA-MRSA cases may be underestimated if many go unnoticed in the community. However, the US experience suggests that CA-MRSA infections are often severe and necessitate A&E visits.

This study suggests that it is possible that a substantial minority of MRSA transmission occurs outside hospital. Hospital strains are either becoming feral in the community or are persisting in long-term carriers in the community, and the substantial minority of the population with recent healthcare exposure may nevertheless acquire non-hospital, epidemic, wild MRSA strains in the community. These wild strains may be a source for clonal expansion producing future epidemic strains with the potential to rapidly take over in the healthcare setting, as seen with USA300 in the USA. The impact of non-hospital based transmission on the success of current hospital-based control measures of MRSA needs to be fully assessed. In order to precisely estimate community transmission large numbers of individuals should be followed prospectively at frequent intervals for long periods of time. In addition, any MRSA found should also be typed, using finer resolutions than MLST, since our findings suggest that definitions of community- or hospital-acquired MRSA based on clinical or molecular epidemiology alone are becoming unhelpful.

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DECLARATION OF INTEREST

None.

NOTE

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/hyg).

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