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Staphylococcus aureus from the German general population is highly diverse

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ABSTRACT

Objectives: This prospective cohort study evaluates colonization dynamics and molecular characteristics of methicillin-susceptible and – resistant *Staphylococcus aureus* (MSSA/MRSA) in a German general population.
Methods: Nasal swabs of 1878 non-hospitalized adults were screened for *S. aureus*. Participants were screened thrice in intervals of 6–8 months. Isolates were characterized by *spa* and *agr* typing, *mecA* and *mecC* possession, respectively, and PCRs targeting virulence factors.
Results: 40.9% of all participants carried *S. aureus* at least once while 0.7% of the participants carried MRSA (mainly *spa* t011). MSSA isolates (n = 1359) were associated with 331 different *spa* types; t084 (7.7%), t091 (6.1%) and t012 (71, 5.2%) were predominant. Of 206 participants carrying *S. aureus* at all three sampling time points, 14.1% carried the same *spa* type continuously; 5.3% carried different *spa* types with similar repeat patterns, but 80.6% carried *S. aureus* with unrelated *spa* types. MSSA isolates frequently harboured genes encoding enterotoxins (*sec*: 16.6%, *seg*: 63.1%, *sei*: 64.5%) and toxic shock syndrome toxin (*tst*: 17.5%), but rarely Panton-Valentine leukocidin (*lukS*-PV/*lukF*-PV: 0.2%).
Conclusions: MSSA colonizing human nares in the community are clonally highly diverse. Among those constantly carrying *S. aureus*, clonal lineages changed over time. The proportion of persistent *S. aureus* carriers was lower than reported elsewhere.

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1. Introduction

The clinical impact and socio-economic burden of *Staphylococcus aureus* as a major pathogen remains unchanged and the global spread of methicillin-resistant *S. aureus* (MRSA) clones led to therapeutic limitations and expensive prevention measures in healthcare facilities (Köck et al., 2014). Most studies on the pathogenís epidemiology during the past decades focused on MRSA and investigated infections due to healthcare-associated (HA-MRSA), community-associated (CA-MRSA) and livestock-associated (LA-MRSA) clonal lineages (Mehraj et al., 2016). However, infections caused by methicillin-susceptible *S. aureus* (MSSA) are still much more frequent than MRSA. Today, it is assumed that up to 30% of the general population permanently carries *S. aureus* and the others show non-persistent carriage, which is a source and risk factor for invasive infections (Kaspar et al., 2016; Kluytmans et al., 1996; van Belkum et al., 2009; von Eiff et al., 2001; Williams, 1963). Since recent investigations have demonstrated higher population dynamics of circulating MRSA strains than previously considered (Hsu et al., 2015; Schaumburg et al., 2012), a much more complex and diverse situation might be anticipated for *S. aureus* (including MSSA) outside healthcare facilities as these are characterized by specific conditions with respect to selection pressure and transmission. However, in contrast to the hospital environment, the clonal "landscape" of *S. aureus* in the community contains many blank areas.

In a prospective cohort study among 1878 non-hospitalized volunteers in the German community, we recently found an overall prevalence of nasal *S. aureus* carriage of 41.0% including a propor-

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Table 1
Phenotypic and genotypic characteristics of cefoxitin-resistant *S. aureus* isolates.

spa type	*spa*-CC	No. of isolates/participants[a]	Genetic profile (all isolates except no. indicated)	Phenotypic resistance profile (all isolates except no. indicated)[a]
t011	CC015	7/4	*nuc*, *mec*A, *agr*I, *sec/seg/sei*(2), *eta*(1), *edin*-A (1)	FOX, TET
t003	CC002	2/2	*nuc*, *mec*A, *agr*II, *sed/seg/sei/sej*	FOX, LEV, MOX, CLI, ERY, TET (1),
t084	CC084	1/1	*nuc*, *mec*A, *agr*I	FOX, CLI, ERY, TET, SXT
t127	CC127/177	1/1	*nuc*, *mec*A, *agr*III, *sea*, *seh*	FOX
t230	CC015	1/1	*nuc*, *mec*A, *agr*II,*seg*, *sei*, *sej*	FOX, CLI, ERY, LEV, MOX
t469	CC081	1/1	*nuc*, *mec*A, *agr*I	FOX, TET
t670	CC005	1/1	*nuc*, *mec*A, *agr*I, *seg*, *sei*	FOX, LEV, MOX
t1017	CC015	1/1	*nuc*, *mec*A, *agr*I,*seg*, *sei*	FOX, LEV, MOX
t1081	CC015	2/1	*nuc*, *mec*A, *agr*I,*tst*(1), *seg* (1), *sei* (1)	FOX, TET
t009	CC008	1/1	*nuc*, *tst*, *sea*, *seg*, *sei*[b]	FOX, CLI, ERY, TET, FOS, FUS
t159	CC645/159	1/1	*nuc*, *agrIV*, *seg*, *sei*	FOX, CLI, FOS

[a] Number of cefoxitin-resistant isolates from number of different participants, *cefoxitin (FOX), clindamycin (CLI), erythromycin (ERY), levofloxacin (LEV), moxifloxacin (MOX), tetracycline (TET), fosfomycin (FOS), fusidic acid (FUS). Vancomycin, linezolid, gentamicin, rifampicin, mupirocin and tigecycline were susceptible for all FOX-resistant isolates.
[b] *agr* type could not be determined with the primers used.

tion of 0.7% MRSA carriers (Köck et al., 2016). Here, we analyse the clonal structure of the *S. aureus* isolates from this cohort including a comparison of consecutive isolates obtained from the same persons as well as data about the occurrence of defined virulence-associated genetic determinants.

2. Results

The structure of the recruited cohort has been described in detail by Köck et al. (Köck et al., 2016). Briefly, demographic data for the study participants were similar to representative data for the German general population (according to the Federal Statistical Office of Germany, DESTATIS) regarding gender (female; census/cohort: 52%/58%), mean age (44 years/45 years), migration background (20%/13%) or working in the healthcare sector (11%/12%) (Köck et al., 2016). Of all 1878 participants, 768 (40.9%) carried *S. aureus* at least once. Within the cohort, 1168 (62.2%) persons provided three nasal swabs within a period of 12–14 months, while 283 (15.1%) provided two swabs and 427 (22.7%) only one swab. The prevalence of *S. aureus* carriage in these sub-cohorts is indicated in Fig. 1.

Of those 206 participants carrying *S. aureus* at three time points, 620 isolates were included (as two persons were colonized with two phenotypically different strains at one time point). Another 387 isolates were from 192 participants carrying *S. aureus* at two time points (three persons carried three strains each) and 371 isolates were from 370 participants carrying *S. aureus* only at one time point (one person carried two strains). In total, 1378 *S. aureus* isolates were detected and characterized and the number of isolates per participant collected during the study period ranged between four (n = 2 participants), three (n = 207), two (n = 190) and one (n = 369) with a median (mean) number of 2 (1.79). All 1378 isolates were tested positive for the *S. aureus*-specific *nuc* gene.

Seventeen isolates from 13 cohort participants (0.7% of all participants) were *mec*A positive MRSA (Table 1) mostly associated with *spa* type t011 (7/17, 41.2%). Besides these MRSA isolates, phenotypic cefoxitin resistance was detected in two further isolates from two additional participants, but these isolates lacked both *mec*A and *mec*C. They belonged to different *spa* types (t009 and t159), which did not cluster in the same *spa*-CC. The source of the cefoxitin-resistant phenotype in these strains is unknown (Table 1). The diversity of *spa* types among MRSA isolates (including those being *mec*A and *mec*C negative) was low (Simpson's index of diversity (1-D) = 0.866; 95% confidence interval (CI) 0.732–0.999).

The 1359 methicillin-susceptible *S. aureus* isolates (Table 2, Fig. S1) belonged to a total of 331 *spa* types with t084 (n = 104; 7.7%), t091 (n = 83; 6.1%), t012 (n = 71; 5.2%) and t015 (n = 56; 4.1%) being predominant. Compared to MRSA, *spa* types of MSSA were more diverse (Simpson's index of diversity (1-D) = 0.980; 95% CI 0.977–0.982). Of all isolates, three were *spa* non-typeable (0.2%) even using alternative primers. The *spa* types were grouped in 24 *spa*-clonal complexes (*spa*-CC) by BURP repeat analysis; 86 isolates (6.3%) belonged to *spa* types excluded from BURP cluster analysis, because they contained less than five *spa* repeats (Fig. S2). Further 5.2% belonged to *spa* types, which showed a repeat pattern not associated with the other isolates detected in the cohort ("singletons").

Within *spa*-CC015, thirteen MSSA isolates (i.e. 1.0% of all MSSA) from twelve persons were associated with *spa* types t011 (n = 3), t034 (n = 5), t1451 (n = 4) and or t3423 (n = 1), respectively. These *spa* types were grouped closely together by BURP based on their repeat patterns and are indicative (as described by other studies) for strains belonging to the clonal complex (CC) 398 as defined by multilocus sequence typing (MLST) (Reischl et al., 2009). They were 100% susceptible against all non-β-lactam antibiotics tested (see below) except clindamycin (84.6% susceptibility), trimethoprim-sulfamethoxazole (84.6%) and tetracycline (69.2%). These isolates were associated with the following genetic markers: *agr*I (n = 12), *agr*III (n = 1), *seg* (n = 5), *sea* and *sec* (each n = 2), *sea*, *seb*, *tst*, *eta*, *etb* and *edin*-B (each n = 1).

Of all MSSA, 692 (50.9%) were associated with *agr*I, 355 (26.1%) with *agr*II, 261 (19.2%) with *agr*III and 47 (3.5%) with *agr*IV, respectively and harboured the virulence determinants as shown in Table 3. Performing the respective PCRs thrice, in four isolates the *agr* type could not be determined with the standard primers and one isolate was positive in PCRs for two *agr* types (*agr*I and *agr*III). Non-discrimination was probably due to point mutations in the *agr* locus. MSSA harboured the following virulence markers: *tst* (17.5%), *sea* (11.3%), *seb* (6.3%), *sec* (16.6%), *sed* (5.5%), *see* (0.1%), *seg* (63.1%), *seh* (7.1%), *sei* (64.5%), *sej* (4.9%), *eta* (3.2%), *etb* (0.8%), *etd* (2.8%), *edin-A* (0.1%), *edin-B* (3.2%) and *edin-C* (0.6%). Two MSSA isolates (0.2%) from different participants harboured PVL-encoding genes *lukS*-PV/*lukF*-PV. These isolates were associated with t216 and t004 and *agr*I. One of these isolates (t216) harboured the additional virulence factors *tst*, *sea*, *seb*, *sed*, *seg*, *sei* and *sej*.

Among all MSSA isolates, 37.7% were susceptible to penicillin, 90.7% to clindamycin, 90.8% to erythromycin, 97.4% to tetracycline, 98.0% to fusidic acid, 98.9% to gentamicin, 99.0% to levofloxacin, 99.1% to moxifloxacin, 99.4% to rifampicin and fosfomycin, 99.6% to trimethoprim/sulfamethoxazole, 99.7% to mupirocin and 100% to linezolid, vancomycin and tigecycline, respectively.

The colonization pattern of all those participants who provided more than one swab is indicated in Fig. 1. Among those 206 participants carrying *S. aureus* at three time-points only 14.1% carried the same *spa* type; 5.3% carried a different *spa* type, but associated with the identical *spa*-CC. Overall, of 398 participants carrying *S. aureus*

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