Introduction

Since its discovery by Dr Alexander Ogston in 1880, *Staphylococcus aureus* has been recognized as a versatile micro-organism worldwide (Ogston, 1881; diekema et al., 2001). *S. aureus* may colonize the human body as a part of the normal flora. Approximately 30 % of healthy people are inhabited by *S. aureus*, mostly in the anterior nares (Akmatov et al., 2014). *S. aureus* is also a leading cause of hospital-associated (HA) and community-associated (CA) bacterial infections in humans, associating with numerous mild skin and soft tissue infections, as well as life-threatening pneumonia, bacteraemia, osteomyelitis, endocarditis, sepsis and toxic shock syndrome (David & Daum, 2010). The increasing prevalence of meticillin-resistant *S. aureus* (MRSA) and its ability to resist multiple drugs has posed a serious challenge for infection control (Junie et al., 2014). HA-MRSA often infects individuals with health care risk factors, such as surgery or residence in a long-term care facility. By contrast, many CA-MRSA and meticillin-susceptible *S. aureus* (MSSA) often infect healthy persons who do not have such risk factors (Tokajian, 2014). However, whether some *S. aureus* clones circulating in hospitals or communities have the ability to cause serious infections (namely hypervirulent clones) and spread internationally remains unclear.

Development of a highly discriminatory method usually benefits deep characterization and understanding of bacterial isolates. Multilocus sequence typing (MLST) methods were developed for the identification of the hyper-virulent clones of *Neisseria meningitidis* (Maiden et al., 1998) and sorting *Streptococcus pneumoniae* strains to the major hypervirulent lineages (Enright & Spratt, 1998; Enright et al., 1999). To understand the basic features of the population and evolutionary biology of *S. aureus*, Enright et al. (2000) developed an MLST scheme based on seven housekeeping genes (*arcC*, *aroE*, *glpF*, *gmk*, *pta*, *tpi* and *yqIL*) to molecularly characterize *S. aureus* isolates as different sequence types (STs). Epidemiological studies have also demonstrated that the majority of *S. aureus* infections are caused by a small number of major clones (Rasigade et al., 2010). For example, the major clones in the UK are EMRSA-15 (ST22) and EMRSA-16 (ST36) (Wyllie et al., 2011), whereas the predominant clones in Japan, Hungary and the US are ST5, ST239 and ST8, respectively (Nakaminami et al., 2014; Kawaguchiya et al., 2013; Conceição et al., 2007). Up until 8/6/2015, there

*Staphylococcus aureus* ST121: a globally disseminated hypervirulent clone

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*Staphylococcus aureus* is a leading cause of bacterial infections in hospitals and communities worldwide. With the development of typing methods, several pandemic clones have been well characterized, including the extensively spreading hospital-associated meticillin-resistant *S. aureus* (HA-MRSA) clone ST239 and the emerging hypervirulent community-associated (CA) MRSA clone USA300. The multilocus sequence typing method was set up based on seven housekeeping genes; *S. aureus* groups were defined by the sharing of alleles at ≥5 of the seven loci. In many cases, the predicted founder of a group would also be the most prevalent ST within the group. As a predicted founder of major *S. aureus* groups, approximately 90 % of ST121 strains was meticillin-susceptible *S. aureus* (MSSA). The majority of ST121 strains carry accessory gene regulator type IV, whereas staphylococcal protein A gene types for ST121 are exceptionally diverse. More than 90 % of *S. aureus* ST121 strains have Panton–Valentine leukocidin; other enterotoxins, haemolysins, leukocidins and exfoliative toxins also contribute to the high virulence of ST121 strains. Patients suffering from *S. aureus* ST121 infections often need longer hospitalization and prolonged antimicrobial therapy. In this review, we tried to summarize the epidemiology of the *S. aureus* clone ST121 and focused on the molecular types, toxin carriage and disease spectrum of this globally disseminated clone.

Abbreviations: AIP, autoinducing peptide; CA, community-associated; HA, hospital-associated; MLST, multilocus sequence typing; MSSA, meticillin-susceptible *S. aureus*; MRSA, meticillin-resistant *S. aureus*; PVL, Panton–Valentine leukocidin; SCCmec, staphylococcal cassette chromosome *mec*; ST, sequence type.
were 3015 STs corresponding to 5703 *S. aureus* isolates collected in the MLST database (http://www.mlst.net/). These strains can be categorized into 51 groups when using five identical loci for group definition. Group 1 is the largest group, which contains 4044 isolates with 1699 STs, including ST1, ST5, ST8, ST15, ST22, ST30, ST45, ST97 and ST239, with ST5 as the predicted founder. Group 2 contains 186 isolates with 136 STs, with ST121 as the predicted founder. ST59, ST398 and ST133 are the predicted founders for Groups 3, 4 and 5, respectively (Fig. 1).

Given that the difference in genome sequence is as high as 22 % in *S. aureus* (Jelsbak et al., 2010), different clones may have variable virulence. The analysis of the global population structure and expansion of pathogenic clones of *S. aureus* revealed that certain clones are more virulent than others (Layer et al., 2006). In 2007, Schefold et al. first reported a sepsis case of a 51-year-old male caused by *S. aureus* ST121 (Schefold et al., 2007). We also characterized a fatal case of a 17-year-old boy with septic multiple organ failure caused by Panton–Valentine leukocidin (PVL)-positive CA-MSSA type ST121/agrIV (Rao et al., 2015). It remains to be elucidated whether *S. aureus* ST121 is a globally disseminated hypervirulent clone or not. In this review, the prevalence of *S. aureus* ST121 in distinct geographical regions, including Africa, Asia and Europe, was summarized. The molecular types and toxin carriage of *S. aureus* clone ST121 were evaluated and the reported diseases caused by *S. aureus* clone ST121 were also discussed.

**Epidemiology of *S. aureus* clone ST121**

The epidemiology of *S. aureus* varies considerably on a global basis and the dominance of *S. aureus* clones in a certain region is geographically restricted (Tokajian, 2014). An investigation on the global population structure of PVL-positive MSSA revealed that the most frequent STs are ST30 (19.9 %, 42/211) and ST121 (19.9 %, 42/211) (Rasigade et al., 2010). ST121 MSSA isolates are distributed in 15 out of the 19 surveyed countries, including Paraguay, New Caledonia, Togo, France, Czech Republic, Germany, Turkey, US, Fr. West Indies, UK, Polynesia, Switzerland, Spain, Algeria and the Netherlands. Another study that typed 292 *S. aureus* strains isolated from patients with uncomplicated skin infections in ten countries also demonstrated that the most common ST is ST121 (13.0 %, 38/292) (Goering et al., 2008). However, only four ST121 *S. aureus* isolates (5.5 %, 4/73) were determined in a recent study with collections from 13 countries between 1961 and 2009 (Tavares et al., 2014). The attention given to the epidemiology of a certain *S. aureus* clone, such as ST121, is study-orientated. Most epidemiological data relevant to the *S. aureus* clone ST121 are available in Africa, Asia and Europe.

**Africa.** The majority of infectious disease research in Africa focused on malaria, acquired immunodeficiency syndrome and tuberculosis, which are the ‘big three diseases’ in that area (Schaumburg et al., 2014). Study on other infectious diseases in Africa, such as infections

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**Fig. 1.** eBURST diagram for all available *S. aureus* STs in the MLST database. The diagram is constructed by eBURST program version 3. Each blue dot represents one ST corresponding at least one strain. The yellow dots represent the predicted founder ST; the major ST founders are indicated by red digital numbers. The dark green dots represent the subgroup that may have diversified to become a founder ST and these subgroup founder STs are indicated by yellow digital numbers.
caused by *S. aureus*, has been largely neglected in the past; hence, epidemiological data on clone ST121 are scarce (Herrmann et al., 2013; Hotez et al., 2011). The data regarding *S. aureus* ST121 infections were not available before 2005 in Africa. Six (9.5%, 6/63) ST121 *S. aureus* isolates were determined in a surveillance study on the two most populated islands of the Cape Verde archipelago in 2006 (Aires-de-Sousa et al., 2006). In 2009, Ghebremedhin et al. collected 346 non-duplicate *S. aureus* isolates from the University Teaching Hospital in Ibadan, Nigeria, where the ST121 isolation rate was 11.0% (38/346) (Ghebremedhin et al., 2009). Egyir et al. (2014) isolated 308 *S. aureus* from six healthcare institutions located across northern, central and southern Ghana, where 39 isolates were typed as ST121 (12.7%, 39/308). In contrast to the rest of the world, the prevalence of *S. aureus* clone ST121 seems to have been increasing in Africa in recent years. In addition, *S. aureus* ST121 can also be a major nasal carriage pathogen in Africa. In November 2010 and April 2012, 332 individuals from Hospital Dr Ayres Menezes in São Tomé and Príncipe were screened for *S. aureus* carriage, where 55 *S. aureus* isolates were identified as 41 MSSA (74.5%). Molecular typing demonstrated high genetic diversity among the MSSA isolates, with four major clones: ST15 (24.4%, 10/41), ST508/2446 (22.0%, 9/41), ST152 (9.8%, 4/41) and ST121 (9.8%, 4/41) (Conceição et al., 2014). With the Millennium Development Goals, the picture of the spread of *S. aureus*, as well as certain clones (such as ST121), will be gradually uncovered despite cultural and geographical diversity in Africa.

**Asia.** Asia is an area with the highest prevalence of *S. aureus* worldwide, including HA-MRSA, CA-MRSA and MSSA (Chen & Huang, 2014). Two pandemic HA-MRSA clones, ST239 and ST5, were reported to have disseminated internationally in Asia. However, the epidemiology of MSSA and CA-MRSA in Asia were characterized by clonal heterogeneity. Driven by the multinational surveillance programs (e.g. RSS, ANSORP and SENTRY), MRSA epidemiological data were obtained (Bell et al., 2002; Song et al., 2011), whereas the data for certain clones remain limited. In China, where epidemiological information on *S. aureus* infections was largely lacking before 1998, Fan et al. (2009) enrolled a total of 801 children in the study of nasal carriage and found that 147 were asymptomatically colonized with *S. aureus*. Among the 147 isolates, 45 were ST121 (30.6%, 45/147), indicating that ST121 is a dominant clone in kindergartens in China, similar to a report in Africa (Conceição et al., 2014). For clinical infections, ST121 clone is rarely dominant in Asia. A total of 466 non-duplicate *S. aureus* isolates recovered from 1994 to 2008 at Peking Union Medical College Hospital in China were molecularly typed, but only six ST121 isolates (1.3%, 6/466) were characterized (Chen et al., 2010). A small study performed in Beijing, China demonstrated that approximately 8.3% (1/12) of skin and soft tissue infections were associated with ST121 (Jiang et al., 2013). In Japan, Kikuta et al. (2011) isolated 136 *S. aureus* isolates (122 MSSA and 14 MRSA) from children with impetigo, but only one (7.1%, 1/14) isolate belonged to ST121 in MRSA strains. In Hokkaido, Japan, the authors did not determine all strains by MLST from 1015 *S. aureus* isolates derived from clinical specimens of outpatients in 2009, but ST121 accounted for 11.8% of the 17 selected strains (2/17) (Kawaguchiya et al., 2011). In January 2006, 17 children were identified with CA-MRSA infection at the Angkor Hospital, Siem Reap, Cambodia, where two (11.8%, 2/17) children were infected by ST121 clone (Chheng et al., 2009). In food poisoning cases, the prevalence of *S. aureus* ST121 clone was similar to other diseases. A survey performed in Yangon, Myanmar, showed that *S. aureus* ST121 was associated with 13.0% (3/23) of food poisoning cases (Aung et al., 2011).

**Europe.** The high diversity of MSSA and MRSA is well studied in Europe. Theoretically, MSSA may capture the mecA gene from domestically circulating MRSA, or an MRSA may obtain mobile toxin genes from MSSA to enhance its virulence. In 2006, Layer et al. analysed 82 MSSA strains derived from the Institute for Microbiology at the University of Magdeburg, Germany; but, only one (1.2%, 1/82) isolate was classified as ST121 (Layer et al., 2006). However, 40.2% (33/82) of the MSSA strains possessed the *tst* (toxic shock syndrome toxin) gene and up to four additional enterotoxin genes, whereas 24 simultaneously circulating MRSA strains harboured two or three genes of the enterotoxin gene cluster. The authors concluded that the pool of circulating MSSA strains is an important parameter with regard to the epidemiology of MRSA clones and their potential virulence. In 2007, 100 *S. aureus* isolates from diverse cases of skin and soft tissue infection at a university hospital in Saxony, Germany, were characterized, where ST121 was one of the predominant clones, which accounted for 12.0% (12/100) (Monecke et al., 2007). Among the 140 participants who were tested by Wiese–Posselt et al. (2007) in a German village, 51 were nasally colonized with *S. aureus*, where nine out of these *S. aureus* strains carried lukS–lukF genes and as ST121 (n=7) and ST30 (n=2).

Several reports about *S. aureus* ST121 have been recorded in Spain. In one report that aimed to investigate the nasal occurrence of *S. aureus* in healthy humans and their healthy companion animals residing within common households, 67 healthy owners and 66 healthy pets were studied. The results revealed that 28 owners carried *S. aureus* (ST121, n=4) and eight (ST121, n=2) pets presented MSSA, with an incidence rate of 16.7% (6/36) for ST121 (Gómez-Sanz et al., 2013). Blanco et al. (2011) characterized 40 PVL-positive *S. aureus* isolates collected between 2005 and 2008 in Bilbao, Spain, and revealed that ST121 accounted for 12.5% (5/40) but did not harbour the mecA gene. However, a study regarding MRSA circulation in a northern Spain community between 2009 and 2010 revealed that only one ST121 strain was discovered among 374 MRSA isolates (0.3%, 1/374) (González-Domínguez et al., 2012).
In 2005, Aires de Sousa et al. compared the genetic background of 312 MRSA strains collected in different periods from three hospitals located in Lisbon and Oporto, and determined 17 (5.4 %, 17/312) ST121 isolates (Aires de Sousa et al., 2005). These epidemiological data hint that most ST121 strains are MSSA. Conceição (16/63) of the isolates from three hospitals located in Lisbon and Oporto, and determined 17 (5.4 %, 17/312) ST121 isolates recovered from 30 children, 19 (50.0 %, 19/38) belonged to ST121.

Epidemiological investigations of ST121 in other European countries are rare. In Vladivostok, Russia, a small survey based on four hospital laboratories revealed that 25.4 % (16/63) of the S. aureus isolates were ST121 (Baranovich et al., 2010). To deeply understand the epidemiology of S. aureus clone ST121, more systematic surveillance of both hospital and community isolates is required for the countries in this region.

Molecular types of S. aureus clone ST121

Characterization of clones in a certain bacterial species is largely dependent on in-depth molecular typing. The first method for typing S. aureus is phage typing, which was introduced in 1944 by Fisk & Mordvin (Fisk & Mordvin, 1944), followed by pulsed field gel electrophoresis (Prévost et al., 1991), spa typing (Shopsin et al., 1999), MLST (Enright et al., 2000) and finally, staphylococcal cassette chromosome mec (SCCmec) typing (Oliveira & de Lencastre, 2002). These methods were developed to successfully characterize S. aureus strains. No typing research specialized for S. aureus ST121 clone is available to date and the information on molecular types associated with this clone was obtained from studies with different research goals. Table 1 summarizes the available molecular data for S. aureus ST121 strain epidemic in Africa, Asia and Europe.

spa types. The spa gene product, protein A, is an important virulence factor involved in host immune system evasion for S. aureus. The repeat region of the spa was amplified by PCR and sequenced to type S. aureus strains (Harmsen et al., 2003). The spa types of S. aureus clone ST121 geographically varied. Rasigade et al. (2010) determined the spa types of 211 PVL-positive MSSA clinical isolates collected in 19 countries throughout the world between 1981 and 2007, and revealed 11 spa types for S. aureus clone ST121, including t159, t645, t284, t435, t940, t169, t1077, t1114, t1596, t3407 and t3635. To date, 164 S. aureus ST121 isolates collected from different countries have been subjected to spa typing and a total of 26 spa types have been determined. The most common spa type for S. aureus ST121 is t159, which accounted for 35.4 % (58/164), followed by t645 (12.8 %, 21/164), t314 (11.0 %, 18/164), t2304 (6.1 %, 10/164), t916 (5.5 %, 9/164), t435 (4.9 %, 8/164), t287 (4.9 %, 8/164) and t1425 (4.3 %, 7/164) (Table 2). No other spa type accounted for more than 3 % of S. aureus ST121 isolates (Fig. 2a).

A certain S. aureus ST clone usually has varied spa types, such as the globally disseminated USA300 (ST8-SCCmec IV) strains have spa types of t008, t121, t197, etc., and t008 is the dominant spa type (Seidl et al., 2014). Among 159 ST239 and 78 ST5 MRSA strains collected in China, ST239 strains contained spa types t030, t037, t138, t459, t632 and t167 and ST5 strains included t002, t010, t570, t2460 and t045 (Cheng et al., 2013). The different spa types carried by one S. aureus ST clone may be helpful for tracing the strains within the ST clone, especially for the new emerging ST clones, such as ST121.

agr types. In S. aureus, the accessory gene regulator (agr) is a global regulatory system composed of two divergent transcripts, RNAII and RNAIII, which are under the control of two distinct promoters, P2 and P3 (Novick, 2003). The P2 transcriptional unit encodes AgrB, AgrD, AgrC and AgrA. An autoinducing peptide (AIP) is produced from AgrD processed by AgrB, and secreted in the extracellular medium to bind to the AgrC transmembrane protein, which in turn, activates the AgrA response regulator. AgrA activates transcription of its own operon (P2) and RNAIII (P3). RNAIII controls the switch between early expression of surface proteins and late production of S. aureus exotoxins, playing an important role in the virulence control of S. aureus (Guilet et al., 2013). According to the diversity of amino acid sequence and length of AgrD and AgrC, S. aureus can be divided into four agr types, namely, agrI, II, III and IV. S. aureus strains with each type of agr can lead to skin and soft tissue infections. To date, 139 S. aureus ST121 strains with agr types have been reported. Almost all S. aureus ST121 strains are agr IV (98.6 %, 137/139) (Fig. 2b) (Holmes et al., 2005; Ghebremedhin et al., 2009; Conceição et al., 2014). Two S. aureus ST121 with agrII (1.4 %, 2/139) have been reported (Aires de Sousa et al., 2005; González-Domínguez et al., 2012) (Table 1). The distinctive carriage of agr IV in S. aureus ST121 strains may contribute to their characterized pathogenesis.

mecA gene carriage. The widespread use of antibiotics facilitates the emergence of multi-drug-resistant bacterial strains. MRSA may be generated from MSSA through the acquisition of SCCmec in its chromosome, which carries a mecA gene that encodes a critical determinant for meticillin resistance (Kondo et al., 2007). The presence of the mecA gene may be simply confirmed by a PCR assay. A total of 192 S. aureus ST121 isolates were collected in literature with the information on mecA gene detection and most S. aureus ST121 strains were mecA negative (89.1 %, 171/192) (Fig. 2c), indicating that the majority of S. aureus ST121 strains belong to MSSA.

Toxins carriage by S. aureus clone ST121

Although the toxin profiles controlled by different agr types in S. aureus need to be explored, most ST121 strains carry agr IV (Fig. 2b). The S. aureus strains circulating in the community, such as CA-MRSA and MSSA, are believed to...
Table 1. Distribution and characteristics of reported ST121 *S. aureus* strains

<table>
<thead>
<tr>
<th>Region</th>
<th>spa types</th>
<th>agr types</th>
<th>PVL-positive/negative</th>
<th>MRSA/MSSA</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>t645</td>
<td>ND</td>
<td>ND</td>
<td>MSSA</td>
<td>Kateete <em>et al.</em> (2013)</td>
</tr>
<tr>
<td>Cape Verde Islands</td>
<td>ND</td>
<td>ND</td>
<td>PVL+</td>
<td>MSSA</td>
<td>Hotez <em>et al.</em> (2011)</td>
</tr>
<tr>
<td>Ghana</td>
<td>t213, t091, t314, t2304, t159, t645, t1077, t7002</td>
<td>ND</td>
<td>PVL+, PVL−</td>
<td>MSSA</td>
<td>Egyir <em>et al.</em> (2014)</td>
</tr>
<tr>
<td>Nigeria</td>
<td>t159, t314</td>
<td>agr IV</td>
<td>PVL+</td>
<td>MSSA, MRSA</td>
<td>Ghebremedhin <em>et al.</em> (2009)</td>
</tr>
<tr>
<td>Sao Tomé and Principe</td>
<td>t159, t2304</td>
<td>agr IV</td>
<td>PVL+</td>
<td>MSSA</td>
<td>Conceição <em>et al.</em> (2014)</td>
</tr>
<tr>
<td>South Africa</td>
<td>ND</td>
<td>ND</td>
<td>PVL+</td>
<td>MSSA</td>
<td>Reva <em>et al.</em> (2009)</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>t1425</td>
<td>agr IV</td>
<td>PVL−</td>
<td>MSSA</td>
<td>Fan <em>et al.</em> (2009); Chen <em>et al.</em> (2010); Jiang <em>et al.</em> (2013); Rao <em>et al.</em> (2015)</td>
</tr>
<tr>
<td>Japan</td>
<td>t159</td>
<td>ND</td>
<td>PVL+</td>
<td>MSSA, MRSA</td>
<td>Kikuta <em>et al.</em> (2011); Kawaguchiya <em>et al.</em> (2011); Reva <em>et al.</em> (2009)</td>
</tr>
<tr>
<td>Cambodia</td>
<td>ND</td>
<td>ND</td>
<td>PVL+</td>
<td>MRSA</td>
<td>Chheng <em>et al.</em> (2009)</td>
</tr>
<tr>
<td>Myanmar</td>
<td>ND</td>
<td>agr IV</td>
<td>PVL+</td>
<td>MSSA</td>
<td>Aung <em>et al.</em> (2011)</td>
</tr>
<tr>
<td>Indonesia</td>
<td>ND</td>
<td>ND</td>
<td>PVL+</td>
<td>MSSA</td>
<td>Severin <em>et al.</em> (2008)</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>England and Wales</td>
<td>ND</td>
<td>agr IV</td>
<td>ND</td>
<td>MSSA</td>
<td>Holmes <em>et al.</em> (2005)</td>
</tr>
<tr>
<td>Germany</td>
<td>t162, t284</td>
<td>agr IV</td>
<td>PVL+, PVL−</td>
<td>MSSA</td>
<td>Layer <em>et al.</em> (2006); Schefold <em>et al.</em> (2007); Monecke <em>et al.</em> (2007); Wiese–Possett <em>et al.</em> (2007)</td>
</tr>
<tr>
<td>Russia</td>
<td>t828, t466, t287, t83, t829, t827</td>
<td>ND</td>
<td>PVL+</td>
<td>MSSA</td>
<td>Baranovich <em>et al.</em> (2010)</td>
</tr>
<tr>
<td>Latvia</td>
<td>t308, t435, t284, t159</td>
<td>ND</td>
<td>PVL+</td>
<td>MSSA</td>
<td>Cupane <em>et al.</em> (2012)</td>
</tr>
<tr>
<td>Spain</td>
<td>t270, t435, t645, t159, t2155, t51, t314</td>
<td>agr II, agr IV</td>
<td>PVL+</td>
<td>MSSA, MRSA</td>
<td>González-Domínguez <em>et al.</em> (2012); Gómez-Sanz <em>et al.</em> (2013); Blanco <em>et al.</em> (2011)</td>
</tr>
<tr>
<td>Portugal</td>
<td>t159, t411</td>
<td>agr II, agr IV</td>
<td>ND</td>
<td>MSSA</td>
<td>Aires de Sousa <em>et al.</em> (2005); Conceição <em>et al.</em> (2011)</td>
</tr>
<tr>
<td>Czech and Slovak</td>
<td>t916, t6645, t6644, t159, t169, t645</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Růžičková <em>et al.</em> (2012)</td>
</tr>
</tbody>
</table>

ND, not determined.
## Table 2. Determined spa types for *S. aureus* ST121 strains

<table>
<thead>
<tr>
<th>spa types</th>
<th>No. of isolates (no. from each corresponding reference)</th>
<th>Origin(s) of isolates of each spa type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>t091</td>
<td>2</td>
<td>Ghana</td>
<td>Egyir et al. (2014)</td>
</tr>
<tr>
<td>t151</td>
<td>1</td>
<td>Spain</td>
<td>Gómez-Sanz et al. (2013)</td>
</tr>
<tr>
<td>t159</td>
<td>58 (1, 5, 1, 19, 4, 25, 3)</td>
<td>Latvia, Ghana, Portugal, Spain, Czech and Slovak, São Tomé and Principe</td>
<td>Tavares et al. (2014); Egyir et al. (2014); Conceição et al. (2014); Gómez-Sanz et al. (2013); Conceição et al. (2011); Cupane et al. (2012); Ružičková et al. (2012)</td>
</tr>
<tr>
<td>t162</td>
<td>1</td>
<td>Germany</td>
<td>Layer et al. (2006)</td>
</tr>
<tr>
<td>t169</td>
<td>1</td>
<td>Czech and Slovak</td>
<td>Ružičková et al. (2012)</td>
</tr>
<tr>
<td>t213</td>
<td>1</td>
<td>Ghana</td>
<td>Egyir et al. (2014)</td>
</tr>
<tr>
<td>t270</td>
<td>1</td>
<td>Spain</td>
<td>Blanco et al. (2011)</td>
</tr>
<tr>
<td>t284</td>
<td>3 (1, 1, 1)</td>
<td>Germany, Latvia</td>
<td>Schefold et al. (2007); Cupane et al. (2012); Ružičková et al. (2012)</td>
</tr>
<tr>
<td>t287</td>
<td>8</td>
<td>Russia</td>
<td>Baranovich et al. (2010)</td>
</tr>
<tr>
<td>t308</td>
<td>2 (1, 1)</td>
<td>Latvia</td>
<td>Tavares et al. (2014); Cupane et al. (2012)</td>
</tr>
<tr>
<td>t314</td>
<td>18 (2, 16)</td>
<td>Ghana, Spain</td>
<td>Egyir et al. (2014); González-Domínguez et al. (2012)</td>
</tr>
<tr>
<td>t435</td>
<td>8 (4, 1, 3)</td>
<td>Latvia, Spain</td>
<td>Tavares et al. (2014); Blanco et al. (2011); Cupane et al. (2012);</td>
</tr>
<tr>
<td>t466</td>
<td>2</td>
<td>Russia</td>
<td>Baranovich et al. (2010)</td>
</tr>
<tr>
<td>t645</td>
<td>21 (5, 1, 5, 10)</td>
<td>Uganda, Spain, Ghana, Czech and Slovak</td>
<td>Egyir et al. (2014); Blanco et al. (2011); Kateete et al. (2013); Ružičková et al. (2012)</td>
</tr>
<tr>
<td>t827</td>
<td>1</td>
<td>Russia</td>
<td>Baranovich et al. (2010)</td>
</tr>
<tr>
<td>t828</td>
<td>1</td>
<td>Russia</td>
<td>Baranovich et al. (2010)</td>
</tr>
<tr>
<td>t829</td>
<td>1</td>
<td>Russia</td>
<td>Baranovich et al. (2010)</td>
</tr>
<tr>
<td>t830</td>
<td>3</td>
<td>Russia</td>
<td>Baranovich et al. (2010)</td>
</tr>
<tr>
<td>t916</td>
<td>9</td>
<td>Czech and Slovak</td>
<td>Ružičková et al. (2012)</td>
</tr>
<tr>
<td>t1077</td>
<td>1</td>
<td>Ghana</td>
<td>Egyir et al. (2014)</td>
</tr>
<tr>
<td>t1425</td>
<td>7 (6, 1)</td>
<td>China</td>
<td>Chen et al. (2010); Jiang et al. (2013)</td>
</tr>
<tr>
<td>t2155</td>
<td>1</td>
<td>Spain</td>
<td>Gómez-Sanz et al. (2013)</td>
</tr>
<tr>
<td>t2304</td>
<td>10 (9, 1)</td>
<td>São Tomé and Principe, Ghana</td>
<td>Egyir et al. (2014); Conceição et al. (2014)</td>
</tr>
<tr>
<td>t6644</td>
<td>1</td>
<td>Czech and Slovak</td>
<td>Ružičková et al. (2012)</td>
</tr>
<tr>
<td>t6645</td>
<td>1</td>
<td>Czech and Slovak</td>
<td>Ružičková et al. (2012)</td>
</tr>
<tr>
<td>t7002</td>
<td>1</td>
<td>Ghana</td>
<td>Egyir et al. (2014)</td>
</tr>
</tbody>
</table>
to have more toxins and are thus more virulent than HA-MRSA strains; however, HA-MRSA strains are more drug resistant than CA-MRSA and MSSA (Thurlow et al., 2012; Drebes et al., 2014). Approximately 90% of S. aureus ST121 strains are MSSA (Fig. 2c). PVL is a bicomponent pore-forming cytotoxin assembled by LukS–PV and LukF–PV and closely related to the development of S. aureus infection (Hu et al., 2015). Most MSSA strains and successful MRSA clones present high frequency of PVL carriage (Ruimy et al., 2008). PVL carriage is a characteristic feature of CA-MRSA clones disseminated in Europe and the Middle East (ST80), Australia and South America (ST30–IV) and the United States (ST8–IV, also known as USA300) (Lina et al., 1999; Deurenberg & Stobberingh, 2009; David et al., 2011). About 201 isolates of S. aureus ST121 are subjected to detect the lukS–lukF genes by well-characterized PCR (Severin et al., 2008) and 92.0% (185/201) of the S. aureus ST121 isolates were PVL-positive (Fig. 2d, Table 1). S. aureus skin and soft tissue infections and severe deep-seated infections, such as necrotizing pneumonia, are frequently associated with pore-forming protein exotoxin PVL (Boyle-Vavra & Daum, 2007),

Fig. 2. Percentage of S. aureus ST121 strains with certain molecular types. (a) spa types for 164 ST121 strains obtained from 15 published studies. Other types included spa t091, t151, t162, t169, t213, t270, t284, t308, t466, t827, t828, t829, t830, t1077, t2155, t6644, t6645 and t7002. (b) agr types for 139 S. aureus ST121 strains obtained from 20 published studies. (c) mecA gene carriage for 192 ST121 strains obtained from 16 published studies. (d) PVL carriage for 201 ST121 strains obtained from 11 published studies.
which can recruit polymorphonuclear cells and monocytes that play important roles in anti-staphylococcal immunity and trigger apoptosis and lysis in these cells (Kaneko & Kamio, 2004). Although the significance of PVL in the increased virulence and pathogenicity of a certain S. aureus clone, such as USA300, is controversial (Márquez-Ortiz et al., 2014), Kreisel et al. (2011) found that 97.0% of USA300 isolates causing bacteraemia in adult patients had PVL and suggested its role as a virulence factor. The high frequency in carriage of PVL in S. aureus ST121 strains may contribute to the hypervirulent features of the clone and favour its successful spread (Conceição et al., 2011; Růžičková et al., 2012).

Except for PVL, enterotoxins (SEB, SEG, SEI, SEL), haemolysin (Hla, Hlb, Hlg, Hlg-V, Hld), leukocidins E and D (LukED) and exfoliative toxins (ETA, ETB) are involved in the infection cases caused by ST121 (Table 3). For the exfoliative toxin-producing (ET-positive) S. aureus strains, a study conducted in one Slovak and 23 Czech maternity hospitals from 1998 to 2011 demonstrated that 37.0% (47/126) of the isolated ET-positive strains were S. aureus ST121 (Růžičková et al., 2012). However, the characteristic toxin profile of S. aureus ST121 clonal strains remains unclear and needs more intensive study on strains collected globally.

**Table 3. Major diseases caused by S. aureus ST121**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of isolates</th>
<th>Toxin profile</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptodermia</td>
<td>1</td>
<td>PVL</td>
<td>Cupane et al. (2012)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>3</td>
<td>PVL</td>
<td>Chheng et al. (2009); Cupane et al. (2012)</td>
</tr>
<tr>
<td>Bursitis</td>
<td>1</td>
<td>PVL</td>
<td>Cupane et al. (2012)</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>1</td>
<td>PVL</td>
<td>Cupane et al. (2012)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>9</td>
<td>LukED, Hlg-V, SEL</td>
<td>Conceição et al. (2011)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>15</td>
<td>PVL, SEB, SEG, SEI</td>
<td>Egyir et al. (2014); Holmes et al. (2005)</td>
</tr>
<tr>
<td>Septic multiple organ failure</td>
<td>1</td>
<td>PVL</td>
<td>Schefold et al. (2007)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2</td>
<td>PVL</td>
<td>Egyir et al. (2014); González-Dominguez et al. (2012)</td>
</tr>
<tr>
<td>Perianal abscess</td>
<td>1</td>
<td>PVL, SEG, SEI</td>
<td>Holmes et al. (2005)</td>
</tr>
<tr>
<td>Neonatal skin blistering disorders</td>
<td>47</td>
<td>ETA, ETB</td>
<td>Růžičková et al. (2012)</td>
</tr>
<tr>
<td>Impetigo</td>
<td>2</td>
<td>LukED, Hlg-V, SEL, ETA</td>
<td>Kikuta et al. (2011); Conceição et al. (2011)</td>
</tr>
<tr>
<td>Cutaneous abscess</td>
<td>3</td>
<td>LukED, Hlg-V, SEL</td>
<td>Conceição et al. (2011)</td>
</tr>
<tr>
<td>Furunculus</td>
<td>1</td>
<td>PVL</td>
<td>Cupane et al. (2012)</td>
</tr>
<tr>
<td>Flegmona</td>
<td>1</td>
<td>PVL</td>
<td>Cupane et al. (2012)</td>
</tr>
<tr>
<td>SSTIs*</td>
<td>32</td>
<td>PVL, Hlg</td>
<td>Egyir et al. (2014); Monecke et al. (2007)</td>
</tr>
<tr>
<td>Soft tissue abscess</td>
<td>1</td>
<td>PVL</td>
<td>Chheng et al. (2009)</td>
</tr>
<tr>
<td>Wound infections</td>
<td>4</td>
<td>PVL, Hla, Hlb, Hlg, Hlg-V, Hld, SEG, SEI, SEL, LukED</td>
<td>Aung et al. (2011); Conceição et al. (2011)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>1</td>
<td>PVL, SEB, SEG, SEI</td>
<td>Holmes et al. (2005)</td>
</tr>
</tbody>
</table>

*SSTIs, Skin and soft tissue infections; LukED, leukocidins E and D; Hlg, γ-haemolysin; Hlg-V, Hlg variant.

Disease spectrum of S. aureus clone ST121

*S. aureus* often causes different diseases, and the spectrum of infections varies from mild and superficial to invasive and life-threatening diseases (Lowy, 1998). Severe invasive infections caused by *S. aureus* include bacteraemia, endocarditis, pneumonia, septic arthritis and osteomyelitis, whereas the mild superficial infections mainly involve the skin or soft tissue. Table 3 summarizes the diseases related to *S. aureus* ST121 as one globally disseminated clone. A total of 126 cases with *S. aureus* ST121 infection have been reported to date. The severe invasive infections include streptodermia (1/126) (Cupane et al., 2012), osteomyelitis (3/126) (Chheng et al., 2009; Cupane et al., 2012), bursitis (1/126) (Cupane et al., 2012), lymphadenitis (1/126) (Cupane et al., 2012), cellulitis (9/126) (Conceição et al., 2011), bacteraemia (15/126) (Holmes et al., 2005) and septic multiple organ failure (1/126) (Rao et al., 2015); whereas, the mild superficial infections include urinary tract infection (2/126) (González-Dominguez et al., 2012; Egyir et al., 2014), perianal abscess (1/126) (Holmes et al., 2005), neonatal skin blistering disorders (47/126) (Růžičková et al., 2012), impetigo (2/126) (Conceição et al., 2011; Kikuta et al., 2011), cutaneous abscess (3/126) (Conceição et al., 2011), furunculus (1/126) (Cupane et al., 2012), flegmona (1/126) (Cupane et al., 2012), SSTIs (32/126) (Monecke et al., 2007; Egyir et al., 2014), soft tissue abscess (1/126) (Chheng et al., 2009), wound infections (4/126) (Aung et al., 2011; Conceição et al., 2011) and skin lesions (1/126) (Holmes et al., 2005).

As an *S. aureus* clone with increased virulence often associated with PVL, patients with ST121 infection may often run an increased risk of longer hospitalization and need prolonged treatment. Cupane et al. (2012) performed a
prospective observational study on 224 patients with *S. aureus* infection. PCR investigations of all 224 corresponding *S. aureus* isolates revealed that 168 (75.0%) carried PVL genes. Importantly, hospitalization was significantly longer in the PVL-positive patient group (median duration 15 days) in comparison with that in the PVL-negative group (median duration 10 days) (*P* < 0.001). Molecular typing demonstrated that the majority of the typed *S. aureus* strains (n = 90) belonged to the *spa* type t435 (n = 52), or closely related types (t159, t308 and t284), and MLST results for PVL-positive isolates with *spa* type t435 and closely related *spa* types revealed that all of them were *S. aureus* ST121 (Cupane et al., 2012). Moreover, the clinical efficacy of the antimicrobial therapy may be insufficient for PVL-positive MSSA causing severe infections, for example, ST121 caused multiple organ failure, even though the favourable in vitro sensitivity testing of the causative *S. aureus* was conducted (Rao et al., 2015). The early, combined and prolonged treatment was usually proposed for serve *S. aureus* ST121 infections. In the case of the first reported *S. aureus* ST121 causing sepsis (Scheinfeld et al. 2007), the patient received triple organism-sensitive antibiotic therapy (linezolid, imipenem and clindamycin) for 2 weeks; however, the metastatic soft tissue infection developed progressively then the antimicrobial therapy was changed to a combination of daptomycin and clindamycin. After continued antimicrobial and surgical therapy, the patient was led to stabilization and discharged from hospital.

**Conclusion**

As a predicted founder of the major *S. aureus* lineages, ST121 is mainly disseminated in Africa, Asia and Europe. The overall prevalence rate was approximately 10% in MSSA isolates, and less than 5% in MRSA isolates. Although epidemiological data from other continents, such as Oceania and South and North America, need to be accumulated, several international studies revealed that *S. aureus* ST121 prevailed in these regions, such as the US (Goering et al., 2008; Rasigade et al., 2010). Moleularly, large numbers of *S. aureus* ST121 isolates harbour PVL and belong to *agr* IV, while *spa* types for *S. aureus* ST121 strains are exceptionally diverse, with t159, t645, t314, t2304, t916, t435, t287 and t1425 as the common predominant types. These molecular characteristics reflect both the consistency and complexity of *S. aureus* clone ST121, facilitating the building of a surveillance system and monitoring for this disseminated *S. aureus* clone. The disease spectrum associated with *S. aureus* ST121 infections is also broad. *S. aureus* ST121 clonal strains can be nasally carried by healthy individuals and cause mild superficial and severe invasive infections.

Although the virulence factor profile for *S. aureus* hyper-virulent ST121 clone needs to be further investigated, the patients with ST121 infection often need longer hospitalization and need prolonged antimicrobial therapy.

**ACKNOWLEDGEMENTS**

This review used the MLST database (http://www.mlst.net). This work was supported by the National Natural Science Foundation of China (grant numbers 31570127, 81471993) and the New Drug Development Project of China (2012ZX09103301-038). The authors declare no conflicts of interest.

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genomes among methicillin-sensitive Staphylococcus aureus strains carried


