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# Molecular epidemiology and antimicrobial susceptibility profiles of methicillin-resistant *Staphylococcus aureus* blood culture isolates: results of the Quebec Provincial Surveillance Programme

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## SUMMARY

The objectives of this study were to characterize methicillin-resistant *Staphylococcus aureus* (MRSA) blood culture isolates and to determine their relative importance in both nosocomial and community-acquired infections. A total of 535 MRSA blood culture isolates were analysed. *In vitro* susceptibility to 14 agents was determined. The genes *nuc, mecA* and coding for PVL toxin were identified by PCR. All isolates were characterized by PFGE or *spa* typing to assess their genomic relationships. Most MRSA isolates were retrieved from nosocomial bloodstream infections (474, 89%) and were of the CMRSA2 genotype. Healthcare-associated (HA)-MRSA bloodstream infections were associated with older age (70–89 years, $P = 0{\cdot}002$) and most often secondary to central line infections ($P = 0{\cdot}005$). Among MRSA strains associated with community-acquired (CA)-MRSA, 28·8% were isolated in intravenous drug users. CA-MRSA genotypes were more frequently found in young adults (20–39 years, $P < 0{\cdot}0001$) with skin/soft tissue as the primary sources of infection ($P = 0{\cdot}006$). CMRSA10 genotype was the predominant CA-MRSA strain. All MRSA isolates were susceptible to doxycycline, tigecycline, trimethoprim/sulfamethoxazole and vancomycin. Both the presence of the genes coding for PVL toxin (89·8%) and susceptibility to clindamycin (86·5%) were predictive of CA-MRSA genotypes. Whereas in the USA, HA-MRSA have been replaced by USA300 (CMRSA10) clone as the predominant MRSA strain type in positive blood cultures from hospitalized patients, this phenomenon has not been observed in the province of Quebec.

**Key words**: Antibiotic resistance, bloodstream infections, molecular epidemiology, *Staphylococcus aureus*.

## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first described in 1961, and quickly became an important nosocomial pathogen worldwide [1, 2]. The mid-1990s witnessed the spread of community-acquired infections caused by MRSA strains (CA-MRSA) associated with clinical and molecular characteristics different from those of healthcare-associated (HA)-MRSA) [3]. CA-MRSA strains are mainly responsible for skin and soft tissue infections but also cause invasive infections such as septic arthritis, bacteraemia, toxic

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shock syndrome, necrotizing fasciitis and necrotizing pneumonia [4]. CA-MRSA has become a major public health problem mainly in children and young adults [5, 6]. HA-MRSA strains predominantly cause invasive infections, such as pneumonia and bacteraemia in elderly individuals exposed to healthcare settings [7–9]. Males tend to have higher rates of HA-MRSA bloodstream infections [10].

CA-MRSA strains have genetic characteristics that distinguish them from HA-MRSA strains. CA-MRSA carry specific staphylococcal cassette chromosome *mec* (SCC*mec*) elements, usually the genes coding for Panton–Valentine leukocidin (PVL) toxin, are polyclonal and pauci-resistant [3, 5, 11, 12]. A recent report on MRSA in Canada revealed a significant increase in the prevalence of CA-MRSA strains mainly due to CMRSA7 and CMRSA10 genotypes [8]. Since 2006, as part of the Surveillance Provinciale des Infections Nosocomiales (Provincial Nosocomial Infection Surveillance programme), surveillance of *S. aureus* bloodstream infections in Quebec has been mandatory [13, 14]. From 2006 to 2012, the total annual number of *S. aureus* bloodstream infections has remained stable with a mean of 1765 episodes per year. The proportion of *S. aureus* bacteraemias caused by methicillin-resistant strains has decreased from 24·5% in 2006 ($n = 421$) to 16·9% in 2012 ($n = 300$). However, during the same time period we have observed a 14·5% increase in the number of CA-MRSA bacteraemias [13]. A change in the epidemiology of MRSA infections has also been observed in many parts of Canada during this same period [8, 10].

Analysis of the clinical data collected through the provincial surveillance programme led to the implementation of a laboratory surveillance programme to characterize all MRSA blood culture isolates in Quebec. The objective was to improve the robustness of the surveillance of CA-MRSA and HA-MRSA bacteraemias by studying the clonal composition of the MRSA isolates and determining their antibiotic susceptibility profiles.

## METHODS

### Study population and bacterial isolates

From 1 April 2009 to 31 March 2010, and 1 April 2011 to 31 March 2012, all hospital laboratories in the province of Quebec were asked to send their MRSA blood culture isolates (one isolate per patient per 28-day period) to the Laboratoire de santé publique du Québec (LSPQ). Demographic, clinical and epidemiological information was collected by infection control practitioners using a standardized questionnaire. A clinical case of community-acquired bacteraemia was defined as an infection diagnosed within 48 h of admission to hospital or an infection not associated with healthcare interventions within the previous 12 months (dialysis treatments, installation of a percutaneous device or indwelling catheter, surgery, any stay in an acute-care facility, long-term care facility or nursing home).

### Antimicrobial susceptibility testing

The minimum inhibitory concentrations (MICs) were determined by broth microdilution according to CLSI guidelines [15–17]. The following antibiotics were tested at concentrations varying from 0·06 to 64 mg/l (except for rifampicin: 0·016–16 mg/l): clindamycin, daptomycin, doxycycline, erythromycin, gentamicin, fusidic acid, levofloxacin, linezolid, oxacillin, rifampicin, trimethoprim-sulfamethoxazole and vancomycin. Inducible resistance to clindamycin was detected by D-test according to CLSI guidelines [16]. The MIC for tigecycline was determined using a gradient dilution method (E-test), as recommended by the manufacturer [18]. High-level mupirocin resistance was determined by disk diffusion according to CLSI guidelines [16]. MICs were interpreted using breakpoints established by CLSI, except for fusidic acid and tigecycline where EUCAST breakpoints were used [19].

### Molecular typing

Confirmation of MRSA identification was performed by PCR amplification of the *nuc* gene [20] and confirmation of methicillin resistance by PCR amplification of the *mecA* gene [21]. The detection of the *lukS-PV* and *lukF-PV* genes coding for PVL toxin was done by PCR [22]. Molecular characterization was performed using either pulsed-field gel electrophoresis (PFGE) [2] or *spa* typing [23]. Genotypes were associated with their corresponding MRSA epidemic type according to the procedure of the National Microbiology Laboratory (NML) [24]. Any MRSA with a PFGE pattern or a *spa* type associated with CMRSA10 and USA1100 were considered as a CA-MRSA genotype, while CMRSA2, CMRSA8 and USA700 were considered as HA-MRSA genotypes. MRSA with a PFGE pattern or a *spa* type not

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associated with one of the known Canadian or American epidemic types were considered as unique genotypes.

### Statistical analysis

HA-MRSA and CA-MRSA epidemiological data were compared by $\chi^2$ test or Fisher's exact test. Significance level for all analysis was $P < 0{\cdot}05$. All statistical analysis were performed using Statistix v. 7·1 (Analytical Software, USA).

## RESULTS

### Clinical and epidemiological data

During the surveillance period, 3522 episodes of *S. aureus* bacteraemia were reported through the provincial surveillance programme. Of these, 647 (18·4%) were caused by MRSA strains. A total of 535 isolates were submitted to the LSPQ and analysed: 270 isolates collected during the 2009–2010 surveillance period and 265 collected during the 2011–2012 surveillance period. The mean age of the patients was 69 years (median 73, range 1–103) and the male/female ratio was 1·6/1. According to the clinical information provided on the questionnaires, 376 (70·3%) bloodstream infections were healthcare-associated, 149 (27·8%) were community-acquired and 10 (1·9%) could not be categorized. Table 1 presents the summary of the demographic data, primary infection sites and site of acquisition of bacteraemias for both HA-MRSA and CA-MRSA genotypes. Healthcare-acquired infections were more common in the elderly and most frequently associated with central line infections and almost all caused by HA-MRSA genotypic strains. Conversely, half the patients with CA-MRSA bacteraemias were agred <50 years and had skin and soft tissue or pulmonary infections identified as the primary sources of infections. Intravenous drug users represented 28% of patients with community-acquired bacteraemias.

### Molecular typing

All 535 isolates were confirmed as MRSA and carried the *nuc* and *mecA* genes. Overall, 472 (88%) isolates were of the CMRSA2 genotype and 58 (11%) of the CMRSA10 genotype. Of the remaining five isolates, there was one CMRSA8 genotype, one USA700 genotype, one USA1100 genotype and two isolates with unique profiles (Table 2). None of the CMRSA2 strains carried the PVL toxin gene while 52 (89·2%) CMRSA10 strains did. The USA1100 and one unique genotype strain also carried the genes coding for PVL toxin (Table 1). There was no change in the pattern of genotype distribution during the two surveillance periods (data not shown). CA-MRSA genotypic strains were responsible for 11% ($n = 59$) of all MRSA bacteraemias in Quebec. As expected from the clinical data collected, CA-MRSA types were most commonly isolated in young adults aged 20–39 years ($P < 0{\cdot}0001$) and in patients with bacteraemias associated with skin/soft tissues infections ($P = 0{\cdot}006$) while HA-MRSA genotypic strains were more frequently isolated in patients aged 70–89 years ($P = 0{\cdot}002$) with central line infections ($P = 0{\cdot}005$). In addition, CA-MRSA types were significantly associated with community-acquired infections while HA-MRSA types caused over 96·5% of healthcare-related episodes ($P < 0{\cdot}0001$). Interestingly and of importance, 22% ($n = 13$) of bloodstream infections caused by CA-MRSA genotypes were deemed to have been acquired in the healthcare setting and 21·9% ($n = 104$) of HA-MRSA genotypes were deemed to have been acquired in the community (Table 1). Overall, CA-MRSA strains were responsible for 3·5% of all HA-MRSA bloodstream infections and 30·2% of CA-MRSA bloodstream infections. Intravenous drug use was significantly associated with CA-MRSA bacteraemias ($P < 0{\cdot}0001$).

### MRSA isolates' antimicrobial susceptibilities

Table 3 summarizes the susceptibility testing results. The majority of strains were resistant to levofloxacin (98·7%), erythromycin (97·4%) and clindamycin (86·5%). Resistance to the following antibiotics was very low: daptomycin (0·2%), gentamicin (0·6%), fusidic acid (5%), linezolid (0·2%) and rifampicin (1·1%). All isolates were susceptible to doxycycline, tigecycline, trimethoprim-sulfamethoxazole and vancomycin. Only three isolates (0·6%) harboured high level resistance to mupirocin. Clindamycin resistance was inducible in 114 (21·3%) isolates. Using susceptibility to clindamycin as a predictor of CA-MRSA genotype had a sensitivity of 86·4% and a specificity of 95·6%. The positive and negative predictive values were 70·8% and 98·3%, respectively. Of the eight CA-MRSA strains which were resistant to clindamycin, seven harboured the *PVL* gene. There was no difference in the antimicrobial susceptibility profiles between CMRSA2 and CMRSA10 types, except for clindamycin, erythromycin and levofloxacin. The susceptibility profiles remained unchanged during the two surveillance periods.

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Table 1. *Clinical, epidemiological and molecular data for MRSA isolates*

| Characteristic | Genotype of the MRSA isolates | | | Total ($N$ = 535) $n$ (%) | HA- *vs.* CA-MRSA $P$ value |
|---|---|---|---|---|---|
| | HA-MRSA ($N$ = 474), $n$ (%) | CA-MRSA ($N$ = 59), $n$ (%) | Unique genotypes ($N$ = 2), $n$ (%) | | |
| Sex | | | | | 0·41 |
| Male | 291 (61·4) | 39 (66·1) | 1 (50) | 331 (61·9) | |
| Female | 183 (38·6) | 20 (33·9) | 1 (50) | 204 (38·1) | |
| Demographic data (age in years) | | | | | |
| ⩽19 | 2 (0·4) | 0 | 0 | 2 (0·4) | 0·62 |
| 20–29 | 5 (1·1) | 6 (10·2) | 1 (50) | 12 (2·2) | <0·0001 |
| 30–39 | 6 (1·2) | 16 (27·1) | 0 | 22 (4·1) | <0·0001 |
| 40–49 | 23 (4·9) | 6 (10·2) | 0 | 29 (5·4) | 0·09 |
| 50–59 | 54 (11·4) | 6 (10·2) | 1 (50) | 61 (11·4) | 0·78 |
| 60–69 | 91 (19·2) | 10 (16·9) | 0 | 101 (18·9) | 0·68 |
| 70–79 | 137 (28·9) | 6 (10·2) | 0 | 143 (26·7) | 0·002 |
| 80–89 | 129 (27·2) | 5 (8·4) | 0 | 134 (25·1) | 0·002 |
| ⩾90 | 27 (5·7) | 4 (6·8) | 0 | 31 (5·8) | 0·74 |
| Primary infection sites | | | | | |
| Central intravenous catheters | 95 (20) | 3 (5·1) | 1 (50) | 99 (18·5) | 0·005 |
| Pulmonary infection | 65 (13·7) | 12 (20·3) | 0 | 77 (14·4) | 0·17 |
| Skin/soft tissue infection | 64 (13·5) | 16 (27·2) | 1 (50) | 81 (15·1) | 0·006 |
| Surgical site infection | 50 (10·6) | 6 (10·2) | 0 | 56 (10·5) | 0·93 |
| Urinary tract infection | 58 (12·2) | 4 (6·8) | 0 | 62 (11·6) | 0·22 |
| Bone and joint infection | 45 (9·5) | 5 (8·4) | 0 | 50 (9·3) | 0·80 |
| Other | 38 (8) | 3 (5·1) | 0 | 41 (7·7) | 0·43 |
| Unknown | 59 (12·5) | 10 (16·9) | 0 | 69 (12·9) | 0·33 |
| Origin of infection | | | | | |
| Healthcare origin | 361 (73·2) | 13 (22) | 2 (100) | 376 (70·3) | <0·0001 |
| Community origin | 104 (21·9) | 45 (76·3) | | 149 (27·8) | <0·0001 |
| Unknown origin | 9 (1·9) | 1 (1·7) | 0 | 10 (1·9) | 0·91 |
| Community-associated risk factors | | | | | <0·0001 |
| Injection drug users | 1 (0·2) | 17 (28·8) | 0 | 18 (3·4) | |
| Inmate | 0 | 3 (5·1) | 0 | 3 (0·6) | |
| PVL toxin gene | | | | | <0·0001 |
| Negative | 474 (100) | 6 (10·2) | 1 (50) | 481 (89·9) | |
| Positive | 0 | 53 (89·8) | 1 (50) | 54 (11·1) | |

MRSA, Methicillin-resistant *Staphylococcus aureus*; HA, healthcare associated; CA, community acquired.

## DISCUSSION

Epidemiological definitions proved useful for differentiating CA-MRSA and HA-MRSA strain types in the past. However, since CA-MRSA strains are now transmitted in healthcare facilities, epidemiological definitions are becoming blurred [25]. Few studies have integrated the clinical and molecular epidemiology of MRSA bacteraemias. In our study, we document the clinical and molecular epidemiology of MRSA bacteraemias in Quebec. Most MSRA bloodstream infections were healthcare related, secondary to central line infections and caused by CMRSA2 genotype strains. This is in agreement with previously published reports [14]. We have also found, as have others, that CA-MRSA bacteraemias were most frequently secondary to skin and soft tissue infections [9, 26, 27], and commonly associated with intravenous drug use, a well-recognized risk factor for CA-MRSA infections [28, 29].

Two MRSA genotypes were responsible for 99% of the bloodstream infections in Quebec. As observed in the rest of Canada, CMRSA2 was the predominant hospital-associated MRSA genotype [3, 8, 12, 27, 30]. CA-MRSA genotypes were isolated in young adults (20–40 years) while HA-MRSA genotypes were more frequently isolated in older adults (⩾70 years). However, only 11% of strains isolated from blood cultures in Quebec were of CA-MRSA genotypes: this rate is lower than those previously reported

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Table 2. *Distribution of pulsed-field gel electrophoresis and spa types for MRSA isolates*

| Epidemic types | Genotyping results | No. of strains |
|---|---|---|
| CMRSA-2 (USA100/800/ New York, ST5) | *spa* type t002 | 209 |
| | t010 | 2 |
| | t045 | 8 |
| | t062 | 3 |
| | t067 | 2 |
| | t105 | 2 |
| | t1062 | 3 |
| | t179 | 1 |
| | t1791 | 1 |
| | t214 | 1 |
| | t2308 | 1 |
| | t306 | 3 |
| | t3136 | 1 |
| | t3469 | 1 |
| | t3979 | 1 |
| | t4052 | 1 |
| | t4865 | 1 |
| | t509 | 1 |
| | t539 | 1 |
| | t586 | 1 |
| | t601 | 1 |
| | t688 | 4 |
| | PFGE type CMRSA-2 | 223 |
| CMRSA-10 (USA300, ST8) | *spa* type t008 | 22 |
| | t009 | 1 |
| | PFGE type CMRSA-10 | 35 |
| CMRSA-8 (ERMSA15, ST22) | *spa* type t5605 | 1 |
| USA1100 (Southwest pacific, ST30) | *spa* type t019 | 1 |
| USA700 (ST72) | *spa* type t148 | 1 |
| Unique | *spa* type t267 | 1 |
| | t091 | 1 |
| Total | | 535 |

in a Canadian study conducted during the 2007–2009 period where rates as high as 25% were observed in some locations [30]. This could be due to the fact that CA-MRSA infections seem to be more prevalent in Western Canada (rural and First Nations communities in Manitoba and Saskatchewan), accounting for more than 90% of MRSA infections in some of those communities [8]. With the exception of one USA1100 strain [31], CMRSA10 was the only CA-MRSA genotype found in bloodstream infections. This is surprising since other CA-MRSA genotypes such as CMRSA7 are frequently isolated from other types of clinical specimens such as wound and sputum in Quebec [32]. Our data does not allow us to conclude that the CMRSA10 genotype is more virulent and invasive than other genotypes. However, Wu *et al*. have shown in a *Caenorhabditis elegans* host model that the CMRSA10 genotype was significantly more virulent than other genotypes including CMRSA7 [33]. In Quebec, very few healthcare-associated bloodstream infections were caused by CA-MRSA clonal strains. This is in contrast to the significant changes that have been observed in the USA where the USA300 (CMRSA10) clone has become the most predominant MRSA genotype recovered in blood cultures from hospitalized patients. This may be explained by the fact that the proportion of USA300 isolates are increasing in individuals colonized by MRSA in community settings [34].

Previous studies have reported differences in antimicrobial susceptibility profiles between CA-MRSA genotypes and HA-MRSA genotypes [30, 35]. Consistent with previous data, CA-MRSA isolates were more susceptible to clindamycin, erythromycin and levofloxacin. There was no difference between the susceptibility patterns according to genotype for other antibiotics tested. As described in other Canadian reports [8, 35], the majority of isolates were susceptible to daptomycin, gentamicin, fusidic acid, linezolid and rifampicin, and all isolates were susceptible to tigecycline and trimethoprim-sulfamethoxazole. Although a significant proportion (12%) of high-level resistance to mupirocin in CA-MRSA isolates has been reported in a previous Canadian study [35], only a few isolates in Quebec are resistant. We did not identify any isolates with reduced susceptibility to vancomycin but systematic screening for heteroresistance (hVISA) was not performed. In Canada, very few isolates with intermediate vancomycin resistance have so far been reported [8, 36]. Overall, resistance to erythromycin, clindamycin, and levofloxacin was relatively common. A significant proportion of our isolates (21·3%) were resistant to clindamycin and harboured an inducible resistance mechanism to clindamycin as detected by the D-test (typically mediated by *erm* genes and in the presence of erythromycin as inducer) [37]. The majority of hospital laboratories in Quebec and elsewhere use this criteria as a proxy for identification of HA-MRSA and CA-MRSA [5]. The use of

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Table 3. *Antimicrobial susceptibilities of MRSA isolates*

| | HA-MRSA ($n = 474$) | CA-MRSA ($n = 59$) | | All isolates ($n = 535$) | | | |
|---|---|---|---|---|---|---|---|
| Antimicrobial agent | Number of resistant isolates (%) | Number of resistant isolates (%) | HA- *vs.* CA-MRSA *P* value | MIC (mg/l) | | | Number of resistant isolates (%) |
| | | | | MIC range | $MIC_{50}$ | $MIC_{90}$ | |
| Clindamycin* | 455 (96) | 8 (13·6) | <0·0001 | ⩽0·06–>64 | >64 | >64 | 463 (86·5) |
| Daptomycin | 2 (0·4) | 0 (0) | 1·0 | 0·12–4 | 0·5 | 1 | 2 (0·2) |
| Doxycycline | 0 (0) | 0 (0) | 1·0 | ⩽0·06–4 | 0·25 | 0·5 | 0 (0) |
| Erythromycin† | 466 (98·3) | 54 (91·5) | 0·0014 | 0·25–>64 | >64 | >64 | 521 (97·4) |
| Gentamicine | 3 (0·6) | 0 (0) | 1·0 | 0·12–>64 | 0·5 | 2 | 3 (0·6) |
| Fusidic acid | 24 (5) | 2 (3·4) | 0·76 | ⩽0·06–>64 | 0·25 | 0·5 | 27 (5) |
| Levofloxacin | 471 (99·4) | 56 (94·9) | 0·02 | 0·25–>64 | 64 | >64 | 528 (98·7) |
| Linezolid | 1 (0·2) | 0 (0) | 1·0 | 1–4 | 4 | 4 | 1 (0·2) |
| Mupirocin‡ | 3 (0·6) | 0 (0) | 1·0 | High level resistance | | | 3 (0·6) |
| Oxacillin | 474 (100) | 59 (100) | 1·0 | 4–>64 | >64 | >64 | 535 (100) |
| Rifampicin | 6 (1·3) | 0 (0) | 1·0 | ⩽0·016–16 | ⩽0·016 | ⩽0·016 | 6 (1·1) |
| Tigecycline | 0 (0) | 0 (0) | 1·0 | 0·06–1 | 0·12 | 0·12 | 0 (0) |
| Trimethoprim/ sulfamethoxazole§ | 0 (0) | 0 (0) | 1·0 | ⩽0·06/1·14–1/19 | ⩽0·06/ 1·14 | 0·12/ 2·28 | 0 (0) |
| Vancomycin | 0 (0) | 0 (0) | 1·0 | 0·5–2 | 1 | 2 | 0 (0) |

MRSA, Methicillin-resistant *Staphylococcus aureus*; HA, healthcare associated; CA, community acquired; MIC, minimum inhibitory concentration.

* The percentage value included both inducible and constitutive resistance. One isolate had intermediate MIC value.

† Two isolates had intermediate MIC values.

‡ High level resistance is defined as isolates for which the mupirocin MICs are ⩾512 mg/l.

§ MIC was not reported for one isolate due to thymidine added in broth which led to a false resistance value [40]. The strain did not grow in free thymidine broth.

clindamycin susceptibility as a predictive value for CA-MRSA strains is excellent, with a specificity of 95·6%. The presence of genes coding for PVL toxin is also a good predictor of CA-MRSA strains. PVL is one of several important factors that may play a key role in the successful dissemination of CA-MRSA [38].

For several years, nosocomial MRSA infections have been a significant problem in Canadian healthcare institutions and major efforts have been devoted to their prevention and control with some success. In Québec, the number and proportion of MRSA bloodstream infections have been decreasing from 2006 to 2012 with a rate of 0·29/10 000 patient-days in 2012, compared to 0·54/10 000 patient-days in 2006 [13]. The epidemiology of MRSA is now changing in Canada with the emergence of CA-MRSA strains as causes of skin and soft tissue infections, pneumonias and bacteraemias [39].

This is the first Quebec provincial report on the systematic characterization of MRSA bloodstream isolates using important data collected through the *S. aureus* bacteraemia surveillance programme. These public health surveillance tools have allowed correlations between the site of acquisition of the organisms (community or healthcare facilities) and the primary sources of infections. We recognize that even though more than 80% of MRSA bacteraemia isolates in the province of Quebec were analysed during the two surveillance years, the number of strains characterized for each 1-year period was too small to detect changes in trends. Moreover, data from this surveillance study can not be extrapolated to other types of infections such as skin and soft tissue infections. At this time, the importance of CA-MRSA strains as causes of skin and soft tissue infections in Québec is not known.

In summary, in contrast with findings observed in the USA, CA-MRSA strains are not frequently isolated in patients with bloodstream infections in Quebec at this time. Two main genotypes are responsible for almost all bacteraemias: CMRSA2 and CMRSA10. With the possible exception of intravenous drug users, cloxacillin remains the treatment of choice for most patients with suspected community-acquired *S. aureus* bacteraemias.

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To improve the robustness of the provincial surveillance and its impact on public health actions, a third year of laboratory surveillance is ongoing.

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## DECLARATION OF INTEREST

None.

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