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Evolution of Nasal Carriage of Methicillin-Resistant Coagulase-Negative Staphylococci in a Remote Population

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Nasal carriage of methicillin-resistant coagulase-negative staphylococci (MR-CoNS) is highly prevalent in community subjects, but its dynamic has been little investigated. Nasal swabbing was performed in 2006 and 2008 in 154 Amerindians living isolated in French Guiana. MR-CoNS strains were identified and characterized by non-β-lactam susceptibility testing and staphylococcal cassette chromosome *mec* element (SCC*mec*) typing, characterizing the associations of *ccr* and *mec* gene complex allotypes, and for MR *Staphylococcus epidermidis* (MRSE), multilocus variable number of tandem repeats analysis (MLVA) was used. The impact of sociodemographic and medical characteristics on the persistence of MR-CoNS carriage was assessed by bivariate analysis. Prevalence of MR-CoNS carriage was 50.6% in 2006 and 46.8% in 2008. The 274 MR-CoNS isolates, including *S. epidermidis* ($n = 89$, 62 MLVA patterns), *Staphylococcus haemolyticus* ($n = 78$), and *Staphylococcus hominis* ($n = 72$), exhibited 41 distinct *ccr* and *mec* gene complex associations. Persistent carriage (in 2006 and 2008), intermittent carriage (either in 2006 or 2008), and noncarriage were documented in 25.3, 47.4, and 27.3% of the participants, respectively. Persistent carriage of a given MRSE isolate was rarely observed ($n = 8$ isolates). Furthermore, no epidemiological factor, including antibiotic exposure, was associated with persistent carriage. The high diversity of MRSE clones and their *ccr* and *mec* gene complex associations contrasted with the high carriage rates in this isolated community, which might reflect the occurrence of SCC*mec* rearrangement and the generation of new MR-CoNS strains.

The emergence of methicillin resistance (MR) in staphylococci results from the acquisition of the *mecA*-encoded penicillin-binding protein 2a, a transpeptidase conferring broad-spectrum β-lactam resistance (21). A mobile genetic element designated staphylococcal cassette chromosome *mec* (SCC*mec*) carries both the *mec* gene complex, i.e., *mecA* and its regulatory genes, and the *ccr* gene complex that encodes the recombinases involved in its chromosomal integration/excision (17, 21). Eight major SCC*mec* types (I to VIII) have been described in methicillin-resistant *Staphylococcus aureus* (MRSA), differing in allotypic combinations of the *mec* and *ccr* gene complexes, with SCC*mec* IVa and V being currently the most prevalent types in community-acquired MRSA (CA-MRSA) strains (17, 21, 34). Furthermore, methicillin-resistant coagulase-negative staphylococci (MR-CoNS) display a higher diversity of SCC*mec* elements with frequent nontypeable patterns, including *ccr-mec* complex combinations that do not fit the classification proposed for MRSA and nontypeable or multiple *ccr* allotypes (1, 14, 22, 41).

MR-CoNS, most notably MR *Staphylococcus epidermidis* (MRSE), probably act as a reservoir of SCC*mec* for *S. aureus*, although the mechanisms of transfer are not yet elucidated. Indeed, similar SCC*mec* patterns were observed in MRSA and MR-CoNS isolates from the same health care environment (2, 13, 20, 48, 51). Moreover, SCC*mec* IVa sequences from MRSE display >98% identity with those carried by MRSA (3, 49), including when CA-MRSE and CA-MRSA strains were compared, suggesting that SCC*mec* transfer can occur in the community (1).

S. epidermidis and other CoNS species, such as *Staphylococcus hominis* and *Staphylococcus haemolyticus*, are major components of the human skin and mucosal flora, including the nasal microbiota (26). Recent studies highlighting the community spread of MR-CoNS have raised concerns, because of the probable role of MR-CoNS as a source of SCC*mec* for CA-MRSA and the increasing prevalence of CoNS in community-acquired diseases, such as native valve endocarditis and late infections of indwelling prosthetic devices (6, 30, 46). Nasal colonization by MR-CoNS has been documented in 11 to 31% of outpatients from contrasting geographic areas (1, 41). Strikingly, high carriage rates were observed in subjects without any previous exposure to the health care system (1). However, little is known about the long-term dynamic of MR-CoNS nasal carriage in the community. A single study assessed this issue and found that 4% of 339 Japanese children were potential persistent MRSE carriers (22). Data from other community environments are lacking, and whether this dynamic

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TABLE 1 Prevalence of non-β-lactam antibiotic resistances in 274 carriage isolates of MR-CoNS isolated from 154 adult Wayampi Amerindians during the two sampling campaigns (2006 and 2008)[a]

Antibiotic	No. (%) of resistant MR-CoNS isolates											
	All species		*S. epidermidis*		*S. haemolyticus*		*S. hominis*		*S. saprophyticus*		Others[b]	
	2006 (141 isolates)	2008 (133 isolates)	2006 (56 isolates)	2008 (33 isolates)	2006 (36 isolates)	2008 (42 isolates)	2006 (44 isolates)	2008 (28 isolates)	2006 (2 isolates)	2008 (25 isolates)	2006 (3 isolates)	2008 (5 isolates)
Kanamycin	50 (33)	39 (29)	21 (33)	7 (21)	12 (32)	18 (43)	17 (39)	12 (43)	0	0	0	2 (40)
Tobramycin	37 (25)	35 (26)	18 (28)	6 (18)	9 (24)	17 (40)	10 (23)	10 (36)	0	0	0	2 (40)
Gentamicin	16 (11)	21 (16)	8 (13)	2 (6)	7 (18)	11 (26)	1 (2)	6 (21)	0	0	0	2 (40)
Erythromycin	51 (34)	45 (34)	31 (48)	11 (33)	3 (8)	3 (7)	13 (30)	5 (18)	2 (100)	22 (88)	2 (67)	4 (80)
Lincomycin	14 (9)	15 (11)	12 (19)	3 (9)	0	0	1 (2)	0	0	9 (36)	1 (33)	3 (60)
Pristinamycin	0	1 (1)	0	1 (3)	0	0	0	0	0	0	0	0
Tetracycline	37 (25)	30 (23)	15 (23)	5 (15)	10 (26)	20 (48)	12 (27)	1 (4)	0	4 (16)	0	0
Ofloxacin	3 (2)	20 (15)	2 (3)	2 (6)	0	1 (2)	0	0	0	15 (60)	1 (33)	2 (40)
Fosfomycin	51 (34)	71 (53)	15 (23)	5 (15)	3 (8)	17 (40)	30 (68)	21 (75)	2 (100)	25 (100)	3 (100)	3 (60)
Rifampin	39 (26)	49 (37)	23 (36)	14 (42)	2 (5)	16 (38)	12 (27)	9 (32)	0	6 (24)	2 (67)	4 (80)
Cotrimoxazole	35 (23)	40 (30)	17 (27)	13 (39)	0	3 (7)	17 (39)	11 (39)	1 (50)	13 (52)	0	0
Vancomycin	0	0	0	0	0	0	0	0	0	0	0	0
Teicoplanin	0	1 (1)	0	0	0	1 (2)	0	0	0	0	0	0

[a] $P = 0.0002$ for the comparison of ofloxacin resistance rates between 2006 and 2008 (P = NS for all other antibiotics).
[b] Including *S. kloosii* ($n = 3$ isolates in both 2006 and 2008), *S. capitis* ($n = 1$ isolate in 2008), and *S. cohnii* ($n = 1$ isolate in 2008).

is impacted by sociodemographic characteristics or antibiotic exposure remains unknown. The latter points are difficult to assess in open populations, where subjects are exposed to multiple antibiotic sources, and where interindividual contacts and thus cross-transmission are untraceable. In this study, we investigated the dynamic of MR-CoNS nasal carriage in the community, with a special focus on MRSE carriage, by using serial nasal samples previously gathered in a cohort of healthy adults from an isolated population and whose antibiotic exposure and sociodemographic characteristics were precisely documented (37, 50).

MATERIALS AND METHODS

Study population and design. Two campaigns of nasal swabbing were performed 16 months apart, in October 2006 and June 2008, in 154 adult Wayampi Amerindians, who were part of a traditional, ethnically homogeneous community of 525 individuals living in Trois-Sauts, a very isolated village in the southernmost area of French Guiana, with limited contacts with the outside world (28, 29). Precise characteristics of this study population have been previously described (12, 37, 50). Carriage rates of methicillin-susceptible *S. aureus* (MSSA) were 42.2% in 2006 and 57.8% in 2008. No MRSA was found in 2006, while two subjects carried MRSA in 2008 (37). The study design was approved by the ethical committee in charge of French Guiana (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, authorization no. 2006/0498-DGS and 2008/C07-44 for the 2006 and 2008 surveys, respectively).

Isolation of MR-CoNS isolates from nasal swab samples. The methodologies used for sampling, isolation, and characterization of MR-CoNS isolates were strictly the same for the 2006 and 2008 campaigns. Samples from our previous *S. aureus* carriage survey (37) were defrosted in a batch, and 100 μl of the suspension was plated on chromID MRSA agar (bioMérieux), a chromogenic agar selective for MR staphylococci (cefoxitin, 4 μg/liter) with a >90% sensitivity and a 94 to 100% specificity to discriminate *mecA*-positive and *mec*A-negative CoNS isolates, including for the *Staphylococcus saprophyticus* species (10, 35, 36). After incubation for 48 h at 37°C, four white colonies were randomly selected from each plate and subcultured on Trypticase soy agar. The DNA of each isolate was extracted with a MagNA Pure LC instrument (Roche, Germany) and stored at −80°C. The isolates confirmed as MR-CoNS (i.e., *mecA* positive) by real-time triplex PCR were retained for further characterization (39).

Antimicrobial susceptibility testing of MR-CoNS isolates. Susceptibility to the antibiotics listed in Table 1 was determined by disk diffusion as recommended by the French Society for Microbiology (http://www.sfm.asso.fr/). A resistance score was calculated for each MR-CoNS carrier (32).

Species identification of MR-CoNS isolates. The isolates were identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (Autoflex MALDI-TOF MS spectrometer, Bruker Daltonics, Wissembourg, France) after ethanol extraction, according to the manufacturer's recommendations. Mass spectra were analyzed using the Flex Control software (Bruker Daltonics). Quality indices (QI) were allocated to assess the accuracy of species identifications (4, 15). Only spectra with high QI (>2) were considered reliable for identification. Isolates with QI of ≤2 were identified by comparison of an internal 1,350-bp fragment of the 16S rRNA gene with sequences available in the National Center for Biotechnology Information databases, using the BLAST algorithm (http://www.ncbi.nlm.nih.gov/blast) (38).

Isolates from a given patient were considered duplicates and not analyzed further if they belonged to the same species and shared the same antibiotic susceptibility patterns.

SCC*mec* typing. SCC*mec* elements were typed by multiplex PCR (M-PCR) amplification of the *ccr* (M-PCR1) and *mec* (M-PCR2) gene complexes (27). Additional primers were incorporated to amplify the *ccrA4B4* and C1 *mec* allotypes (41). SCC*mec* elements were designated by the association of the *ccr* gene complex allotype(s) (i.e., 1, 2, 3, 4 for *ccrA1B1*, *ccrA2B2*, *ccrA3B3*, and *ccrA4B4*, respectively, and 5 for *ccrC1*) and the *mec* gene complex allotype (A, B, C1, or C2) (21). MRSA strains COL/SCC*mec* I (1B), BK2464/SCC*mec* II (2A), ANS46c/SCC*mec* III (3A), 300-FPR3757/SCC*mec* IV (2B), WCH100/SCC*mec* V (5C2), and HDE288/SCC*mec* VI (4B) were used as references. Nondetectable *ccr* gene complexes were defined based on the positivity of the *mecA* internal control and the lack of a *ccr* amplicon with M-PCR1. Nontypeable *mec* gene complexes were defined based on either the lack of an *mec* amplicon or an amplicon of unreported size with M-PCR2. Nontypeable SCC*mec* isolates were defined by a nondetectable *ccr* gene complex and/or the absence of a typeable *mec* gene allotype or an unreported association between a typeable *ccr* gene complex and a typeable *mec* gene complex.

Multilocus variable number of tandem repeats analysis (MLVA) of MRSE isolates. MRSE isolates were typed by MLVA, a method that assesses the length polymorphism of five chromosomal variable-number tandem repeats designated Se1 to Se5 (23). The phylogenetic relationship between MLVA patterns was evaluated by the unweighted pair group method with arithmetic mean (UPGMA) using the BioNumerics software version 6.0 (Applied Maths, Ghent, Belgium). MRSE isolates with the

same number of tandem repeats for each loci were defined as having the same MLVA profile (23).

Classification of MR-CoNS carriers. Given the absence of a consensual definition for CoNS nasal carriage, subjects in whom no MR-CoNS strain was isolated in 2006 or 2008 were defined as noncarriers, those carrying at least one MR-CoNS isolate in either 2006 or 2008 were considered intermittent carriers, and those carrying at least one isolate in both 2006 and 2008 were defined as persistent carriers.

Epidemiological data. Demographic, lifestyle, and environmental data as well as medical events and antibiotic consumptions during the year preceding the first swabbing campaign, previously gathered both for the study population and the rest of the villagers (37), were used to investigate factors associated with MR-CoNS carriage (Table 2).

Statistical analysis. Continuous data were presented as the mean (±standard deviation [SD]) or median and range, and categorical data were presented as numbers (proportions). Associations between species, year of sampling, antibiotic susceptibility profile, *mec* gene complex, *ccr* gene complex, and SCC*mec* type were investigated using Fisher's exact test. A P value of <0.05 was considered statistically significant. We compared the epidemiological characteristics of MR-CoNS nasal carriers with others, using the R software (version 2.6.1) (http://cran.r-project.org/). For bivariate analysis, we used Pearson's χ^2 test, Fisher's exact test, Student's t test, and McNemar's χ^2 test. All the tests were two sided, and the significance level was set at 5%. Because of the large number of explanatory variables, bivariate analyses were adjusted by Holm's test for multiple testing (18, 43).

RESULTS

Study population and overall MR-CoNS carriage rates. A total of 525 Wayampi Amerindians (238 adults and 287 children) were living in Trois-Sauts at the time of our first campaign in 2006, and 163 adults (68.5%) volunteered to participate. A total of 154 of the 163 volunteers in 2006 (94.5%) were resampled in 2008 (female/male ratio = 1.09, mean age = 35.1 years) and were included in the present study (Table 2). The overall carriage rates of MR-CoNS were 50.6% (78/154 samples) and 46.8% (72/154 samples) for the 2006 and 2008 campaigns, respectively (P = not significant [NS]). Among the MR-CoNS carriers, 30 (38.5%) in 2006 and 34 (47.2%) in 2008 cocarried *S. aureus* (P = NS).

Isolation and characterization of MR-CoNS isolates. After exclusion of duplicates, 274 MR-CoNS isolates were analyzed, including 141 and 133 isolates from the 2006 and 2008 campaigns, respectively. The mean numbers of strains per individual were 0.93 ± 1.09 in 2006 and 0.86 ± 1.10 in 2008 (P = NS). Most of the carriers (83% in 2006 and 76% in 2008) carried 1 or 2 MR-CoNS isolates, with the remaining ones carrying 3 to 4 distinct isolates. This distribution did not differ significantly between the two periods.

The MR-CoNS isolates were divided into seven distinct species, including *S. epidermidis* (n = 89), *S. haemolyticus* (n = 78), *S. hominis* (n = 72), *Staphylococcus saprophyticus* (n = 27), *Staphylococcus kloosii* (n = 6), *Staphylococcus capitis* (n = 1), and *Staphylococcus cohnii* (n = 1) (Table 2). The proportion of *S. epidermidis* isolates decreased between 2006 and 2008 (39.7% versus 24.8%, respectively; P = 0.012), while that of *S. saprophyticus* isolates increased (1% versus 19%; $P < 0.0001$). The proportions of *S. haemolyticus* and *S. hominis* isolates did not change significantly.

The overall resistance rates for non-β-lactam antibiotics were high (notably for kanamycin, tobramycin, erythromycin, rifampin, and cotrimoxazole) but remained stable over the study period, except for ofloxacin (2% in 2006 versus 15% in 2008; P = 0.0002) (Table 1). The mean resistance scores for MR-CoNS carriers were 22% ± 16% in 2006 and 27% ± 16% in 2008 (P = NS).

The results of SCC*mec* typing are shown in Table 3. Half of the MR-CoNS isolates (137/274 [50%]) carried a typeable SCC*mec*, including type 2A (8/274 [2.9%]), type 2B (24/274 [8.8%]), type 5C2 (65/274 [23.8%]), type 4B (2/274 [0.7%]), and type 4A (38/274 [13.8%]). No SCC*mec* type 1B was found. The remaining 137 isolates carried a nontypeable SCC*mec* pattern, including 3 isolates with a single *ccr* allotype but a *ccr-mec* combination not described in MRSA, 36 isolates with multiple *ccr* allotypes, 16 isolates with multiple *mec* allotypes, and 82 isolates with nondetectable *ccr* or nontypeable *mec* allotypes. The complete list of *ccr-mec* combinations is available in Table S1 in the supplemental material. Associations were noted between SCC*mec* types and CoNS species, namely, SCC*mec* type 2B and *S. epidermidis* (23/89 isolates versus 1/185 isolates for other species; $P < 0.0001$), SCC*mec* type 5C2 and *S. haemolyticus* (40/78 isolates versus 25/196 isolates; $P < 0.0001$), and SCC*mec* type 4A and *S. hominis* (35/72 isolates versus 3/202 isolates; $P < 0.0001$). All but one MR *S. saprophyticus* (MRSS) isolate carried a nontypeable SCC*mec* element (26/27 isolates versus 111/247 isolates from other species; $P < 0.0001$) (Table 4). The two MRSA isolates collected in 2008 carried SCC*mec* type 1B.

MLVA typing of MRSE. The 89 MRSE isolates showed highly heterogeneous MLVA patterns, regardless of their SCC*mec* types and year of isolation. Indeed, 62 distinct patterns were observed, including 42 in 2006 and 27 in 2008, with only 7 found in both 2006 and 2008. Forty-five patterns were found in only 1 MRSE isolate (singletons), 12 in 2, and the remaining 5 patterns were found in 3 to 5 isolates. By combining MLVA and SCC*mec* profiles, we observed that only seven (7.8%) MRSE isolates were carried by more than one volunteer (maximum, n = 4) (Fig. 1). The remaining 82 isolates were found in only one subject.

Dynamic of MR-CoNS nasal carriage. We found that 39 (25.3%), 73 (47.4%), and 42 (27.3%) subjects were persistent carriers, intermittent carriers, or noncarriers, respectively (Table 5). Interestingly, most of the persistent carriers (21/39) carried isolates from different species in 2006 and 2008. Persistent carriage of MRSE, MR *S. haemolyticus*, and MR *S. hominis* was documented in only 12 (8%), 3 (2%), and 3 (2%) of the 154 subjects, respectively. However, based on non-β-lactam resistance patterns, SCC*mec* typing, and MLVA profile (for *S. epidermidis*), none of these subjects carried the same isolate in 2006 and 2008. No persistent carriage of MRSS or MR *S. kloosii* was observed.

Factors associated with nasal carriage of MR-CoNS by bivariate analysis. Strikingly, neither MR-CoNS nasal carriage at inclusion (i.e., in 2006) nor persistent MR-CoNS carriage was associated with sociodemographic or medical characteristics (Table 2). Previous antibiotic use was, at first, significantly associated with persistent carriage (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.1 to 5.5; P = 0.03), but the P value dropped to nonsignificance after Holm's adjustment for multiple testing (P = 0.71).

DISCUSSION

The spread of MR-CoNS out of the hospital setting has been reported in several recent works. However, data on the dynamics of MR-CoNS carriage in community subjects are currently very scarce. Here, we investigated the persistence and biodiversity of MR-CoNS nasal colonization in a population of 154 adult Amer-

TABLE 2 Factors associated with MR-CoNS nasal carriage at study inclusion in 2006 and with persistent nasal carriage of MR-CoNS between 2006 and 2008 in 154 adult Wayampi Amerindians

Sociodemographic characteristic	No. (%) of isolates						
		2006			2006–2008		
	All volunteers ($n = 154$)	MR-CoNS carriers ($n = 78$)	Noncarriers ($n = 76$)	P/Pa[a]	Persistent MR-CoNS carriers ($n = 39$)	Other volunteers ($n = 115$)[b]	P/Pa[a]
Female	79 (51.3)	41 (52.6)	38 (50.0)	0.87/1.00	22 (56.4)	57 (49.6)	0.58/1.00
Age (yr)							
18-24	38 (24.6)	19 (24.4)	19 (25.0)	0.55/1.00	9 (23.1)	29 (25.2)	0.29/1.00
25–30	37 (24.0)	22 (28.2)	15 (19.7)		9 (23.1)	28 (24.3)	
31–40	30 (19.5)	12 (15.4)	18 (23.7)		4 (10.3)	26 (22.6)	
41–50	28 (18.2)	13 (16.7)	15 (19.7)		9 (23.1)	19 (16.5)	
51–81	21 (13.7)	12 (15.4)	9 (11.8)		8 (20.5)	13 (11.3)	
Marital status							
Single	23 (15.0)	15 (19.2)	8 (10.5)	0.18/1.00	9 (23.1)	14 (12.2)	0.12/1.00
Couple	131 (85.0)	63 (80.8)	68 (89.5)		30 (76.9)	101 (87.8)	
No. of children							
≤2	56 (36.3)	33 (42.9)	23 (31.5)	0.31/1.00	16 (42.1)	40 (35.7)	0.20/1.00
3-5	57 (37.0)	28 (36.4)	29 (39.7)		10 (26.3)	47 (42.0)	
6-10	37 (26.7)	16 (72.0)	21 (28.8)		12 (31.6)	25 (22.3)	
Babysitting children ≤5 yr old	112 (72.7)	54 (72.0)	58 (79.5)	0.34/1.00	25 (67.6)	87 (78.4)	0.19/1.00
Hamlet (household distance from the health post)							
Hamlet 1 (0 m)	92 (59.7)	48 (61.5)	44 (57.9)	0.84/1.00	29 (74.4)	63 (54.8)	0.19/1.00
Hamlet 2 (1,000 m)	36 (23.4)	17 (21.8)	19 (25.0)		5 (12.8)	31 (27.0)	
Hamlet 3 (3,500 m)	12 (7.9)	7 (9.0)	5 (6.6)		2 (5.1)	10 (8.7)	
Hamlet 4 (5,500 m)	14 (9.0)	6 (7.7)	8 (10.5)		3 (7.7)	11 (9.6)	
No. of inhabitants per household							
≤3	14 (9.1)	8 (10.3)	6 (7.9)	0.36/1.00	5 (12.8)	9 (7.8)	0.40/1.00
4-7	80 (51.9)	44 (56.4)	36 (47.4)		17 (43.6)	63 (54.8)	
8-12	60 (39.0)	26 (33.3)	34 (44.7)		17 (43.6)	43 (37.4)	
Presence of animals in the household	125 (81.2)	63 (80.8)	62 (81.6)	1.00/1.00	32 (82.1)	93 (80.9)	1.00/1.00
Type of drinking water							
River	78 (50.6)	41 (54.7)	37 (52.1)	0.81/1.00	19 (50.0)	59 (54.6)	0.71/1.00
Cove	70 (45.4)	35 (46.7)	35 (49.3)	0.87/1.00	20 (52.6)	50 (46.3)	0.57/1.00
Tap	27 (17.5)	14 (18.7)	13 (18.3)	1.00/1.00	8 (21.1)	19 (17.6)	0.63/1.00
Medical characteristics							
Intestinal carriage of ESBL-E[f]	27 (17.5)	14 (18.7)	13 (18.3)	1.00/1.00	8 (21.1)	19 (17.6)	0.63/1.00
Chronic disease[c]	8 (5.2)	1 (1.3)	7 (9.2)	0.03/0.91	0	8 (7.0)	0.20/1.00
Pregnancy	10 (12.6)	6 (13.0)	4 (9.1)	0.74/1.00	2 (9.1)	8 (14.0)	1.00/1.00
Hospitalizations[d]	23 (14.9)	10 (12.8)	13 (17.1)	0.50/1.00	5 (12.8)	18 (15.7)	0.80/1.00
Surgery[d]	11 (7.1)	4 (5.1)	7 (9.2)	0.37/1.00	2 (5.1)	9 (7.8)	0.73/1.00
Antibiotic use by the volunteer[d]	70 (45.4)	38 (48.7)	32 (42.1)	0.42/1.00	24 (61.5)	46 (40.0)	0.03/0.71
No. of antibiotic treatments	84 (54.5)	40 (51.3)	44 (57.9)	0.61/1.00	15 (38.5)	69 (60.0)	0.07/1.00
0	26 (16.9)	15 (19.2)	11 (14.5)		10 (25.6)	16 (13.9)	
1	26 (16.9)	12 (15.4)	14 (18.4)		7 (17.9)	19 (16.5)	
2	18 (11.7)	11 (14.1)	7 (9.2)		7 (17.9)	11 (9.6)	
≥3							
Antibiotic use among volunteer's relatives[d,e]	147 (95.4)	73 (93.6)	74 (97.4)	0.44/1.00	37 (94.9)	110 (95.7)	1.00/1.00

[a] Bivariate analysis was performed using the Pearson χ^2 test or Fisher test ($\alpha = 0.05$). *Pa*, *P* value after adjustment by Holm's method.
[b] Other volunteers include intermittent carriers ($n = 73$) and noncarriers ($n = 42$).
[c] Defined in the Charlson's comorbidities score (5).
[d] Within the year preceding study inclusion, i.e., between October 2005 and October 2006.
[e] Relatives were defined as members of the same family living in the same household (in case of multiple life partners, second/third wives and children were included as relatives even if they lived in a different household), and the number of relatives ranged from 1 to 11.
[f] ESBL-E, extended spectrum β-lactamase-producing *Enterobacteriaceae*.

TABLE 3 SCC*mec* typing of 274 carriage isolates of MR-CoNS isolated from 154 adult Wayampi Amerindians during the 2006 and 2008 sampling campaigns

SCC*mec* type/*ccr-mec* combinations	No. (%) of MR-CoNS isolates											
	All species		*S. epidermidis*		*S. haemolyticus*		*S. hominis*		*S. saprophyticus*		Others[a]	
	2006	2008	2006	2008	2006	2008	2006	2008	2006	2008	2006	2008
2A	7 (5)	1 (1)	6 (11)	1 (3)	0	0	1 (2)	0	0	0	0	0
2B	12 (8)	12 (9)	12 (21)	11 (33)	0	0	0	1 (4)	0	0	0	0
5C2	24 (17)	41 (31)	11 (19)	11 (33)	11 (31)	29 (69)	0	1 (4)	0	0	2 (66)	0
4B	1 (1)	1 (1)	0	1 (3)	0	0	1 (2)	0	0	0	0	0
4A	25 (17)	13 (10)	0	0	0	1 (2)	25 (57)	10 (36)	0	1 (4)	0	1 (20)
Nontypeable[b]	72 (51)	65 (49)	27 (48)	9 (27)	25 (69)	12 (29)	17 (39)	16 (57)	2 (100)	24 (96)	1 (33)	4 (80)
Total	141	133	56	33	36	42	44	28	2	25	3	5

[a] Including *S. kloosii* ($n = 3$ isolates in both 2006 and 2008), *S. capitis* ($n = 1$ isolate in 2008), and *S. cohnii* ($n = 1$ isolate in 2008).
[b] The complete list of nontypeable SCC*mec* patterns is available in Table S1 in the supplemental material.

indians forming part of a remote and precisely characterized community.

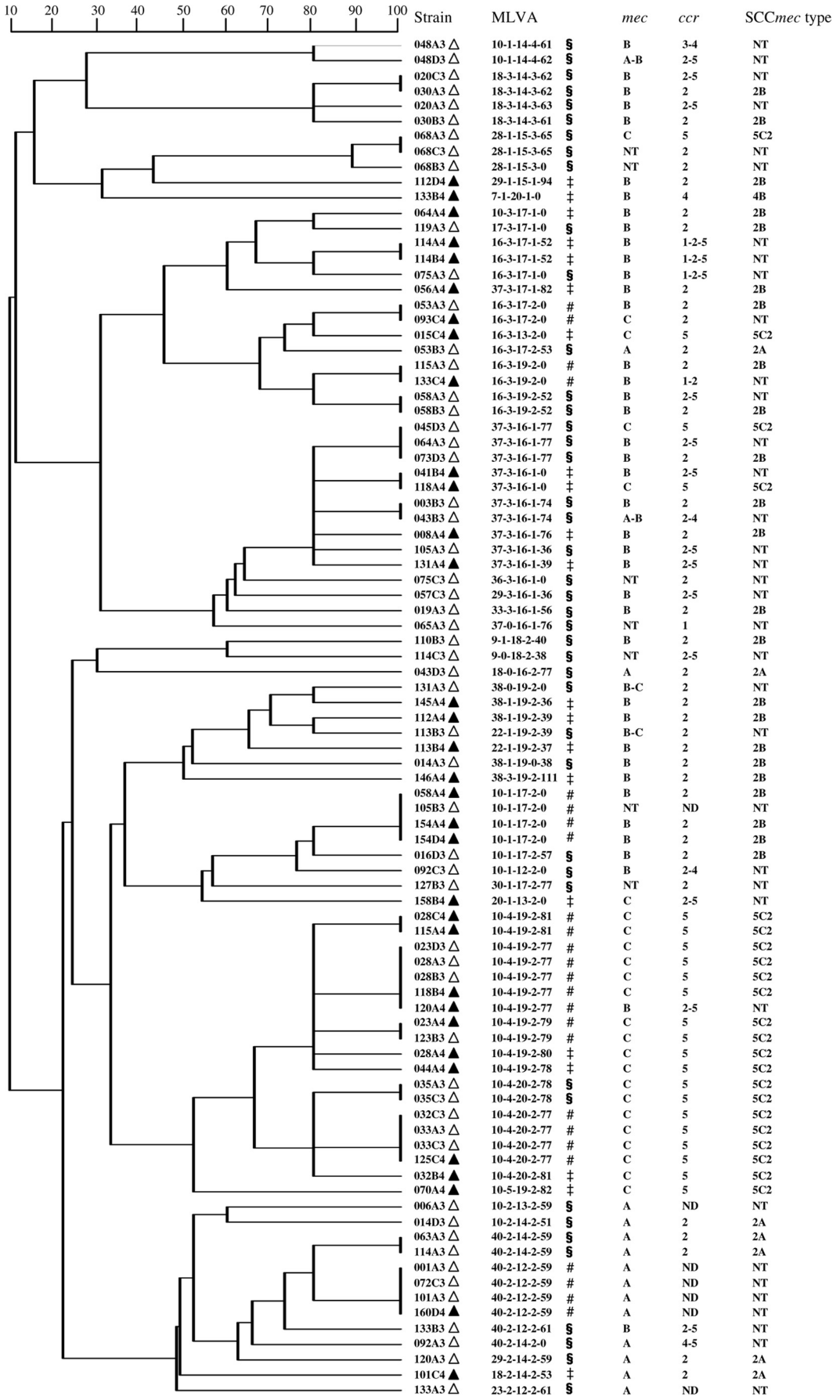
Prevalence of MR-CoNS carriage was 51% in 2006 and 47% in 2008, which contrasts with previous community-based surveys, where the reported rates ranged from 11 to 30% (1, 22, 41, 44). Rates similar to ours have been reported only in inpatients, notably those hospitalized in long-term-care facilities (20, 25). Promiscuity and suboptimal hygienic conditions in this traditional population may contribute to this finding. Indeed, cross-transmission is a major determinant of MR-CoNS dissemination in the hospital setting (7, 47) and was shown to be an important mechanism for *S. aureus* dissemination in this community (37). However, the extreme biodiversity (i.e., the lack of patent clonality) of MR-CoNS isolates in our work pleads against this hypothesis. The impact of antibiotic selective pressure is another possible explanation for this high overall prevalence of MR-CoNS carriage. Non-β-lactam coresistances were actually frequent in MR-CoNS isolates, and antibiotic use in this cohort (Table 2) (37) may be higher than that in other populations, including the metropolitan French population (42). Moreover, non-β-lactam resistances might have been underestimated, since we used the CASFM methods, which detect only clinically relevant resistances. Our use of a medium selective for MR staphylococci to ease and enhance MR-CoNS isolation from the subdominant nasal flora may also explain these discrepancies with previous studies (41). Lastly, equatorial climatic conditions in south French Guiana, with precipitations above 80 mm per month and temperatures higher than 20°C all year long, may also play a role. Indeed, an increase in MR-CoNS nasal carriage rates was previously observed during the hot and rainy season (22), even though the determinants of this climatic impact remain to be investigated.

TABLE 4 Comparison of non-β-lactam resistances and SCC*mec* types between MR *S. saprophyticus* and MR-CoNS isolates from other species collected during the 2008 campaign

Variable	No. (%) of MR-CoNS isolates		*P* value
	S. saprophyticus ($n = 25$ isolates)	Other species ($n = 108$ isolates)	
Antibiotic resistance			
Kanamycin	0 (0)	39 (36)	<0.001
Tobramycin	0 (0)	35 (32)	<0.001
Gentamicin	0 (0)	21 (19)	0.013
Vancomycin	0 (0)	0 (0)	NS
Teicoplanin	0 (0)	1 (1)	NS
Erythromycin	22 (88)	23 (21)	<0.001
Lincomycin	9 (36)	6 (6)	NS
Pristinamycin	0 (0)	1 (1)	NS
Tetracycline	4 (16)	26 (24)	NS
Ofloxacin	15 (60)	5 (5)	<0.001
Fosfomycin	25 (100)[a]	46 (43)	<0.001
Rifampin	6 (24)	43 (40)	NS
Cotrimoxazole	13 (52)	27 (25)	0.014
SCC*mec* type[b]			
Nontypeable	24 (96)	41 (38)	<0.001
2A	0	1 (1)	NS
2B	0	12 (11)	NS
5C2	0	41 (38)	NS
4B	0	1 (1)	NS
4A	1 (4)	12 (11)	0.0014

[a] Natural resistance in *S. saprophyticus*.
[b] Indicated as type (*ccr-mec* gene complexes).

The most striking result of this study is that up to 25.3% of the participating subjects were persistent carriers of MR-CoNS between 2006 and 2008, while 47.4% were intermittent carriers and only 27.3% were noncarriers. Factors associated with persistent carriage of MR-CoNS in the community have not been previously investigated. Here, precise characterization of the study population enabled us to search for such factors. However, we found no association between persistent MR-CoNS carriage and sociodemographic features, such as age and lifestyle. Most notably, persistent carriage was not associated with medical characteristics, namely, chronic diseases, previous hospitalization and surgery, intestinal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (50), and a history of antibiotic exposure in the sampled subject or his or her relatives. Consequently, we hypothesize that this high frequency of persistent MR-CoNS colonization depends on the overall prevalence of MR-CoNS carriage in the studied population rather than on the individual's characteristics. In this instance, when CoNS species were considered, only 8% of the subjects were persistent MRSE carriers, and according to MLVA data, none of them carried the same isolate twice. Persistent carriage of MR *S. haemolyticus* and MR *S. hominis* was even more uncommon (2% for each), and based on non-β-lactam resistance patterns, it involved distinct isolates in all cases. Persistent MR-CoNS carriage thus appears as the result of successive acquisitions of distinct isolates from the community environment and not as the long-term colonization by a given isolate.



Strain	MLVA		*mec*	*ccr*	SCC*mec* type
048A3 △	10-1-14-4-61	§	B	3-4	NT
048D3 △	10-1-14-4-62	§	A-B	2-5	NT
020C3 △	18-3-14-3-62	§	B	2-5	NT
030A3 △	18-3-14-3-62	§	B	2	2B
020A3 △	18-3-14-3-63	§	B	2-5	NT
030B3 △	18-3-14-3-61	§	B	2	2B
068A3 △	28-1-15-3-65	§	C	5	5C2
068C3 △	28-1-15-3-65	§	NT	2	NT
068B3 △	28-1-15-3-0	§	NT	2	NT
112D4 ▲	29-1-15-1-94	‡	B	2	2B
133B4 ▲	7-1-20-1-0	‡	B	4	4B
064A4 ▲	10-3-17-1-0	‡	B	2	2B
119A3 △	17-3-17-1-0	§	B	2	2B
114A4 ▲	16-3-17-1-52	‡	B	1-2-5	NT
114B4 ▲	16-3-17-1-52	‡	B	1-2-5	NT
075A3 △	16-3-17-1-0	§	B	1-2-5	NT
056A4 ▲	37-3-17-1-82	‡	B	2	2B
053A3 △	16-3-17-2-0	#	B	2	2B
093C4 ▲	16-3-17-2-0	#	C	2	NT
015C4 ▲	16-3-13-2-0	‡	C	5	5C2
053B3 △	16-3-17-2-53	§	A	2	2A
115A3 △	16-3-19-2-0	#	B	2	2B
133C4 ▲	16-3-19-2-0	#	B	1-2	NT
058A3 △	16-3-19-2-52	§	B	2-5	NT
058B3 △	16-3-19-2-52	§	B	2	2B
045D3 △	37-3-16-1-77	§	C	5	5C2
064A3 △	37-3-16-1-77	§	B	2-5	NT
073D3 △	37-3-16-1-77	§	B	2	2B
041B4 ▲	37-3-16-1-0	‡	B	2-5	NT
118A4 ▲	37-3-16-1-0	‡	C	5	5C2
003B3 △	37-3-16-1-74	§	B	2	2B
043B3 △	37-3-16-1-74	§	A-B	2-4	NT
008A4 ▲	37-3-16-1-76	‡	B	2	2B
105A3 △	37-3-16-1-36	§	B	2-5	NT
131A4 ▲	37-3-16-1-39	‡	B	2-5	NT
075C3 △	36-3-16-1-0	§	NT	2	NT
057C3 △	29-3-16-1-36	§	B	2-5	NT
019A3 △	33-3-16-1-56	§	B	2	2B
065A3 △	37-0-16-1-76	§	NT	1	NT
110B3 △	9-1-18-2-40	§	B	2	2B
114C3 △	9-0-18-2-38	§	NT	2-5	NT
043D3 △	18-0-16-2-77	§	A	2	2A
131A3 △	38-0-19-2-0	§	B-C	2	NT
145A4 ▲	38-1-19-2-36	‡	B	2	2B
112A4 ▲	38-1-19-2-39	‡	B	2	2B
113B3 △	22-1-19-2-39	§	B-C	2	NT
113B4 ▲	22-1-19-2-37	‡	B	2	2B
014A3 △	38-1-19-0-38	§	B	2	2B
146A4 ▲	38-3-19-2-111	‡	B	2	2B
058A4 ▲	10-1-17-2-0	#	B	2	2B
105B3 △	10-1-17-2-0	#	NT	ND	NT
154A4 ▲	10-1-17-2-0	#	B	2	2B
154D4 ▲	10-1-17-2-0	#	B	2	2B
016D3 △	10-1-17-2-57	§	B	2	2B
092C3 △	10-1-12-2-0	§	B	2-4	NT
127B3 △	30-1-17-2-77	§	NT	2	NT
158B4 ▲	20-1-13-2-0	‡	C	2-5	NT
028C4 ▲	10-4-19-2-81	#	C	5	5C2
115A4 ▲	10-4-19-2-81	#	C	5	5C2
023D3 △	10-4-19-2-77	#	C	5	5C2
028A3 △	10-4-19-2-77	#	C	5	5C2
028B3 △	10-4-19-2-77	#	C	5	5C2
118B4 ▲	10-4-19-2-77	#	C	5	5C2
120A4 ▲	10-4-19-2-77	#	B	2-5	NT
023A4 ▲	10-4-19-2-79	#	C	5	5C2
123B3 △	10-4-19-2-79	#	C	5	5C2
028A4 ▲	10-4-19-2-80	‡	C	5	5C2
044A4 ▲	10-4-19-2-78	‡	C	5	5C2
035A3 △	10-4-20-2-78	§	C	5	5C2
035C3 △	10-4-20-2-78	§	C	5	5C2
032C3 △	10-4-20-2-77	#	C	5	5C2
033A3 △	10-4-20-2-77	#	C	5	5C2
033C3 △	10-4-20-2-77	#	C	5	5C2
125C4 ▲	10-4-20-2-77	#	C	5	5C2
032B4 ▲	10-4-20-2-81	‡	C	5	5C2
070A4 ▲	10-5-19-2-82	‡	C	5	5C2
006A3 △	10-2-13-2-59	§	A	ND	NT
014D3 △	10-2-14-2-51	§	A	2	2A
063A3 △	40-2-14-2-59	§	A	2	2A
114A3 △	40-2-14-2-59	§	A	2	2A
001A3 △	40-2-12-2-59	#	A	ND	NT
072C3 △	40-2-12-2-59	#	A	ND	NT
101A3 △	40-2-12-2-59	#	A	ND	NT
160D4 ▲	40-2-12-2-59	#	A	ND	NT
133B3 △	40-2-12-2-61	§	B	2-5	NT
092A3 △	40-2-14-2-0	§	A	4-5	NT
120A3 △	29-2-14-2-59	§	A	2	2A
101C4 ▲	18-2-14-2-53	‡	A	2	2A
133A3 △	23-2-12-2-61	§	A	ND	NT

TABLE 5 Type of nasal carriage of MR-CoNS in 154 adult Wayampi Amerindians sampled during the two sampling campaigns (2006 and 2008)

Type of MR-CoNS nasal carriage[a]	No. (%) of all subjects	No. (%) who carried MR-CoNS species:				
		S. epidermidis	*S. haemolyticus*	*S. hominis*	*S. saprophyticus*	Others[b]
Persistent carrier	39 (25)	12 (8)	3 (2)	3 (2)	0	0
Intermittent carrier	73 (47)	43 (28)	58 (38)	41 (27)	15 (10)	6 (4)
Noncarrier	42 (27)	99 (64)	93 (60)	110 (71)	139 (90)	148 (96)

[a] Noncarrier, subject in whom no MR-CoNS strain (indicated for all species together and then detailed species by species) was isolated in 2006 or 2008; intermittent carrier, subject carrying at least one MR-CoNS isolate in either 2006 or 2008; persistent carrier, subject carrying at least one isolate in both 2006 and 2008.
[b] Including *S. kloosii*, *S. capitis*, and *S. cohnii*.

S. epidermidis increasingly appears as a major actor of MR dissemination among community strains of staphylococci. This species represents 69 to 84% of the MR-CoNS isolates collected in previous community-based studies (1, 41, 44), and several data strongly support its potential role as a reservoir of SCC*mec* for *S. aureus* (1–3, 13, 20, 49), including CA-MRSA (1). Two previous surveys in open communities found an extremely high diversity of MRSE in terms of SCC*mec* structures and genetic background (1, 22). In our work, the 89 MRSE isolates displayed large polymorphisms of SCC*mec* elements, including 36 isolates with untypeable patterns, and divided into 62 distinct MLVA profiles. Most of these profiles were found in only one or two MRSE isolates, with only five of them accounting for more than three isolates. Moreover, only six MLVA patterns were found in both 2006 and 2008. These data provide further evidence that, even in a nearly closed population, the community spread of MRSE is not clonal. This situation contrasts with the one observed for CA-MRSA, whose worldwide spread currently involves only a limited number of clones (34) and might result from the easiest SCC*mec* recombinations and intraspecies transfers in *S. epidermidis*. Indeed, the few available SCC sequences from *S. epidermidis* strains suggest that both new SCC*mec* and SCC non-*mec* variants may arise by recombination of DNA fragments from distinct SCC elements (1, 8, 51). Moreover, a previous work based on MLST data analysis indicated that SCC*mec* transfers were probably frequent in *S. epidermidis* compared to in *S. aureus* (31). Plasticity of the *S. epidermidis* genome (11, 52) may constitute an auspicious background for the chromosomal integration of SCC*mec* elements and allow the frequent rise of new MRSE strains, making this species a wide and dynamic reservoir of SCC*mec* in the community and explaining this lack of patent clonality.

Regardless of the species, we found that SCC*mec* elements were highly polymorphous among MR-CoNS. Half of our isolates harbored a nontypeable SCC*mec*, with a new association between known *mec* and *ccr* gene complexes (18%) or a nondetectable *ccr* and/or nontypeable *mec* gene complex (31%). Thirty-five (13%) MR-CoNS isolates were found to carry 2 or 3 distinct *ccr* allotypes, a finding that corroborates those of previous works (14, 20, 41), and one *S. hominis* strain gave 4 typeable *ccr* amplicons (*ccrA1B1* with *ccrA2B2*, *ccrA3B3*, and *ccrA4B4*). We cannot firmly exclude that a lack of primer specificity might have led to the amplification of several DNA fragments from a single, new *ccr* variant. However, all MR-CoNS strains that we reported as carrying multiple *ccr* allotypes gave *ccr* amplicons with band sizes that matched exactly with those from reference MRSA strains. Further studies including sequencing data are needed to better describe such MR-CoNS strains harboring multiple *ccr* allotypes. Furthermore, the associations of class A and class B *mec* gene complexes have been described in health care-associated MR strains of *S. epidermidis* and *S. capitis* (19, 20). In this study, we found three strains with new associations of *mec* gene complexes, namely, class A with C2, with or without C1, and class B with C2. These results, in line with those of other works (1, 11, 14, 22, 41, 44, 52), emphasize the extreme plasticity of SCC*mec* elements among CoNS, with frequent rearrangements and continuous generation of new composite cassettes.

SCC*mec* types 2B and 5C2 were carried by 8.7% and 23.7% of the 274 MR-CoNS isolates, respectively. These types account for nearly all of the CA-MRSA lineages described to date (34). Considering the high rate of cocarriage of MSSA and MR-CoNS, the lack of evidence of SCC*mec* transfer between CoNS and *S. aureus* in this community is surprising (37). In addition, 92 (61.7%) of the 149 MSSA isolates isolated during the two campaigns belonged to clonal complex 1 (CC1), CC5, CC8, CC30, or CC398, which might constitute suitable phylogenic backgrounds for SCC*mec* acquisition (9, 24, 34). Indeed, only two MRSA isolates were found (both during the 2008 campaign), and both carried SCC*mec* type I (1B), this profile being not found in MR-CoNS isolates. However, although the role of MR-CoNS as a reservoir of SCC*mec* for *S. aureus* appears undeniable (1–3, 13, 20, 49), this transfer has been directly observed only once (3), suggesting that it may occur at a very low frequency.

The prevalence of MRSS among MR-CoNS isolates increased from 1% to 19% over the study period. Other community-based surveys have recently highlighted the emergence of MR in this species (16, 22), including the nasal carriage isolates (22). The implantation of MRSS in the nasal flora is unexpected, as this uropathogenic species colonizes mainly the female genital tract, with an overall colonization rate of ~7% (16, 40). This shift toward a novel colonization site might result from a selective advan-

FIG 1 Genetic relationship of multiple-locus variable-number tandem repeat analysis (MLVA) patterns of the 89 methicillin-resistant *Staphylococcus epidermidis* isolates collected during the 2006 (△) and 2008 (▲) sampling campaigns, as implemented by the BioNumerics version 6.0 software (Applied Maths NV, Sint-Martens-Latem, Belgium) by using the unweighted pair group method with arithmetic mean (UPGMA). The symbols §, ‡, and # indicate MLVA genotypes that were found only in 2006, only in 2008, or both, respectively. Staphylococcal cassette chromosome *mec* elements (SCC*mec*) are defined by the *ccr-mec* allotype combination according to the current classification used in methicillin-resistant *S. aureus* (21). MLVA patterns are defined as the number of tandem repeats for each of the five Se loci (Se1, Se2, Se3, Se4, Se5) (23). *ccr* allotypes are classified as types 1 to 4 (i.e., *ccrA1B1* to *ccrA4B4*) and 5 (i.e., *ccrC*). ND, nondetectable *ccr* gene complex; NT, nontypeable *mec* allotypes or SCC*mec*.

tage in terms of antibiotic pressure, because *S. saprophyticus* is usually more resistant to non-β-lactam agents than other CoNS species (33), as observed in our work. Besides, all but one of our 27 MRSS strains carried an untypeable SCC*mec* element, mostly because of a nondetectable *ccr* gene complex (see Table S1 in the supplemental material). These difficulties to type *ccr* in MRSS have been previously reported (45) and suggest that *S. saprophyticus* carries undescribed *ccr* variants more often than other CoNS species.

In conclusion, this study brings new insights on the biodiversity and dynamic of MR-CoNS carriage in the community and provides further evidence of their role as a large and evolutionary reservoir of SCC*mec* in this setting. Fortunately, SCC*mec* transfers between MR-CoNS and the highly pathogenic *S. aureus* are probably exceptional compared with inter-CoNS exchanges.

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