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Multiple introductions of methicillin-resistant *Staphylococcus aureus* ST612 into Western Australia associated both with human and equine reservoirs

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ABSTRACT

Staphylococcus aureus is a serious human and animal pathogen. Multilocus sequence type 612 (ST612) is the dominant methicillin-resistant *S. aureus* (MRSA) clone in certain South African hospitals and is sporadically isolated from horses and horse-associated veterinarians in Australia. Colonisation and infection by ST612-MRSA is increasing in Western Australia. Whole-genome sequencing was performed for 51 isolates of ST612-MRSA from Western Australian patients and healthcare workers, South African hospital patients, Australian veterinarians and New South Wales horses. Core genome phylogenies suggested that Australian equine and veterinarian-associated ST612-MRSA were monophyletic. Individual Western Australian isolates grouped either with this equine-associated lineage or more diverse lineages related to those in South African hospitals. Bioinformatic analyses of the complete ST612-MRSA reference genome SVH7513 confirmed that ST612-MRSA was closely related to ST8 USA500 MRSA. Common use of rifampicin in South Africa and equine veterinarian practice may favour ST612-MRSA in these settings. Humans and horses colonised with ST612-MRSA are potential reservoirs for MRSA in Australia.

1. Introduction

Staphylococcus aureus is a versatile and virulent opportunistic pathogen of humans and animals [1]. The organism is increasingly resistant to multiple antimicrobials, which has led to reduced therapeutic options and increased morbidity and mortality. The emergence of methicillin-resistant *S. aureus* (MRSA) within hospitals has prompted increased surveillance and infection control measures. Since the 1990s, MRSA has also been increasingly associated with infections acquired outside of the hospital environment, referred to as community-associated MRSA (CA-MRSA). Although MRSA is associated with human hosts, MRSA carriage, infection and transmission is also observed in domestic animals such as cats, dogs, horses and livestock, e.g. pigs and cows. As such, animals may also act as MRSA reservoirs and may account in part for the rise of CA-MRSA [2].

Expansion of the MRSA host range can be attributed to the acquisition of host-specific virulence and colonisation factors carried by a variety of mobile genetic elements [3]. Multilocus sequence type 612 (ST612) is a member of clonal complex 8 (CC8), which includes the dominant CA-MRSA USA300 and the closely related USA500 lineage [4]. Although ST612-MRSA is frequently identified in South Africa [5], where it is over-represented in bacteraemia cases [6], it is not a frequently reported cause of human infections elsewhere. In Australia, ST612-MRSA has been isolated from veterinarians and from New South Wales (NSW) horses [7]. Furthermore ST612-MRSA is also increasingly detected in human patients living in Western Australia (WA), with at least one case leading to seri-

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ous bacteraemia [8]. In brief, ST612-MRSA was cultured from the nasal swab of WA Patient 9. The isolate was resistant to trimethoprim/sulfamethoxazole (co-trimoxazole), rifampicin, erythromycin and doxycycline. Within a year, the partner of WA Patient 9, called WA Patient 1, had bacteraemia with ST612-MRSA. The couple had a close association with horses. Here we collected and analysed the genome sequences of human-associated ST612-MRSA from WA, NSW, South Australia and South Africa, along with horse-associated ST612-MRSA from NSW, in an attempt to identify potential origins of ST612-MRSA in WA.

2. Materials and methods

2.1. Isolates

The ST612-MRSA isolates ($n = 51$) used in this study included: isolates from patients ($n = 10$) and healthcare workers ($n = 3$) living in WA; patient isolates from Tygerberg Hospital (Cape Town, South Africa) ($n = 8$); isolates from the Scone Veterinary Hospital (Scone, NSW, Australia) isolated from horses ($n = 24$) and veterinarians ($n = 3$) [7]; and isolates from South Australian veterinarians attending a series of Australian veterinary conferences in 2009 ($n = 3$) (previously described [9]). Isolate details are provided in Supplementary Table S1.

2.2. Genome sequencing and assembly

All isolates were grown in overnight cultures of tryptic soy broth with shaking at 37 °C. Whole DNA extraction was performed as described previously [10]. Genomic DNA libraries were prepared using a Nextera XT Library Prep Kit (Illumina Inc., San Diego, CA, USA) and were sequenced on an Illumina MiSeq platform (Illumina Inc.). Reads were cleaned, assembled and annotated using the nullarbor bioinformatic pipeline software package (github.com/tseemann/nullarbor). Isolate SVH7513 from the Scone Veterinary Hospital collection was sequenced using long-read SMRT (single molecule, real-time) cell sequencing to produce a finished high-quality reference genome as previously described [10]. Genome sequence assemblies have been deposited in GenBank under BioProject accession **PRJNA558684**.

2.3. Typing and identification of mobile genetic elements

Multilocus sequence typing (MLST) was performed with MLST v.2.10 (github.com/tseemann/mlst). Staphylococcal protein A (*spa*) and staphylococcal cassette chromosome *mec* (SCC*mec*) typing were performed in silico using spaTyper 1.0 (https://cge.cbs.dtu.dk/services/spatyper) and SCCmecFinder (https://cge.cbs.dtu.dk/services/SCCmecFinder/) software, respectively. Plasmids were detected using PlasFlow [11]. Antimicrobial resistance and virulence genes were detected using abricate v.0.8 (github.com/tseemann/abricate) to query the ResFinder database (https://bitbucket.org/genomicepidemiology/resfinder_db.git) and Virulence Factor Database (VFDB), respectively. *Staphylococcus aureus* pathogenicity island (SaPI) elements were identified manually with BLASTn by searching genomes for previously described *att* sites [12], whilst comparisons of SaPIs were made with a BLASTn library of SaPI elements retrieved from GenBank (Supplementary Table S2) and visualised in UGENE v.1.3.

2.4. Comparison of genomes and phylogenetics

The reference ST612-MRSA genome SVH7513 (**CP029166.1**) was aligned with USA500 (**CP007499**) using BRIG v.0.95 [13] as were their associated plasmids pSVH7513a (**CP029167.1**) and pUSA500 (**CP007500.1**), respectively. Core genome alignments were produced using Snippy v.3.2 (github.com/tseemann/snippy). Approximately maximum-likelihood phylogenetic trees were computed using FastTree v.2.1.10 [14] with the generalised-time reversible substitution model. Trees were visualised with Interactive Tree of Life (iTOL) v.3 (https://itol.embl.de/).

3. Results

3.1. Genome composition of the ST612-MRSA reference genome SVH7513

SVH7513, isolated from an Australian horse in 2008, was selected as a reference genome. Initial queries of the National Center for Biotechnology Information (NCBI) database confirmed that SVH7513 was closely related to the ST8 strain USA500. The closest related USA500 strains were from CC8-USA500 clade I, the same clade as the USA500 clinical isolate reference genome USA500 2395 [15,16]. Whole-genome comparisons revealed that SVH7513 and USA500 2395 (**CP007499**) shared 99% identity and >97% coverage of the genome. USA500 is a highly virulent hospital and CA-MRSA strain whose virulence has been attributed to the modulation of virulence gene expression through the acquisition of insertion sequence (IS) elements within virulence-associated gene-regulatory regions. Sixteen copies of IS*256* are found throughout the USA500 chromosome, whilst fourteen copies were found in the SVH7513 chromosome. Seven copies of IS*256* were located in identical positions to those in USA500 2395 (Supplementary Table S3), including a copy located upstream of the virulence-associated fibrinogen-binding gene *sdrD* and one copy interrupting the 'repressor of toxins' gene *rot*, to which to the enhanced virulence of USA500 is attributed [16]. Of the seven unique IS*256* disruptions in SVH7513, five were within intergenic regions, whilst two occurred within coding sequences for predicted genes with no homologues (Supplementary Table S3).

Sequence queries of SVH7513 and USA500 2395 genomes with the VFDB revealed both lineages share the same number of known virulence-associated genes ($n = 68$), including leukotoxin *lukEv–lukDv* and cytotoxin genes (*hla, hld* and *hlgABC*). Like USA500, SVH7513 carried a type IVd SCC*mec* element and a 27 887-bp multiresistance plasmid named pSVH7513a (**CP029167**), which was 99% identical (98% coverage) to pUSA500. pSVH7513a carried resistance genes for trimethoprim (*dfrC*), cadmium (*cadC*), aminoglycosides (*aac6–aph2*) and β-lactams (*blaZ*). In addition, SVH7513 carried a small 2496-bp plasmid, named pSVH7513b (**CP029165.1**), which encodes the inducible erythromycin resistance gene *ermC* and the *repL*-family rolling circle replication initiation gene. USA500 2395 and SVH7513 shared several prophage and pathogenicity islands, including *hlb*-converting prophage φSA3, which carries the human immune evasion genes *sak* and *scn* and enterotoxin *sea*, and the staphylococcal pathogenicity island SaPI3 encoding enterotoxin genes *seb, selk* and *selq*. The SVH7513 genome was 40.3 kb smaller than the USA500 2395 genome, primarily due to variations within SaPI elements and prophage φSA2 and the absence of prophage φSA7. SVH7513 contained a previously unidentified SaPI, named here SaPIsvh7513 (Fig. 1).

3.2. Sequencing and whole-genome comparisons of ST612-MRSA isolated from humans and horses in Australia and from humans in South Africa

To determine the origin of ST612-MRSA in WA, ST612-MRSA ($n = 51$) genomes were sequenced with an average 56-fold depth of coverage. The majority of isolates (42/51; 82%) were *spa* type t064. The remaining isolates were t1257 (6/51; 12%), t723 (2/51;

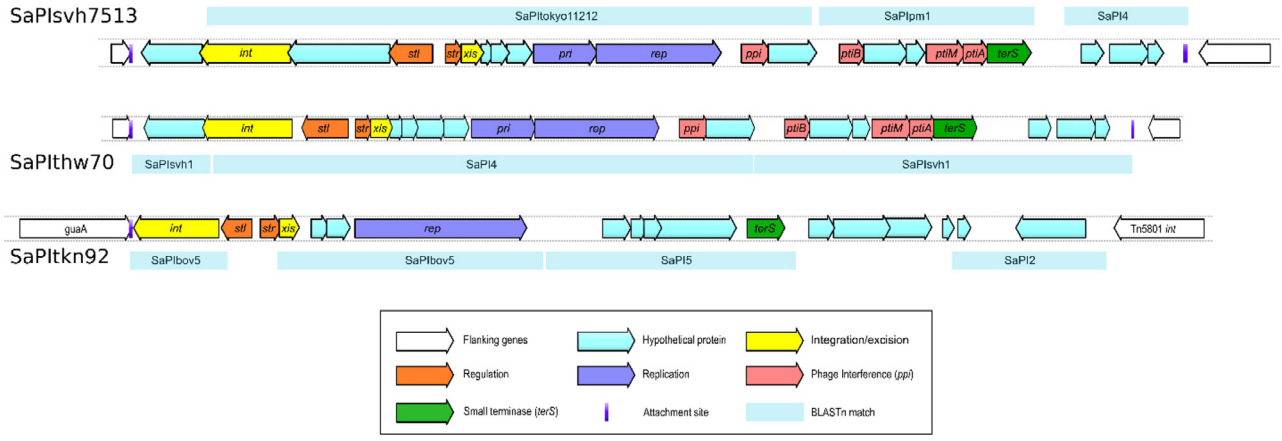

Fig. 1. Unique *Staphylococcus aureus* pathogenicity island (SaPI) elements found in ST612-MRSA genomes. BLASTn matches represent regions of >95% nucleotide identity to the indicated SaPI elements. SaPIsvh7513 and SaPIthw70 both integrate into the 30S ribosomal S18 gene, whilst SaPItkn92 has displaced Tn*5801* at the *guaA* GMP synthase gene site. Distribution of these SaPI among ST612-MRSA isolates is indicated in Fig. 2. ST, sequence type; MRSA, methicillin-resistant *S. aureus*.

4%) and a single t7571, all of which are closely related to t064, containing either insertions, rearrangements or deletions of *spa* repeat sequences. Overall, there was little variation in the core genome between ST612-MRSA genomes. All isolates harboured SCC*mec* IVd, *lukEv–lukDv* and carried a tetracycline resistance gene (*tetM*) on an integrative and conjugative element (ICE) related to Tn*5801*, integrated at the 3′ end of the GMP synthase gene *guaA*. The isolates shared identical RNA polymerase subunit B (*rpoB*) genes conferring rifampicin resistance (His481→Asn, Ile527→Met). All isolates carried pSVH7513a (described above), whilst the erythromycin resistance plasmid pSVH7513b was sporadically present in 59% of isolates (30/51). The β-lactamase gene *blaZ* was present in all isolates and was disrupted by an IS*256* insertion in all but three isolates (NSW Horse 18 and 21, and South African Patient 4). Some resistance genes were present only sporadically, such as the macrolide–streptogramin resistance gene *msrA* ($n = 3$), the quaternary ammonium disinfectant resistance gene *qacB* ($n = 1$), and the chloramphenicol (*catA7*) and streptomycin (*str*) resistance genes ($n = 1$). In two isolates, loss of prophage φSA3 resulted in restoration of the β-haemolysin gene *hlb*. Two unique SaPIs were identified among the South African isolates, named SaPItkn92 and SaPIthw70 (Fig. 1). Differences in virulence-associated and antimicrobial resistance genes are depicted in Fig. 2.

3.3. Equine-associated ST612-MRSA form a distinct clade and both human and equine-associated lineages are possible sources of ST612-MRSA in Western Australia

A maximum-likelihood phylogenetic tree was constructed using the core genomes of the 51 ST612-MRSA isolates and represented a total of 3988 single nucleotide polymorphisms (SNPs) across a core genome of 2 915 384-bp. All horse and veterinarian-isolated ST612-MRSA grouped within a single clade together with several WA patient isolates (Fig. 2). The greatest SNP difference was between WA Patient 2 and South African Patient 3 (134 bp), whilst the minimum number of SNP differences were between NSW Horses 16, 18 and 22 (0 bp) and NSW Horses 1 and 15 (0 bp). Five of the WA human isolates grouped with the equine-associated clade, whilst the remaining eight clustered with various more diverse South African ST612-MRSA isolates.

4. Discussion

This study aimed to identify the origins of ST612-MRSA in WA. Characterisation of ST612-MRSA was performed by comparison with a high-quality ST612-MRSA genome and a closely-related and well-characterised USA500 MRSA genome (**CP007499**) [16]. Except for variation in prophages and SaPIs, ST612-MRSA SVH7513 shared many mobile genetic elements and an identical suite of characterised virulence-associated genes.

'Hypervirulence' of USA500 has been attributed to the increased expression of virulence genes mediated by chromosomal insertions of IS*256*. Many IS*256* sites of USA500 were shared with SVH7513, including a copy inserted into the 'repressor of toxins' gene *rot*. Insertion of IS*256* in *rot* causes increased toxin production, resulting in enhanced spleen colonisation and survival in the presence of neutrophils [16]. Disruption of *rot* suggests that SVH7513 may share a similar virulence gene expression profile as the hypervirulent USA500. Variations in IS*256* distribution amongst ST612-MRSA genomes, such as the absence of a disruptive IS*256* insertion in the *blaZ* gene of three isolates, as well as the different distributions of seven IS*256* in SVH7513 relative to USA500, demonstrates the mobility of IS*256* in these isolates.

The ST612-MRSA core genome phylogeny was consistent with multiple introductions of ST612-MRSA into WA. The phylogenetic tree formed a single low-diversity clade containing all horse and veterinarian-associated ST612-MRSA along with several WA ST612-MRSA isolated from humans. The remainder of Western Australian and South African ST612-MRSA were relatively more diverse, but groupings suggested multiple exchanges of distinct ST612-MRSA. WA has a significant South African population (1.7% of the WA population [17]), so the potential for direct introductions of ST612-MRSA from South Africa by travel is not unreasonable.

The monophyletic grouping of equine and veterinarian-isolated ST612-MRSA in this study is unsurprising, as previous studies have identified an increased risk of carriage of ST612-MRSA for equine veterinarians [9]. It is possible that this lineage of ST612-MRSA has adapted to persistently colonise horses and may therefore present a reservoir of MRSA for human infections. Indeed, the most serious case of ST612-MRSA infection in WA (WA Patient 1) occurred in a patient who had direct contact with horses, suggesting transmission of virulent ST612-MRSA to and from horses. However, we additionally sampled 39 horses on the property of WA Patient 1 by nasal swab in March 2016 in an attempt to isolate ST612-MRSA, but no MRSA were detected. Thus, the source may have been a different stable, introduced for example by personnel working between stables or following interstate travel.

The equine and veterinarian-associated ST612-MRSA in this study were isolated in 2008–2009, whilst the most recent and

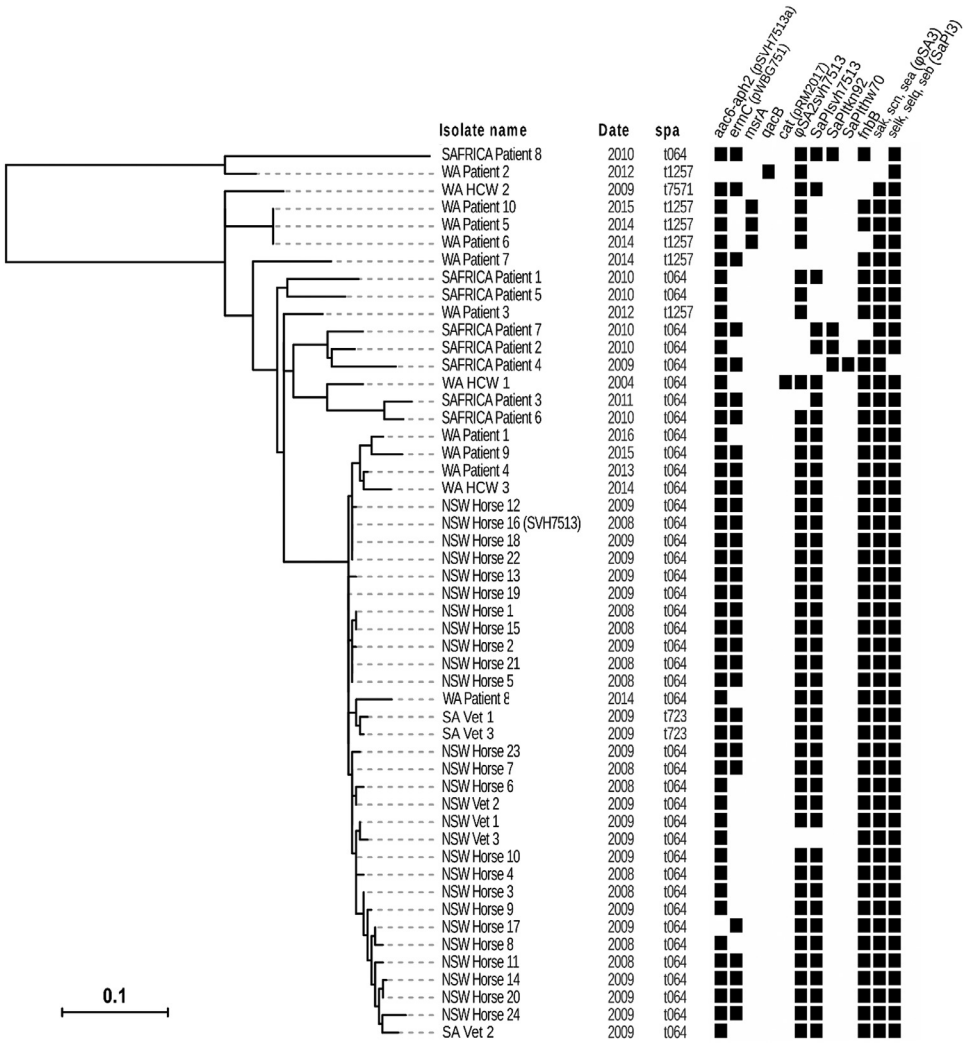

Fig. 2. Maximum-likelihood phylogenetic tree of core genomes from 43 Australian and 8 South African ST612-MRSA. Isolate names indicate origins of the represented genomes: SAFRICA, South Africa; WA, Western Australia; NSW, New South Wales; and SA, South Australia. Year of isolation (date) and staphylococcal protein A (*spa*) type are shown. The scale bar indicates average substitutions per site. Presence of resistance and virulence genes, prophage φSA3 and *S. aureus* pathogenicity island (SaPI) is indicated by filled squares. Names of associated mobile genetic elements are bracketed if known. ST, sequence type; MRSA, methicillin-resistant *S. aureus*; HCW, healthcare worker.

likely zoonotic infection from a member of this clade occurred in 2016, suggesting that ST612-MRSA has been circulating in Australian horse populations for at least 7 years with little genetic change occurring during that time. The presence of genetically close ST612-MRSA in horses and humans over a wide span of years and geographic range suggests that ST612-MRSA may have a combination of virulence factors and antimicrobial resistance determinants that allow it to persist in at least one of these hosts. The equine-adaptation phage ΦSaeq1 was not identified in any of the isolates here and therefore is not a requisite for colonisation or infection of horses. The presence of a φSA2-type prophage (φSA2svh7513) and SaPIsvh7513, all of which encode genes of unknown function within accessory gene regions, could contribute to equine host adaptation. The ability of ST612-MRSA to persist in South Africa and the Australian horse population, however, may be an unfortunate consequence of antimicrobial selection favouring ST612-MRSA. All ST612-MRSA in this study had an identical mutant *rpoB* gene providing constitutive rifampicin resistance and are consistent with those previously identified in ST612-MRSA from South Africa [5]. In addition, all ST612-MRSA carried the trimethoprim resistance plasmid pSVH7513a. Jansen van Rensburg et al. suggested that the prevalence of ST612-MRSA in South Africa could be the result of selection by the use of rifampicin and co-trimoxazole [18]. Rifampicin is used in South Africa for the treatment of tuberculosis [5], whilst co-trimoxazole is used prophylactically for the control of bacterial and *Pneumocystis* infections in human immunodeficiency virus (HIV)-infected patients. Rifampicin is uncommonly prescribed in Australia, with only 6020 prescriptions recorded in 2015 by the national Prescribing Benefit Scheme compared with 5.6 million prescriptions for the commonly prescribed antibiotic cefalexin [19]. However, Saputra et al. suggest that the prevalence of rifampicin-resistant ST612-MRSA in Australian horses is the result of the treatment of foals with rifampicin, in combination with macrolides, for the prevention of *Rhodococcus equi* infection [20]. Trimethoprim has been used orally in horses for the treatment of respiratory infections, which would further select for ST612-MRSA in Australian horses.

These findings support current local policy of MRSA screening at the time of hospital admission for patients recently treated in overseas health facilities, but a targeted campaign raising awareness among equine veterinarians may also be warranted. The zoonotic potential of ST612-MRSA also raises the question of whether the problem could be greater in nations with larger populations both of HIV infection and domesticated horses.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.08.022.

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