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Accessory gene regulators and virulence genes associated with the pathogenicity of *Staphylococcus aureus* from clinical and community settings in Lagos, Nigeria

Staphylococcus aureus is a prominent pathogen that causes serious community and hospital-acquired infections globally. Its pathogenicity is attributed to a variety of secreted and cell surface associated proteins that are modulated by the quorum-sensing accessory gene regulator (*agr*) system. In this study, we investigated the presence of toxin genes and *agr* involved with *S. aureus* from clinical samples and apparently healthy individuals. Unequivocal identification of the isolates was obtained with the Vitek 2 system. We screened 70 clinical (CL) and 22 community (C) *S. aureus* strains for the methicillin resistance (*mec*A) gene, *agr* and superantigens (SAg) (enterotoxins and toxic shock syndrome toxin-1) using PCR techniques. A total of 12 clinical isolates were classified as methicillin-resistant *S. aureus* (MRSA); 89 isolates belonged to one of the four *agr* groups ($agr^{1\text{-}4}$), and 3 isolates were non-typeable. Of the *agr* groups, agr^1 was the most prominent and mostly consisted of isolates from pus/wounds. The methicillin-susceptible *S. aureus* (MSSA) isolates were distributed within the four *agr* groups while MRSA strains were restricted to agr^1 and agr^3. The most common enterotoxin gene, *sei*, was likewise more prevalent in MSSA strains than in MRSA strains, where *sea* predominated. The co-existence of two or more enterotoxins was confirmed in 40% of the isolates. *sea* occurred through all the *agr* groups except agr^3 and *sei* was not found in agr^1 and agr^4. The toxic shock toxin (*tst*) gene was detected in six MSSA. These findings suggest that MSSA may cause more lethal infections than MRSA because of the increased frequency of toxic genotypes seen in MSSA strains.

Significance:

- Isolates in the $agr^{1,3}$ groups had more SAg toxin genes, whereas isolates in the agr^4 groups possessed more *tst* genes.
- The MSSA isolates contained higher proportions of virulence genes than MRSA.
- The clinical implications of this discovery include that MSSA may cause more lethal infections than MRSA due to the greater number of toxigenic genotypes discovered.

Introduction

Staphylococcus aureus is a dynamic Gram-positive pathogen that lives as a harmless commensal bacterium on the skin and mucosal surfaces of humans and other animals.[1] It has the potential to multiply in the blood and other tissues, triggering serious medical conditions.[2] It is widely considered as one of the leading causes of hospital- and community-acquired infections globally.[3] Evidently, the organism features prominently in 8–33% of cases of skin, soft-tissue, and bloodstream infections that can result in significant morbidity and mortality.[4]

Depending on its growth phases, *S. aureus* is able to utilise a wide range of virulence factors to initiate and establish infections in susceptible hosts. Typically, in the lag and early exponential growth phrases, the pathogen releases cell-wall-associated factors that aid in tissue adhesion and immune system evasion.[5] When the bacterial population gets to the late exponential growth phase, it begins to secrete a wide range of exoproteins, including proteases, haemolysins, and superantigens (SAgs) while also down-regulating cell-wall-associated factors, resulting in biofilm dispersion and dissemination of infection.[5]

Staphylococcal superantigens (SAgs) are notable exotoxins which play a critical role in *S. aureus* infections. They have been categorised into staphylococcal enterotoxins (SE), staphylococcal enterotoxin-*like* (SE*l*) proteins and toxic-shock syndrome toxin[6] encoded by the *tst* gene. The adhesion and invasion phases of *S. aureus* development are characterised pre-eminently by its population-density-dependent behaviour. The synchronisation and swift transition between these two phases is achieved through a cell-to-cell communication mechanism known as quorum sensing (QS). The majority of these virulence genes are regulated by the accessory gene regulator (*agr*) system which is divided into four (1-4) *agr* groups.[7,8]

The *agr* region is crucial in pathogenesis and actively controls the expression of virulence factors, heterogeneous resistance in methicillin-resistant *S. aureus* (MRSA), and biofilm development.[9-11] It co-regulates the expression of several exoproteins including α-, β-, γ-haemolysin as well as lipases, phenol-soluble modulins and TSST-1 while down regulating the synthesis of cell-wall-associated proteins such as protein A, coagulase, and fibronectin binding protein.[12,13] Several studies have been conducted to investigate the association of *agr* groups with certain biological traits in *S. aureus* and the outcomes have indicated that some enterotoxin clusters – namely *seg, sei, sem, sen*, and *seo* – are linked to agr^4 in a number of strains.[14]

In Tehran, Choopani et al.[15] noticed that MRSA isolates had the *seb* gene but that the TSST-1 precursor antigen was predominantly expressed by *agr*-III and IV strains. A study Some studies in southwest Nigeria indicated that 89% of the isolates screened had at least one SE: *seo* (34%) was the most prominent SE, then *seg* (30%) and *sea* (21%), whereas toxic shock syndrome toxin (TSST), *seb, sec, see, sej, sel, sem, ser* and *seu* were not detected. Similarly, the co-existence of *seo*/*seg* and *sei*/*seg* genes were recognised.[16]

Also, Akinduti et al.[17] reported that the bulk of the enterotoxins detected among clinical methicillin-sensitive *S. aureus* isolates in their study were confined to *agr*[2]. Nonetheless, information on the extent of superantigen genetic heterogeneity in community and clinical *S. aureus* populations in Nigeria is limited. Consequently, in the present study, we focused on determining the presence of staphylococcal superantigen genes in *S. aureus* isolates from two healthcare institutions and apparently healthy volunteers. Co-existence of the toxigenic genes with the *agr* groups and sources of the isolates was also assessed.

Materials and methods

Bacterial isolates

We analysed 92 previously described non-duplicated *S. aureus* strains collected over a period of 2 years from two tertiary care hospitals (Lagos University Teaching Hospital (LUTH), Idi-araba and National Orthopaedic Hospital, Igbobi).[18] The sample consisted of 22 nasal (NS) isolates obtained from apparently healthy individuals and designated as community (C) strains and 70 isolates obtained from various specimens submitted to the microbiological laboratories of the hospitals, classified as the clinical (CL) strains.

Bacterial identification and methicillin resistance determination

The isolates were identified using Vitek 2 automated systems (BioMérieux, Marcy L'Étoile, France). Antibiotic susceptibility testing of the isolates, also carried out by the Vitek 2 automated system, had been determined previously.[18]

Genomic DNA extraction

Genomic DNA for the evaluation of *mec*A, enterotoxin, toxic shock syndrome toxin-1 genes and *agr* determinants was extracted as previously described.[18] The quality and concentration of DNA were estimated spectrophotometrically.

mecA PCR

Strains that demonstrated phenotypic resistance to methicillin were subjected to *mec*A PCR as previously described.[19] The PCR amplification was carried out in a 25 μL reaction volume containing 1 μL of template DNA, 10 μL of 2 x master mix of 1 x PCR buffer, 1.5 mmol/L $MgCl_2$, 0.15 mmol/L dNTP, and 1.25 IU Taq DNA polymerase, 0.7 μL of 0.8 μmol/L of each primer and 12.6 μL of deionised water. For the amplification of the 533 base pair (bp) fragment, the *mec*A-specific primer pairs employed were MECAP4: 5' - TCCAGATTACAACTTCACCAGG - 3', and MECAP7: 5' - CCACTTCATATCTTGTAACG - 3'. The PCR products were then separated by agarose gel electrophoresis and visualised with ethidium bromide staining. A 100 bp DNA ladder was used as a molecular weight marker.

Determination of agr groups

We used the primers and thermal cycling conditions for *agr* groups differentiation described by Shopsin et al.[20] The *S. aureus* strains RN6390 (*agr* group I), RN6607 (*agr* group II), RN8465 (*agr* group III), and RN4850 (*agr* group IV), graciously provided by the Medical Microbiology Laboratory, Otto-von-Guericke University, Germany, were used as controls.

Detection of superantigen genes

Multiplex PCR was used to determine enterotoxin genes associated with *S. aureus*.[21] We employed the primers for classical staphylococcal enterotoxin genes (*sea, seb, sec* and *sed*) as well as toxic shock syndrome toxin-1 (*tst*) and the SE/ (*see, seg, seh, sei, sej*). For quality control, *S. aureus* ATCC 19095 was used for *sec, seh, seg* and *sei* while *S. aureus* FR I913 was employed for *sea, see, tst* and *S. aureus* ATCC 14458 for *seb* gene.

Statistical analyses

The data were analysed using GraphPad Prism 7 software (San Diego, CA, USA) and Microsoft Excel. Data for frequencies in percentages and absolute values are shown in charts and tables.

Ethical approval

The study was approved by the Institutional Review Board (IRB) of the College of Medicine, University of Lagos, Nigeria (reference number: CM/COM/8/VOL.XIX).

Results

Staphylococcus aureus *distribution and methicillin resistance*

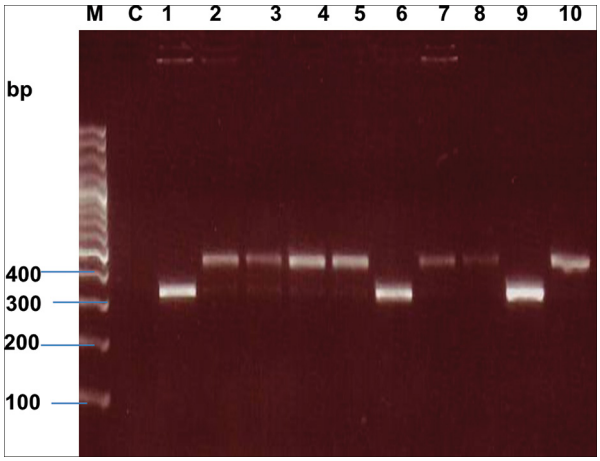
The *S. aureus* isolates investigated in this study originated mainly from three body sites: the genitourinary tract, nasal cavity and dermatological region of the body. Additionally, isolates were obtained from sputum (4.3%), blood (7.6%), and the ear or eye (6, 6.5%). Twelve clinical isolates were identified as MRSA and harboured the *mec*A gene (Table 1).

Classification of agr alleles

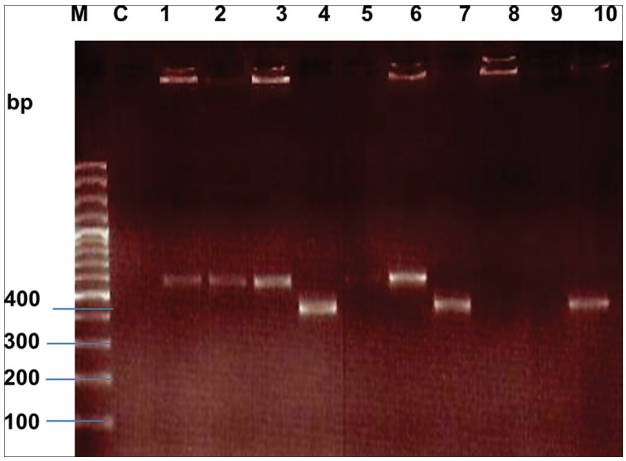
With the exception of three isolates that were non-typeable, the *S. aureus* isolates were classified into four groups using the *agr*-PCR technique (Figure 1). Of the MRSA strains, 67% were classified into *agr*[1] and 33% into *agr*[3]. Among the CL-MSSA strains, Of the CL-MSSA strains23 (42%) belonged to *agr*[1], 14 (25%) to *agr*[2], 11 (20%) to *agr*[3], and 7 (13%) to *agr*[4]. Also, 9 (41%) of the C-MSSA strains belonged to *agr*[1], followed by *agr*[2] (8; 36%), *agr*[3] (4; 18%) and *agr*[4] (1; 5%) (see Figure 2).

Table 1: Distribution of *Staphylococcus aureus* determined as methicillin-resistant strains

Isolate source	Number of *S. aureus* isolates (%)	Number of MSSA	Number of MRSA
Genitourinary tract			
High vaginal swabs	3	2	1
Seminal fluid	1	–	1
Urethral swabs	2	1	1
Catheter tips	3	3	0
Urine	8	7	1
Nasal cavity	22 (23.9)	22	–
Dermatological region (pus or wound swabs)	33 (35.7)	27	6
Other			
Blood	7 (7.6)	6	1
Ears or eyes	5 (5.5)	5	0
Sputum	6 (6.5)	5	1



(a) Clinical methicillin-resistant *Staphylococcus aureus* (CL-MRSA). Lane M: molecular weight marker (100 kb). Lane C: negative *S. aureus* control. Lanes 1, 6 and 9 are PCR amplicons from the primer set of *agr*[3] alleles using DNA from CL-MRSA strains. Lanes 2–5, 7, 8 and 10 are PCR amplicons from the primer set of *agr*[1] alleles using DNA from MRSA strains.



(b) Clinical methicillin-susceptible *Staphylococcus aureus* (CL-MSSA). Lane M: molecular weight marker (100 kb), Lane C: negative *S. aureus* control. Lanes 1–3, 5 and 6 are PCR amplicons from the primer set of *agr*[4] alleles using DNA from CL-MSSA strains and show *agr4* with 657 kb. Lanes 4, 7, and 10 are PCR amplicons from the primer set of *agr*[2] alleles using DNA with 572 kb.

Figure 1: Agarose gel electrophoresis of PCR products of *agr* alleles of *Staphylococcus aureus*.

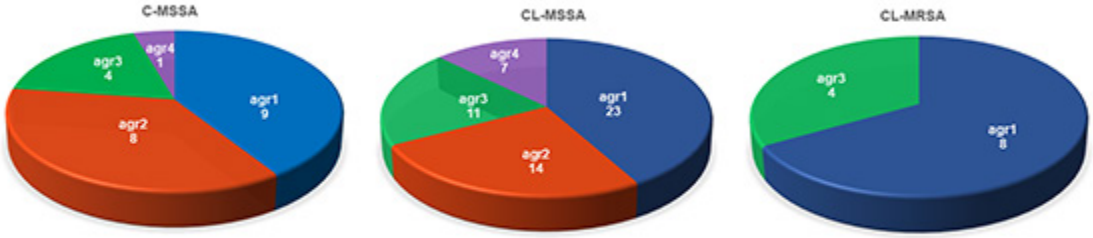


Figure 2: Prevalence of *agr* types among the *Staphylococcus aureus* strains.

Staphylococcal superantigen (SAg) gene profile among the isolates

Eight (8) distinct SE genes (*sea, seb, sec, sed, seg, seh, sei* and *sej*) were recognised and none of the isolates was positive for *see* gene. Unlike the MSSA strains, only three types of SAg gene were detected among the MRSA strains, with *sea* accounting for the majority (10, 83%), followed by *seh* (6, 50%), and *sei* (2, 17%) (Figure 3). The 70 MSSA strains had *sei* (47, 67.1%) as the most prominent enterotoxin gene and *sed* was detected only in C-MSSA. CL-MSSA had 40 (60%) *sei*, 16 (22.9%) *sea*, 10 (14.3%) *seb*, 5 (7.1%) *sec*, 16 (22.9%) *seg* and no *sed, seh* nor *sej* were detected. In addition, 4 (5.7%) *sea, seb, seg*, 7 (10%) *sei*, 2 (2.9%) *sed* and 1 (1.4%) *sej* were identified amongst the C-MSSA strains. In all, 8 C-MSSA strains had no detectable SAg genes and the 6 *tst* genes discovered were peculiar to MSSA strains.

Enterotoxin genes co-existence and agr *groups*

In all, 18 CL-MSSA strains had 2 or 3 SAg gene combinations, with the highest number (*sea-sei*) occurring in 7 strains. Other combinations of the enterotoxin genes were also detected among the community strains; 5 MRSA strains co-harboured *sea* and *seh* genes and *sea, seh* and *sei* co-existed in 1 MRSA strain. The distribution of the toxin genes within the *agr* groups is shown in Table 2.

The *sea* and *seh genes* were associated with *agr*[1] among the MRSA while *sea, seh* and *sei* were associated with *agr*[3]. For the CL-MSSA, *sea, seb, sec, seg, seh* and *sei* genes were connected to *agr*[3], whereas *sea, seb, sec, seg, sei* and *tst* genes were related to *agr*[4]. Regarding C-MSSA, the *sea, seb, sed* and *sei* genes were associated with *agr*[1], while *sea* and *sei* genes were found within *agr*[2]. *seb, sed, seg, sei* and *tst* genes were in *agr*[3] and *sea, seg* and *tst* genes were associated with *agr*[4]. Two *tst* genes were found in *agr*[1] and *agr*[4] groups in the CL-MSSA, and one each in the *agr*[3] and *agr*[4] groups among the C-MSSA.

Distribution of agr genes and SAg in relation to specimen types

Whilst some specimens fitted into certain *agr* classes, all specimen types were represented in *agr*[1] group except the ear/eye samples (Table 3). The most prevalent genes (*sea* and *sei*) were predominantly detected in pus (35%) and wound (50%) isolates. Table 4 shows other observed frequencies.

Discussion

In this study, the occurrence of methicillin resistance among the *S. aureus* isolates examined was 13%. Individuals harbouring MRSA, which is frequently multidrug resistant, are at risk of serious threat to themselves, and also play a role in the dissemination of the pathogen in hospital and community settings. Although the 29/307 MRSA recorded among hospitalised oncology patients examined in Ahvaz, Khuzestan Province, southwest of Iran[22] was much lower, it could not be ruled out that the higher rate observed in this study is unconnected to the antibiotic use pattern in Nigeria.[23] The isolates we examined were mostly from clinical sources and about 24% of the whole collection were from individuals who had no known indications for antibiotic use. The National Orthopaedic Hospital in Lagos has the capacity to accommodate up to 450 trauma

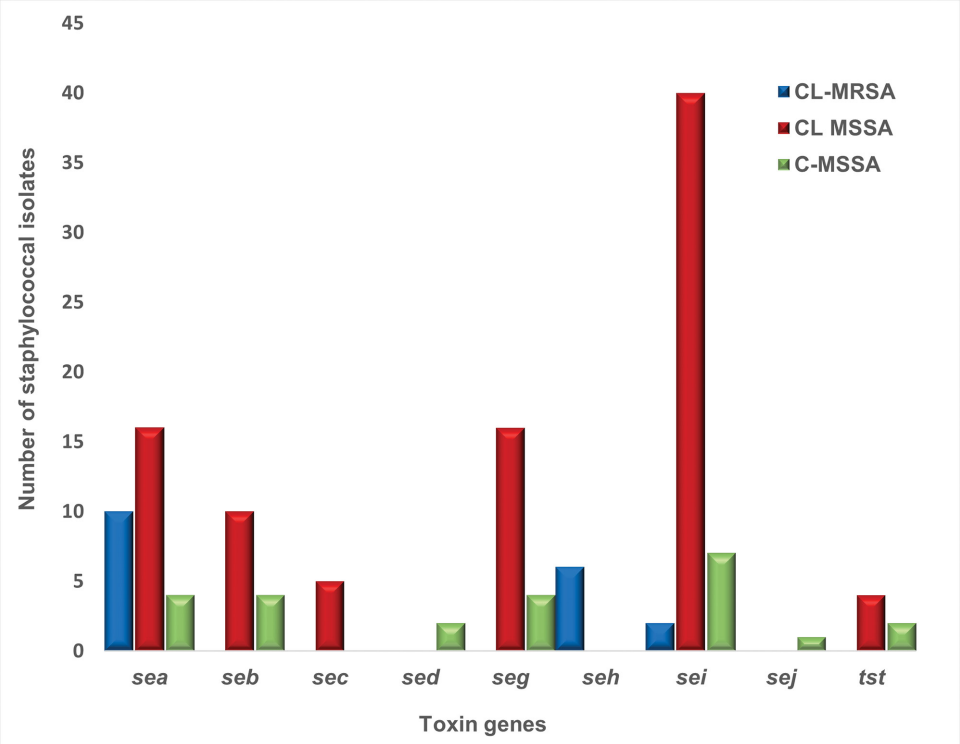


Figure 3: Superantigen gene profiles of the *Staphylococcus aureus* strains.

Table 2: Co-existence of staphylococcal superantigen genes in relation to *agr* types

Toxin genes	Number of CL-MRSA (12)		Number of CL-MSSA (55)				Number of C-MSSA (22)				Total
	agr[1] (8, 67%)	*agr*[3] (4, 33%)	*agr*[1] (23, 42%)	*agr*[2] (14, 25%)	*agr*[3] (11, 20%)	*agr*[4] (7, 13%)	*agr*[1] (9, 41%)	*agr*[2] (8, 36%)	*agr*[3] (4, 18%)	*agr*[4] (1, 5%)	
sea	8	2	6	4	3	2	1	2	–	1	29 (36%)
seb	–	–	4	2	1	3	3	–	1	–	14 (15%)
sec	–	–	1	–	3	1	–	–	–	–	5 (6%)
sed	–	–	–	–	–	–	1	–	1	–	2 (2%)
see	–	–	–	–	–	–	–	–	–	–	0 (0%)
seg	–	–	3	2	4	4	–	–	3	1	17 (18%)
seh	4	2	–	–	2	–	–	–	–	–	8 (9%)
sei	–	2	9	8	11	6	2	2	3	–	43 (47%)
sej	–	–	–	–	–	–	–	–	–	1	1 (1%)
tst	–	–	2	–	–	2	–	–	1	1	6 (7%)

Table 3: Distribution of *agr* groups of the *Staphylococcus aureus* isolates by specimen types

agr groups	Number of *S. aureus* isolates from the samples					
	Pus/wound	Genitourinary tract	Blood	Sputum	Ears/eyes	Nasal swab
agr[1]	14	11	2	4	–	9
agr[2]	7	2	3	–	2	8
agr[3]	7	6	1	–	1	4
agr[4]	4	2	–	–	1	1
Total	32	21	6	4	4	22

Table 4: Relative incidence of SAg genes in relation to the various types of specimen

SAg genes	Type of specimen					
	Pus/wound ($n = 34$)	Genitourinary tract ($n = 19$)	Blood ($n = 7$)	Sputum ($n = 4$)	Ears/eyes ($n = 6$)	Nasal swab ($n = 22$)
sea	12	9	3	1	1	4
seb	1	2	2	–	1	4
sec	5	2	–	–	–	–
sed	–	–	–	–	–	2
see	–	–	–	–	–	–
seg	7	6	2	–	1	2
seh	3	2	2	–	–	–
sei	17	13	4	2	3	7
sej	–	–	–	–	–	1
tst	2	–	–	1	1	2

(–) denotes negative

patients, while the Lagos University Teaching Hospital, a leading tertiary hospital with over 761 admission beds, is the facility of last resort and referral for all disease conditions. As tertiary healthcare institutions, both hospitals may have a high prescription culture for antibiotics. Furthermore, antibiotics are widely accessible and can be purchased without a prescription over the counter. This has conferred selective pressure on the majority of bacterial pathogens in our environment.

With the exception of three non-typeable *S. aureus* isolates, all isolates examined in this study were defined into the four *agr* groups. In *S. aureus*, the accessory gene regulator (agr) plays a vital role in the temporal expression of a wide range of bacterial virulence factors. A large proportion of the MRSA strains (58.6%) fitted into the *agr*[1] and *agr*[3] clusters. The CL-MSSA and NS-MSSA strains, on the other hand, belonged to *agr*[1-4]. These outcomes are in contrast to those of a study conducted in Poland[24] in which no *agr*[4] was detected, but are comparable to the findings of Elazhari et al.[21] Likewise, the majority (42%) of the isolates belonging to *agr* group 1 were MRSA, which was in agreement with the findings of other studies.[20,23]

In the present communication, the number of superantigen (SAg) genes detected varied significantly across the population of the *S. aureus* analysed, but was more pronounced among the methicillin-susceptible strains than their methicillin-resistant counterparts. The clinical relevance of this observation is that MSSA acquisition can be more deleterious. Elsewhere, Elazhari and others[21] indicated that 19 of the MSSA strains examined in their study harboured SAg genes varying from 1 to 11, which supports our assumption. From another perspective, Ayeni et al.[16] discovered neither *seb* or *sec* among their collection of *S. aureus* strains in southern Nigeria, which contradicts our findings. Additionally, our findings revealed a significant relationship between *sea, seh* and MRSA: 83% and 50% of MRSA strains had the *sea* and *seh* genes, respectively. In contrast, Ali et al.[14] discovered the presence of the *seb* gene in MRSA strains. This signifies that the enterotoxin gene profiles of *S. aureus* may vary substantially depending on geographical area and population structure.[25]

We also found the simultaneous presence of *sea* and *seh* genes in five MRSA strains, as well as the occurrence of two or more distinct enterotoxin genes in 18 CL-MSSA. Four toxin genes (*seb, seg, sei, tst*) co-existed in one C-MSSA strain. The *tst* gene was exclusively present in CL-MSSA and C-MSSA isolates and was not detected in MRSA. Previously, Danelli and colleagues[26] explained that *tst* carriage is commonly related with MSSA, which is consistent with our findings. Besides the possibility that MSSA isolates may have a lower genetic fitness burden because they do not have the SCC*mec* element[27], Varshney et al.[28] postulated that MSSA strains have an increased potential to secrete toxins than MRSA. *S. aureus* is known to have an outstanding array of virulence characteristics for initiating infections. This event may have major implications for public health.[29] It has also been insinuated that even modest quantities of staphylococcal enterotoxins could elicit T-cell activation[30], resulting in systemic infections including staphylococcal enterotoxin-induced shock and autoimmunity[31]. Similarly, Schmidt et al.[32] speculated that TSST-1 expression was independent of *S. aureus* methicillin sensitivity. This could further explain the carriage of *tst* genes among the MSSA analysed in this study, albeit at low prevalence. Therefore, it is possible that there may be additional, as yet unexplained, variables that affect *tst* carriage. Further studies are needed to better understand TSST-1 expression mechanisms in *S. aureus*.

In our analysis, the *agr*[1] group was represented in all specimens investigated, except for ear/eye samples, demonstrating some similarity with the results of Javdan and co-workers[33]. However, its dominance was higher in pus/wound and genitourinary tract samples. This is in contrast to the findings of Elazhari et al.[21] These authors observed that *agr*[2] and *agr*[3] were prevalent in isolates from pus/wounds. This disparity between our findings and those of others may not be unconnected to sampling variability and study timeframe. While the *agr*[1]-MRSA had more enterotoxin genes, most of the toxigenic CL-MSSA and NS-MSSA belonged to *agr*[3]. The findings of this study also indicate that the expression of SAg genes was not unconnected to the types of specimens. The capacity to categorise infections based on sites or specimen types may give insight into the extent to which microorganisms play a role in disease initiation and progression. *sei*, the most prominent enterotoxin gene, was identified in all samples anaysed, but no *seb, sec, seg*, and *seh* were found among sputa isolates.

Meanwhile, the *sej* gene was only detected in sputum samples, while the *tst* genes were mainly present in pus/wound and nasal samples. Evidence from our study also shows that isolates that tested positive for *sei* and *sea* were significantly related with pus/wounds ($p<0.05$). This could alter the pathophysiology of wounds and present survival of the pathogen. Gergova et al.[34] noted that more virulence genes were found in invasive *S. aureus* compared to isolates from non-invasive sites (nasopharyngeal secretion, skin lesion, urogenital tract and eye secretion). Their result corroborates our findings. They also reported that several of the genes (*sei, sea*, and *seg*) were found in individuals who had died from staphylococcal bacteraemia, underlining the possible serious clinical consequences of superantigenic *S. aureus* strains.

Conclusions

Our findings indicate that *agr*[1] expression seems to be important for colonisation and establishment of *S. aureus* infections. Although the superantigen gene content of the pathogen differs significantly between MRSA and MSSA, the presence of the genes in MRSA poses an increased public health risk. The preponderance of MSSA and the connection of superantigenic genes may result in an expansion of strains with higher pathogenicity, which could lead to therapeutic dead ends. Future research may be required to determine the relationships between MSSA and *tst* carriage, as well as whether these associations are restricted to certain *agr* groups.

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Competing interests

We have no competing interests to declare.

Authors' contributions

N.V.E., S.A.A. and C.A.E.: Conceptualisation, methodology, data collection and analysis, writing – initial draft and proofreading. N.V.E., C.A.E., S.A.A., U.E.M.: Validation, project leadership, supervision. All authors read and approved the final manuscript.

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