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Prevalence and determinants of nasal colonization with antibiotic-resistant *Staphylococcus aureus* among unselected patients attending general practitioners in Germany

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SUMMARY

Although the great majority of antibiotics are prescribed outside hospitals, little is known about the prevalence and determinants of antibiotic resistance in the group of outpatients. Nasal swabs were taken from 627 consecutive patients aged 40 years or above attending general practitioners in Southern Germany. *Staphylococcus aureus* was cultured and minimal inhibitory concentrations to various antibiotics were tested. Nasal swabs of 152 patients were positive for *S. aureus*. Prevalence of resistance was 68·3, 8·3 and 0·7% for penicillin G, erythromycin, and oxacillin respectively. Antibiotic use within the last month was associated with erythromycin resistance [adjusted odds ratio (OR) 7·4; 95% confidence interval (CI) 1·0–53]. Besides a high prevalence of resistance to penicillinase-instable antibiotics we found only one (0·7%) methicillin-resistant *S. aureus*. Recent antibiotic use was associated with increased resistance to erythromycin.

INTRODUCTION

Antibiotic resistance is an emerging problem worldwide [1, 2]. Widespread use of antibiotics is likely to be the main reason for the rise in antibiotic resistance [3–5]. Among the most alarming observations is the increasing prevalence of resistant *Staphylococcus aureus* in the clinical setting [6].

In this sector, *S. aureus* is responsible for large proportions of nosocomial infections, ranging from minor skin infections to life-threatening invasive infections including sepsis, endocarditis or pneumonia [7]. In the early 1960s, soon after methicillin was launched onto the market, the first methicillin-resistant *S. aureus* (MRSA) strains were reported. Over the years, MRSA strains have become resistant to more and more antibiotics that were effective against staphylococci. In 1997, even MRSA strains with reduced susceptibility to glycopeptides had been isolated, and in 2002, the first clinical infection with a vancomycin-resistant strain was reported [8, 9]. Prevalence of MRSA in the hospitals in the United States is at an alarming level. Because MRSA strains had started to spread from hospitals to the community [10, 11], population-based studies were initiated to survey the prevalence of MRSA in outpatients within the United States [12, 13].

Epidemiological data from the ambulatory setting in Europe are only available for a few countries, for example Portugal, Finland and the United Kingdom [14–16]. Although in Germany the prevalence of MRSA increased in the clinical setting [17], no studies were performed to monitor the situation of resistance in the community.

We therefore conducted a population-based study to assess prevalence and determinants of antibiotic resistance of *S. aureus* strains cultured from nasal

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swabs of unselected patients attending general practitioners (GPs) in Southern Germany.

METHODS

Study population and data collection

All patients aged 40 years or older who visited one of three cooperating GPs in the city of Ulm, located in Southern Germany, and nearby communities, for various reasons, including but not restricted to infections, were eligible for recruitment. From May to July 1999 and from November 1999 to January 2000 patients were recruited at defined days of the week. Out of 840 eligible patients, 627 (74·5%) were willing to participate, gave written informed consent, and were recruited into the study. Data on use of antibiotics and other medication, sociodemographic variables, lifestyle factors and comorbidity were obtained from patients aged below 75 years by self-administered standardized questionnaire and from patients aged 75 years and older by standardized interviews conducted by trained personnel. In addition, medical data were obtained from the patients' health charts. During the consultation with the GP, nasal swabs were collected from all participants. The samples were brought to the Department of Medical Microbiology and Hygiene at the University of Ulm on the same day.

Antibiotic use

The questionnaire contained detailed queries about the intake of antibiotics during the past 12 months. Several categories were offered to rate the timing of last antibiotic intake: current use or use stopped during the last month, use stopped during the last 12 months (but not last month) and no use within last year. We also collected detailed data on antibiotics prescribed by GPs from the patients' health charts.

Although the data on antibiotic use from the patients' health charts were more specific with respect to the drugs actually prescribed and overall concordance between self-reported antibiotic use and antibiotic prescriptions by GPs during the last 12 months was moderate to good, we decided to use patients' self-reports for this analysis, because patients might have received antibiotics from other sources (prescriptions by other doctors, antibiotics left over from previous or family members' prescriptions). Also, not all antibiotics prescribed by GPs are actually used.

S. aureus culturing and antibiotic-resistance testing

Nasal swabs were obtained using sterile cotton swabs (Amies medium; Hain Diagnostika, Nehren, Germany). The presence of *S. aureus* was determined by culture of samples on CASO blood agar plates incubated at 36 °C for 24 h followed by the 'Slidex' test (latex-haemagglutination). The isolates were kept frozen at −80 °C until susceptibility testing was performed. Susceptibility to a wide array of antibiotics ($n=32$) was determined for *S. aureus* isolates. Minimal inhibitory concentrations (MIC) were tested using micro-well plates with various concentrations of antibiotics and an optical reader (Merlin, Bornheim, Germany) according to German national standards [18]. Weekly testing of *S. aureus* strains ATCC 29213 and 43300 was used for quality control. Oxacillin resistance was confirmed by detection of the *mecA* gene by PCR.

Statistical analyses

We used descriptive statistics to characterize the patients with respect to various sociodemographic and lifestyle factors and compared the groups of participants colonized with *S. aureus* and those who were not. Furthermore descriptive statistics were used to assess the prevalence of resistance of *S. aureus* strains to the various selected antibiotics. For the prevalences of resistance, exact binominal 95% confidence intervals (CIs) were calculated using a computer program by Staehelin and Sullivan (Version 1.0, CDC, 1998).

The analyses of potential determinants of resistance were performed for penicillin G and erythromycin, since the resistance values were sufficiently high to allow a statistical analysis and since the compounds are relevant in the treatment of infectious diseases. In a first step, prevalences of substance specific antibiotic resistance were cross-tabulated with possible determinants of resistance in bivariate analyses. In a second step, separate multivariable logistic regression models with substance-specific antibiotic resistance as the dependent variable were used to estimate the independent contribution of possible determinants for the development of specific antibiotic resistance. In these models, only the variables associated with antibiotic resistance in bivariate analyses or thought

Table 1. *Demographic data of 627 consecutive patients attending general practitioners and possible determinants for antibiotic resistance*

	Total ($n=627$)	*S. aureus* cultured from nasal swabs ($n=152$)
Age, mean (S.D.)	61·2 (11·8)	59·1 (11·4)
Body mass index, mean (S.D.)	26·7 (4·0)	26·7 (4·1)
Male, *n* (%)	294 (46·9)	81 (53·3)
Smoking, *n* (%)		
Never	324 (51·8)	82 (54·0)
Former	226 (36·2)	55 (36·2)
Current	75 (12·0)	15 (9·9)
Regular alcohol consumption, *n* (%)	427 (68·5)	100 (67·1)
Anamnestic comorbidity, *n* (%)		
Coronary heart disease	160 (25·6)	39 (25·7)
Cancer	58 (9·3)	18 (11·8)
Hypertension	271 (43·4)	68 (44·7)
Hyperlipidaemia	172 (27·6)	43 (28·5)
Kidney diseases	89 (14·2)	25 (16·6)
Diabetes	69 (11·2)	20 (13·3)
Antibiotic use within last month, *n* (%)	29 (4·6)	7 (4·6)
Antibiotic use within last 12 months, *n* (%)	176 (28·2)	35 (23·0)
Hospital stay within last 12 months, *n* (%)	98 (15·9)	24 (15·9)
Visit to a hospital or nursing home within last 12 months, *n* (%)	336 (55·3)	81 (54·7)

to be possible confounders of the association of antibiotic resistance with other factors were included. All analyses were carried out with the statistical software package SAS, version 8.2.

RESULTS

Overall, 627 patients participated in the study. *S. aureus* could be cultured and identified among 152 patients (24·3%). Seven strains were no longer viable after storage, thus the MIC could be determined from 145 isolates. The characteristics of the total study population and of the patients with *S. aureus* cultured from nasal swabs are shown in Table 1. There was no major difference between these populations. This indicates that nasal colonization with *S. aureus* did not depend on factors listed in the table, neither sociodemographic characteristics nor medical history.

The mean (±S.D.) age was 61 (±12) years and approximately half of the persons were male (46·9%). Approximately 10% of the patients were current smokers and slightly more than half of them had never smoked in their life. Approximately two thirds of the people who completed the questionnaire reported that they consumed alcoholic beverages regularly. Comorbidity was common in this population with hypertension being the most frequent condition among those specifically asked for, followed by hyperlipidaemia and coronary heart disease. Regarding possible determinants for carrying resistant *S. aureus* we ascertained that more than 10% of the patients suffered from diabetes mellitus. This proportion conforms to the average of the community for this age distribution. Approximately 5% of the patients reported use of antibiotics during the last month and approximately 16% had been admitted to a hospital in the past 12 months.

The Figure presents the prevalences of *S. aureus* resistance to representative antibiotics. Resistance to penicillin G was observed in 68% of all isolates. One out of 145 strains was oxacillin resistant, none was identified as a borderline oxacillin-resistant strain.

Eight per cent of the isolates showed resistance to erythromycin, and one strain was resistant to clindamycin. None of the 145 isolates were resistant or showed intermediate susceptibility to vancomycin.

For further analyses of determinants of resistance, penicillin G and erythromycin were selected. Resistance to penicillin G and erythromycin according to age, sex, antibiotic use during last month and last

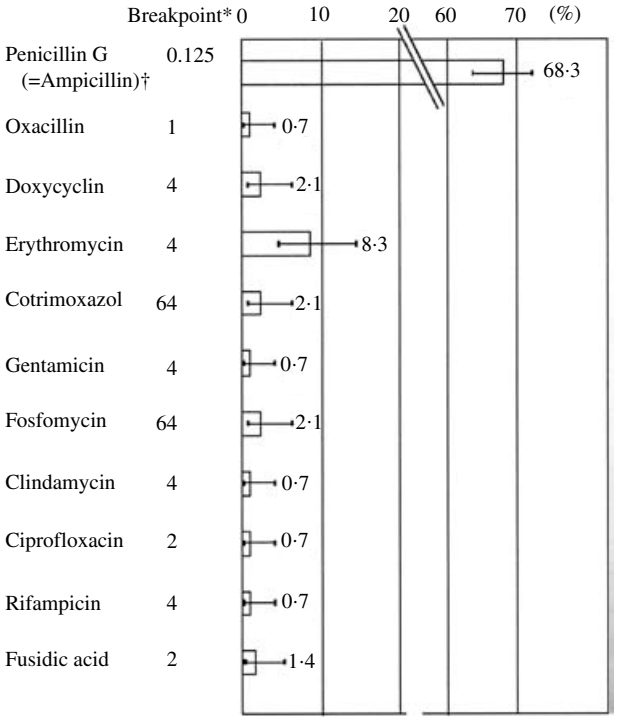

Fig. Prevalence of *S. aureus* resistance to various antibiotics in patients attending general practitioners in Southern Germany. Bars represent exact 95% binominal confidence intervals. No resistance was observed to the following substances: moxifloxacin, clinafloxacin, linezolid, netilmicin, synercid, teicoplanin and vancomycin (upper limit of exact 95% CI 2·5%). * Breakpoint gives the highest intermediate value. † According to DIN criteria, Staphylococci test results for penicillin G have to be adopted for ampicillin.

12 months as well as hospital stay within the last 12 months is presented in Tables 2 and 3. None of the other variables considered in the bivariate analyses – visiting family or friends in hospitals or nursing homes during the last 12 months, nursing a relative or friend at home, household characteristics, potential occupational risk factors, dietary habits, body mass index, education, smoking and alcohol consumption as well as comorbidity (i.e. coronary heart disease, cancer, diabetes and hypertension) – was significantly associated with antibiotic resistance to these substances, and therefore they were not included in the multivariate analyses shown in the tables.

We found no indication that age is associated with antibiotic resistance. Furthermore, no significant association between prevalence of resistance and antibiotic intake or hospital stay within the last 12 months was observed for penicillin G (Table 2).

Use of antibiotics within the last month was associated with resistance to erythromycin (Table 3), and, albeit somewhat weaker, an association also persisted,

Table 2. *Penicillin G resistance in* S. aureus *according to selected characteristics in patients attending general practitioners in Southern Germany*

		Penicillin G resistance*			
	n	*n*	(%)	OR	(95% CI)
Age (years)					
40–54	49	34	(69)	1·0	Reference
55–64	50	35	(70)	1·0	(0·4–2·5)
65–75	46	30	(65)	0·9	(0·4–2·2)
Sex					
Male	76	49	(65)	1·0	Reference
Female	69	50	(73)	1·4	(0·7–3·0)
Antibiotic use within last 12 months					
No	112	74	(66)	1·0	Reference
Yes	33	25	(76)	1·6	(0·7–4·0)
Within last month	7	5	(71)	1·3	(0·6–4·7)
More than 1 month ago	26	20	(77)	1·7	(0·5–3·8)
Hospital stay within last 12 months					
No	122	82	(67)	1·0	Reference
Yes	22	16	(73)	1·4	(0·5–3·8)

* MIC >0·125 mg/l.
Odds ratio (OR) and 95% confidence intervals (CI) from multivariate logistic regression adjusted for all variables are presented in the table.

if the last use of antibiotics was 1–12 months ago. Overall, patients who had used antibiotics within the last 12 months had a 4·4-fold elevated risk (95% CI 1·2–16) to carry erythromycin-resistant *S. aureus*.

Again, no association between resistance and hospital stay within the last 12 months was observed.

Among 145 cultured strains, only one (0·7%, 95% CI 0–3·8) was identified as methicillin-resistant, and this finding was confirmed by analyses of the genotype. The strain showed resistance to ciprofloxacin, clindamycin and aminoglycosides, but was sensitive to glycopeptides.

The carrier of the MRSA was a female aged over 65 years with known risk factors for MRSA including diabetes and chronic renal failure. Antibiotic intake in the last 12 months was not reported, but the person had contact with the clinical sector or a nursing home more than once a week.

DISCUSSION

To our knowledge this is the first community-based study on prevalence of antibiotic resistance of

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Table 3. *Erythromycin resistance in* S. aureus *according to selected characteristics in patients attending general practitioners in Southern Germany*

		Erythromycin resistance*			
	n	*n*	(%)	OR	(95% CI)
Age (years)					
40–54	49	2	(4)	1·0	Reference
55–64	50	8	(16)	5·3	(1·0–27·7)
65–75	46	2	(4)	1·5	(0·2–11·5)
Sex					
Male	76	5	(7)	1·0	Reference
Female	69	7	(10)	1·4	(0·4–5·0)
Antibiotic use within last 12 months					
No	112	6	(5)	1·0	Reference
Yes	33	6	(18)	4·4	(1·2–15·6)
Within last month	7	2	(29)	7·4	(1·0–53)
More than 1 month ago	26	4	(15)	3·7	(0·9–15·0)
Hospital stay within last 12 months					
No	122	12	(10)		
Yes	22	0	(0)		

* MIC >4 mg/l.
Odds ratio (OR) and 95% confidence intervals (CI) from multivariate logistic regression adjusted for all variables are presented in the table; hospital stay was dropped because of zero cell.

S. aureus in Germany, whereas several studies had assessed the situation in the clinical setting (see Table 4). Our study confirmed that colonization with penicillin G-resistant *S. aureus* is very common even in the community setting (68%). This prevalence was nevertheless somewhat lower than the result from the clinical setting found in a project from German Network on Antimicrobial Resistance Surveillance (GENARS) conducted between May and September 2000 (75%) [19] (Table 4). A survey from the Paul-Ehrlich-Society (PEG) during November 2001 [20] also yielded higher prevalences, with 78% for the intensive care units (ICU) and 79% for other wards. But these different outcomes were not particularly striking. Our results suggest that the prevalence of penicillin resistance has not changed substantially in Germany, although the prevalence in the community slowly reaches figures formerly found only in the clinical setting.

By contrast, prevalences of resistance to erythromycin (the most commonly prescribed macrolide in Germany [21]) and to fluoroquinolone and oxacillin were much lower in our study than those in previous studies conducted in the clinical setting.

In accordance with other publications, recent antibiotic intake was a statistically significant risk factor for colonization with resistant *S. aureus* [5, 16, 22]. Antibiotic use during the last month was identified as a determinant of erythromycin resistance, but not penicillin G resistance.

Our findings do not imply that resistance to erythromycin develops during antibiotic treatment. It seems more plausible that resistant strains are widespread, but usually outnumbered by sensitive strains. During antibiotic treatment, sensitive strains are reduced or eliminated and the normally outnumbered resistant strains are more likely to grow. The time period shortly after antibiotic treatment might be important for the individual, because of the possibility of an infection from their own reservoir, and for the community, because of a potential transmission of resistant strains.

For the last 50–60 years β-lactam antibiotics have been the most commonly prescribed antibiotics and one has to assume that, during this time, the majority of people receiving a prescription received a substance from this class. The very wide spread of β-lactam-resistant *S. aureus* strains in the population may explain that recent antibiotic intake does not seem to be associated with colonization with a penicillin-resistant strain.

So far antibiotic resistance of *S. aureus* has mainly emerged as a clinical problem. A study from the Robert Koch Institute confirmed that the prevalence of MRSA isolates is continuously increasing in German hospitals. In blood and other clinical isolates the proportions of MRSA were 1·5% in 1990, 8·7% in 1995 and reached a level of 15·2% in 1998 [17, 23]. The Paul-Ehrlich-Society reported even higher prevalences for 2001 (Table 4), a quarter of all *S. aureus* isolates from ICU and 21·5% of the strains from other wards were resistant to oxacillin [20]. In their community sample, 13% of the isolates were analysed as methicillin-resistant, but according to the authors, this high value is due to the fact that the received isolates originated only from patients with acute and maybe even hospital-acquired infections.

There is increasing evidence that the epidemiology of antibiotic resistance in *S. aureus* is changing [10, 11]. MRSA occurs in the community [15], although prevalence still appears to be quite low in many countries, including Germany. Studies about

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Table 4. *Comparison of the prevalence of* S. aureus *resistance in different settings in Germany*

Setting …	GENARS* (May–Sep. 2000) Hospital	PEG† (November 2001) ICU	PEG† (November 2001) Other wards	PEG† (November 2001) CAI‡	Ulm (1999–2000) Community
n	319	133	507	146	145
Penicillin G (%)	74·6	78·2	78·5	73·3	68·3
Erythromycin (%)	15·7	30·1	26·8	16·4	8·3
Fluoroquinolone 2. Generation (%)	21·3	27·8	24·3	13·0	0·7
Oxacillin (%)	9·7	25·6	21·5	13·0	0·7

* GENARS, German Network on Antimicrobial Resistance Surveillance [19].
† PEG, Paul-Ehrlich-Society of Germany [20].
‡ CAI, Community-acquired infection.

the spread from MRSA into the community have recently been reviewed by Salgado et al. [24]. Studies that have been conducted among randomly selected healthy community members observed a prevalence among individuals without any risk factor of 0·2% [12, 14, 25]. Higher prevalences have been found in community studies among high-risk populations [25, 26], such as homeless people in San Francisco (2·8%) [13] or residents in German nursing homes in the Rhine–Neckar region (1·1%) [27]. The prevalence of MRSA of 0·7% in our study is in good agreement with the average level found by Salgado et al.

The MRSA case from our study had contact with hospitals and nursing homes during the last year. Hospital contact is an important risk factor for the acquisition of MRSA [28–31]. In addition to the contact to medical institutions, the patient had severe comorbidity like diabetes mellitus and renal failure. Our results thereby suggest that occurrence of MRSA strains in the community of our study population still seems to be restricted to certain high-risk patients.

Our study has several limitations, which should be kept in mind when interpreting the results. We conducted a cross-sectional study without longitudinal assessment of participants. The study population included patients attending their GP and might, therefore, not be fully representative of the general population. However, we recruited consecutive patients irrespective of the reason for their visit. These patients are, therefore, representative of the population attending GPs (who prescribe the majority of antibiotics), a population for which antibiotic resistance might be even more relevant than for general population samples. Since in Germany adults can get antibiotics prescribed by several physicians and not all prescribed antibiotics are actually used, we relied on the self-report of antibiotic intake for our analyses rather than on medical records. On the other hand, self-reports of antibiotic intake may also be prone to error and we were unable to address the role of specific antibiotics.

Although for most antibiotics the number of resistant isolates was small, the size of the study population resulted in precise estimates of the prevalence of antibiotic resistance. We can therefore exclude high prevalences of resistance for many substances used for infections outside the hospital with a high level of certainty. Furthermore, the sample size allowed for analyses of determinants of resistance to two important antibiotics with a high prevalence of resistance.

We conclude that *S. aureus* resistance to penicillins and erythromycin is at a relatively high level in the community in Germany, although erythromycin resistance is still considerably lower than in clinical settings, while MRSA remains predominantly a hospital pathogen [27], spread into the community might occur among high-risk persons. Most strains are susceptible to penicillinase-resistant β-lactams, the first choice treatment for infections outside the hospital. Recent antibiotic use was identified as a determinant of increased prevalence of resistance to erythromycin. Although the prevalence of resistance to other commonly prescribed antibiotics was generally low, extension of the monitoring of antibiotic resistance from specialized centres to the general population appears to be warranted.

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