Methicillin-susceptible *Staphylococcus aureus* clonal complex 398: high prevalence and geographical heterogeneity in bone and joint infection and nasal carriage

F. Valour[1,2,3,*], J. Tasse[3,*], S. Trouillet-Assant[3], J.-P. Rasigade[1,3], B. Lamy[4], E. Chanard[5], P. Verhoeven[6], J.-W. Decousser[7], H. Marchandin[4], M. Bès[3,8,9], C. Chidiac[2,3], F. Vandenesch[3,8,9], T. Ferry[2,3] and F. Laurent[1,3,8,9] on behalf of the Lyon Bone and Joint Infection study group[†]

1) *Bacteriology Department, Groupement Hospitalier Nord,* 2) *Infectious Diseases Department, Hospices Civils de Lyon,* 3) *International Centre for Research in Infectious Diseases, INSERM U1111, Université Claude Bernard Lyon 1, Lyon,* 4) *Bacteriology Department, Montpellier University Hospitals, Montpellier,* 5) *Bacteriology Department, Novescia, Lyon,* 6) *Bacteriology Department, Saint Etienne University Hospitals, St Etienne,* 7) *Bacteriology Department, Hôpital Henri-Mondor, Assistance Publique – Hôpitaux de Paris, Paris,* 8) *Bacteriology Department, Groupement Hospitalier Est, and* 9) *French National Reference Centre for Staphylococci, Hospices Civils de Lyon, Lyon, France*

Corresponding author: F. Valour, Laboratoire de Bactériologie, Groupement Hospitalier Nord, 103 Grande-Rue de la Croix-Rousse, 69004 Lyon, France
E-mail: florent.valour@chu-lyon.fr

*These authors contributed equally to this work.
[†]Lyon Bone and Joint Infection study group members are given in Appendix 1.

Abstract

The prevalence of clonal complex (CC) 398 methicillin-susceptible *Staphylococcus aureus* (MSSA) was unexpectedly high among bone and joint infections (BJIs) and nasal-colonizing isolates in France, with surprising geographical heterogeneity. With none of the major, most-known staphylococcal virulence genes, MSSA CC398 BJI was associated with lower biological inflammatory syndrome and lower treatment failure rates.

Keywords: Clonal complex 398, bone and joint infection, methicillin-susceptible *Staphylococcus aureus*, molecular epidemiology, nasal carriage, virulence factors
Original Submission: 1 September 2013; **Revised Submission:** 15 December 2013; **Accepted:** 21 January 2014
Editor: P. Tassios
Article published online: 26 January 2014
Clin Microbiol Infect 2014; **20**: O772–O775
10.1111/1469-0691.12567

In addition to being a frequent colonizing organism, *Staphylococcus aureus* is one of the leading causes of human suppurative infections, such as bone and joint infections (BJIs). Although wild isolates are susceptible to methicillin (methicillin-susceptible *S. aureus* (MSSA)), methicillin-resistant *S. aureus* (MRSA) isolates emerged from MSSA initially in hospital settings (so-called hospital-acquired MRSA) and then in the community (community-acquired MRSA) by acquiring the SCC*mec* element harbouring the *mec*A gene, which encodes a specific penicillin-binding protein (PBP2a). In the past 10 years, livestock has been described as a third MRSA reservoir (livestock-associated MRSA), notably because of the worldwide spread of MRSA of sequence type (ST) 398 or related STs clustered in clonal complex (CC) 398 [1,2]. Initially reported as an animal colonizer, MRSA CC398 has been shown to be responsible for various human infections [2]. Whole genome sequence analysis has provided evidence that this MRSA clone probably originated in humans as MSSA, and then jumped to livestock, where it acquired methicillin resistance-associated genes [1]. However, little is known about this MSSA CC398 counterpart. Poorly described in animals, this clone was recently reported in people lacking livestock-associated risk factors as a rare pathogen in various conditions such as bloodstream, respiratory tract and skin and soft tissue infections, and infective endocarditis in several countries, as well as a rare human nasal commensal [3–7]. However, the role of MSSA CC398 in BJIs has not been described.

To investigate MSSA CC398 in BJIs, we conducted a retrospective study of all patients with monomicrobial or polymicrobial MSSA BJI (i.e. clinical evidence of infection and at least one reliable MSSA-positive bacteriological sample) diagnosed in four French geographical areas between 2009 and 2012 (Fig. 1). Because nasal carriage of staphylococci is associated with a high risk of *S. aureus* infection, a control population of nasal-colonizing isolates was established in two of the participating centres, obtained by nasal sampling of patients admitted for orthopaedic surgery (excluding patients with BJIs) or in intensive-care units. *S. aureus* characterization was initially performed with the automated system Vitek-2 (bioMérieux, Marcy l'Etoile, France).

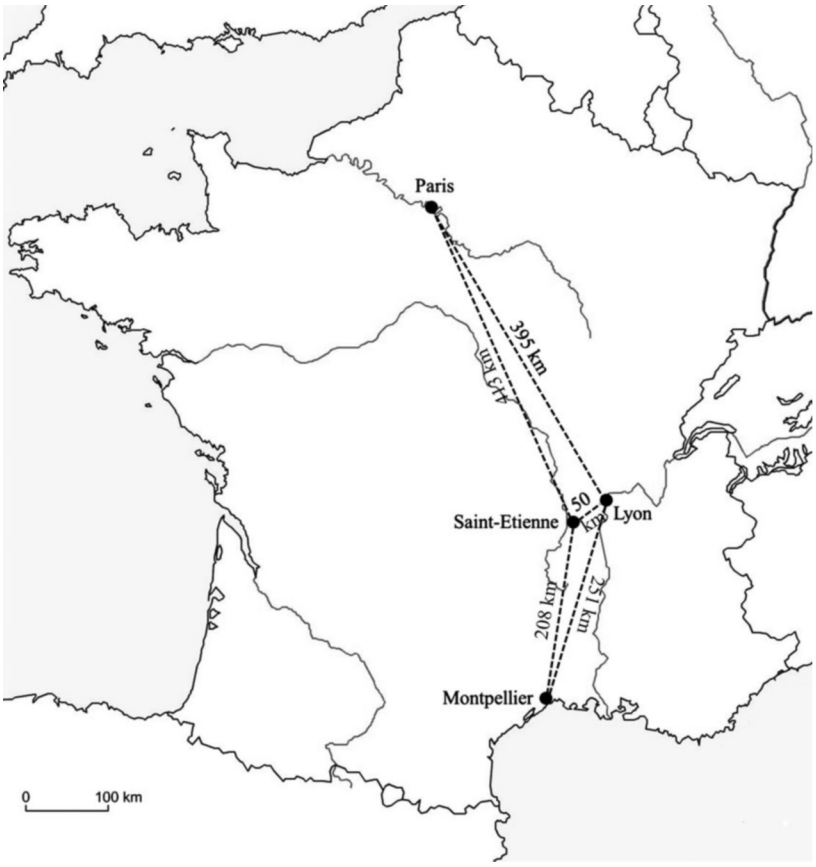

FIG. 1. Map showing the four geographical areas included in the study.

A total of 485 isolates from patients with MSSA BJIs (Lyon, *n* = 173 (Hospices Civils de Lyon, *n* = 75; Novescia, *n* = 98); Montpellier, *n* = 132; Saint-Etienne, *n* = 96; Paris, *n* = 84) were screened by the use of CC398-specific PCR targeting the *sau1–hsdS1* gene, as previously described [8]. Within this MSSA BJI collection, 68 of the 485 isolates (14.0%) belonged to CC398. For comparison, 31 (9.0%) of the 346 nasal-colonizing MSSA isolates (Hospices Civils de Lyon, from 2010 to 2012, *n* = 228; Montpellier, 2012, *n* = 118) were CC398. Because most previous international staphylococcal clonal distribution studies have mainly focused on MRSA, it is difficult to determine whether this clone is emerging or has been neglected thus far. However, several facts argue for emergence. Concerning nasal-colonizing strains, CC398 accounted for only two of 829 (0.2%) MSSA isolates in a Dutch study published in 2008, and two of 52 (3.8%) Spanish MSSA isolates in 2009 [3,4]. With respect to BJIs, Luedicke *et al.* reported a high diversity of staphylococcal genetic backgrounds for the 2005–2006 period in Germany, with a distribution of the major CCs similar to that in our study, but no CC398 [9]. These differences may have been influenced by geographical area, but the hypothesis that this clone emerged and rapidly spread is supported by the fact that only one CC398 strain was identified in 2008 during screening of BJI MSSA strains isolated in our hospital in the period between 2001 and 2008 among 52 isolates (1.9%; p 0.081).

Surprisingly, heterogeneity in geographical distribution was observed. The prevalence of CC398 among MSSA BJI isolates was only 3.1% in Saint-Etienne, reached 10.4% in Lyon, and was as high as 19.0% in Paris and 23.5% in Montpellier. The frequency in Montpellier was significantly different from that observed in Saint-Etienne (p 0.002) and Lyon (p 0.009), and the frequency in Paris was different from that in Saint-Etienne (p 0.002) and Lyon (p 0.046). It is of note that the lower prevalence of MSSA CC398 was found in two cities that are close to each other (Lyon and Saint-Etienne; 50 km). Similarly, an important difference was observed in MSSA CC398 rate among nasal-colonizing isolates between Lyon (*n* = 9/228; 3.9%) and Montpellier (*n* = 22/118; 18.6%; p 0.013). This heterogeneity in geographical prevalence raises the question of the driving mechanism. It may lie in greater endemic diffusion in some areas, possibly related to specific routes of transmission, risk factors, and environmental conditions, or the emergence of subpopulations associated with the acquisition of particular genetic traits in other areas.