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ARTICLE

Epidemiology of MRSA in southern Sweden: strong relation to foreign country of origin, health care abroad and foreign travel

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Abstract All notified MRSA cases in Skåne County have been followed since 2000. We have investigated the MRSA epidemiology over time, method of acquisition, whether some *spa* types are more prone to spread, and/or cause more infections, and the connection between *spa* type and country of acquisition/origin. All cases between 2000 and 2010 were included. Infection or colonization and the presence of PVL genes were noted. The *spa* types of the index cases were correlated with community or healthcare acquisition, proportion of MRSA-positive household contacts, country of origin of families and country of acquisition of MRSA. The number of cases increased from 31 in 2000 to 315 in 2010. Most cases were community-acquired and the median age was 30 years. Thirty-two per cent of the MRSA cases were found because of a clinical infection. Of the household contacts 35 % were MRSA-positive. Only 24 % of the MRSA cases were both of Swedish origin and had contracted MRSA in Sweden. An association between *spa* type and certain regions of acquisition/origin was noted. *Spa* types t044, t002 and t008 were the most predominant strains. PVL-positive *spa* types t008, t019 and t044 caused more skin infections than the other *spa* types. Our results support screening for MRSA in patients with health care contacts abroad, culturing of patients with skin infections contracted outside Sweden and performing contact tracing among household members. Knowledge of *spa* type might give guidance in the process of contact tracing. Eradication treatment of MRSA *spa* types causing more skin infections may be warranted.

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Introduction

The increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is a cause for concern in many countries. In 2010, MRSA accounted for 25–50 % of *S. aureus* septicaemia cases in southern Europe and Great Britain [1, 2]. The proportion in Sweden was 1 % [3]. Previously, colonization or infection with MRSA has been a problem predominantly in elderly people with healthcare-associated risk factors. However, community-associated cases of MRSA have become more frequent during the past decade. Children, young adults and previously healthy individuals without any apparent risk factors for colonization are now being affected [4]. In Sweden, MRSA is seen as a threat to public health and is therefore regulated by the Swedish Communicable Diseases Act. In 2000, MRSA became a mandatory notifiable disease, all detected cases have to be reported and registered, and contact tracing has to be performed for each new case. Additionally, patients and medical staff who have recently (within the previous 6 months) been hospitalized or employed at a hospital or a nursing home outside Sweden or in a hospital or nursing home in Sweden known to have had an outbreak of MRSA are screened for MRSA .

This retrospective study was performed on MRSA cases in Skåne County from 2000 to 2010 (11 years). For each case, MRSA *spa*-typing [5] and screening for the Panton–Valentin

leukocidin (PVL) gene [6] was performed on the first positive MRSA culture. Our focus was to study whether some *spa* types were more prevalent than others in the community, in connection with healthcare, and among household contacts. The correlation of various *spa* types with clinical infection at the time of MRSA detection was also investigated. The relation between *spa* types and the country of acquisition by travel and/or the country of origin of foreign-born MRSA index cases was also investigated. Knowledge of these parameters may influence the management of MRSA cases in Sweden.

Patients and methods

Background

Skåne County in southern Sweden has 1.2 million inhabitants with 19.4 % of the population either born outside Sweden or with both parents born outside Sweden. Skåne is considered a low prevalence area for MRSA with an incidence of 25 MRSA carriers per 100,000 inhabitants in 2010 [3]. The Regional Centre for Communicable Disease Control in Skåne has registered all known cases of MRSA and contact tracing has been performed since 1999. All isolates identified since 2000 have been *spa* typed.

Patients

All individuals with an MRSA-positive culture in Skåne County during the period 2000–2010 (n=1,807) were eligible for the study. Of these, 1,020 were index cases and the remaining 787 cases were found by contact tracing. Epidemiological data were collected from the database at the Regional Centre for Communicable Disease Control in Skåne and the culture results were collected from the three clinical microbiology laboratories in the county. The Swedish Population Registration provided information about household contacts and the country of origin of family and family members.

Age, *spa* type and the presence or absence of the PVL encoding genes were registered for each MRSA case together with culture results. For the index cases, the number of household contacts and whether or not they were positive for MRSA was registered together with the country of origin of the family. It was noted if the case was infected or colonized at the time of detection and whether the cases were community- or healthcare-acquired. The latter assessment was based on reported epidemiological data. Individuals who were hospitalized or who had stayed in a nursing home within the previous 6 months were defined as having "healthcare-acquired" MRSA. The same applied to medical staff working in hospitals or nursing homes. Cases with no such contacts were defined as having a "community-acquired" MRSA. Cases with recent immigration, recent travel to or recent health care in a foreign country (≤ 6 months), were defined having as MRSA "acquired abroad".

Screening samples were routinely taken from patients, when seeking medical care in Sweden, and medical staff who had recently (≤ 6 months) been employed or who had stayed at a hospital or nursing home outside Sweden at the time of return to Sweden, or in a hospital or nursing home in Sweden known to have had an outbreak of MRSA. Contact tracing was performed in patients and medical staff at wards where a previously unrecognized MRSA patient had stayed. Household contacts of MRSA index patients were screened for MRSA. MRSA cultures were taken from the anterior nares, throat, perineum, and skin lesions.

Patients were followed with repeated monthly cultures. To be declared free of MRSA, 4 to 5 sets of negative MRSA cultures with the final culture after 1 year and no skin lesions were required. In addition, all household contacts had to be negative for MRSA. For deregistered patients household contacts were screened at least twice; when the index patient was found to be MRSA-positive and when the patient was deregistered, but household contacts to index patients still positive for MRSA were screened at least once.

Eradication treatment is not routinely given to MRSA carriers in our county. It is given to healthcare workers and on an individual basis to patients with recurrent MRSA infections, sometimes if the patients have a lot of healthcare contacts and sometimes if the carriage is prolonged. The treatments used are topical intranasal mupirocin and chlorhexidine washings for nasal carriers. For carriage in other locations topical treatment is combined with systemic treatment with two antibiotics (mainly rifampicin in combination with clindamycin or fusidic acid) for 2 weeks. All carriers in the household are treated at the same time. In 70 % of cases the eradication treatment is successful.

Microbiological methods

Colonies were presumptively identified as *S. aureus* by morphology on blood agar and/or by giving a coloured reaction on *S. aureus* selective plates [5]. Coagulase-positive colonies were tested for isoxacillin susceptibility using the disk diffusion method according to the instructions of the Swedish Reference Group for Antibiotics (www.srga.org). Enrichment broths to detect staphylococci were used on all samples from patients in whom MRSA was actively searched for, i.e. patients designated "screening" or "contact tracing", but not on samples from patients where MRSA was not initially suspected, i.e. patients designated "clinical infection" [5]. Tests for penicillin-binding protein 2a (PBP2 a ; MRSA-screen, Denka Seiken, Tokyo, Japan) and/or polymerase chain reaction (PCR) for the detection of *nuc* and *mecA* genes were used for verification of MRSA. PCR was performed as described elsewhere [5].

Molecular characterization was performed on one of the initial MRSA isolates collected from a case by *spa*-typing (sequencing of the polymorphic X-region of the *S. aureus* protein A gene), as described elsewhere [6].

The PVL genes *lukS*-PV and *lukF*-PV were detected by PCR, as described elsewhere [6].

Statistical analysis

The data were analysed using SPSS software (version 18; IBM SPSS, Chicago, IL, USA). Descriptive statistics were used. In the analysis of differences between *spa* types regarding the ability to cause infection and spread to household contacts statistical calculations were performed with logistic regression using R (version 2.14.1, R Development Core Team) [7]. In post-hoc calculations we used the multcomp library, version 1.2-10, by Hothorn et al. [8]. In the analysis of the ability to cause infections *spa* types with less than 10 cases and the heterogeneous group "other" were excluded.

The study was approved by the Regional Ethical Review Board in Lund.

Results

Between January 2000 and December 2010, 1,807 MRSA cases were registered in Skåne County. There was a constant increase in the number of cases each year, with 31 cases detected in 2000 and 315 in 2010. MRSA isolates from 19 of the 1,807 cases were not *spa* typed and were therefore excluded from the study. The remaining 1,788 cases were included. The median age was 30 (1–101) and 913 (51 %) were female. Of the cases 790 (44 %) were found by contact tracing, 566 (32 %) had a clinical infection and the remaining 432 (24 %) cases were found by screening after hospitalization abroad. The proportion of patients in the three groups remained constant during the study period. The PVL genes were demonstrated in 631 (35 %) cases. For seven strains information about the PVL gene was missing. The majority of the persons with MRSA, 1,028 (58 %), were asymptomatic carriers with MRSA in the nose, throat and/or perineum. In 750 cases (42 %) MRSA was found in a skin lesion at some point, indicating a clinical infection. Of these, 252 (34 %) had MRSA only in the lesion and 498 (66 %) had MRSA in the lesion and in the nose, throat and/or perineum. The majority of the clinical infections were relatively mild skin infections that did not require hospitalization and could be treated either with or without oral antibiotics. Only 16 patients had a positive blood culture.

Most cases of MRSA contracted in Sweden were community-acquired (Fig. 1). During the study period there were a total of 11 hospital outbreaks of MRSA in Skåne County, of which none included more than 9 cases (median 2, range 2–9). There were 11 outbreaks in long-time-care facilities, with no more than 15 (median 2, range 2–15) cases in a single outbreak. The cases infected or colonized abroad were mainly associated with being hospitalized or having other forms of contact with

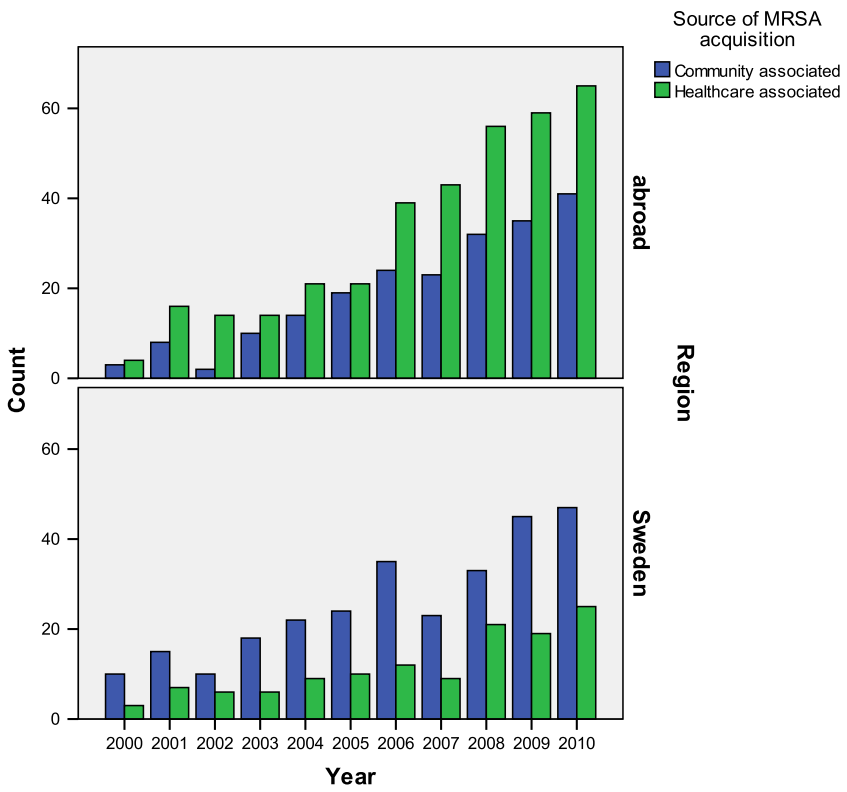

Fig. 1 Number of MRSA cases that had acquired their MRSA in Sweden and abroad in 2000–2010 and the number community- and healthcare-acquired

health care institutions abroad. However, during the last couple of years the number of cases of community-acquired MRSA cases abroad has increased (Fig. 1). Only 231 (24 %) of the index cases were both of Swedish origin and had contracted their MRSA in Sweden.

During the study period a wide spectrum of MRSA strains with 233 different *spa* types was seen. The ten most common types (Table 1), representing 54 % of all cases, were investigated separately and the remaining types were grouped together as "other". *Spa* types t044, t002 and t008 were the most predominant strains during the period. For most of the patients with the various *spa* types the median age was around 20–30 years. For patients with *spa* type t223 the median age was lower (16 years) and for patients with *spa* type t032, it was higher (52 years; Table 1).

A comparison of the proportion of clinical infections showed that PVL-positive MRSA with the *spa* types t008, t019 and t044 were associated with significantly more clinical infections than all other investigated strains. On the other hand, PVL-negative MRSA with the *spa* types t032, t127, t002 and t437 were associated with fewer clinical infections (Table 1).

In the analysis of the 1,020 index cases, 44 were excluded. Of the 44 cases, 6 were not *spa* typed, 15 were tourists on a temporary stay in our county, 11 could not be identified in the regional population register, and 12 had missing information about the number of contacts.

In the remaining 976 index cases there was a shift over time in the prevalence of the ten most common *spa* types (Fig. 2). *Spa* types t044, t002, t032 and t015 were present during the entire study period, while *spa* type t008 was first seen in 2003 and had become the predominant type in 2010. During the last few years there has been an increase in *spa* types t355, t437, t127, t223 and t019 (Fig. 2).

For the index patients, the majority of the ten most common *spa* types were community-acquired (Table 2). Only *spa* types t127 and t032 were more often acquired in healthcare settings. *Spa* types t002 and t223 were equally associated with community and healthcare settings.

There was a wide variety regarding the country of origin of the family between different *spa* types (Fig. 3) and the region of acquisition (Fig. 4), but some patterns were apparent. For example *spa* type t044 was most often acquired in Sweden by

Table 1 All MRSA cases with *spa* types. Numbers, age, and the presence of PVL gene and MRSA cultured from a skin lesion (representing a skin infection)

Spa type	Frequency *n* (%)	Median age (min-max)	PVL, *n* (%) positive or negative	MRSA cultured from skin lesions representing a clinical infection *n* (%)	OR* (odds ratio)	*P* value*
t044	209 (11.7)	22 (0–93)	+209 (100) −0 (0)	113 (54)	1.75	0.005
t002	214 (12.0)	29 (0–101)	+ 25 (12)	16 (64)	1.13	1
			−189 (88)	59 (31)	0.18	<0.001
t008	132 (7.4)	28 (0–88)	+95 (72)	62 (65)	3.09	<0.001
			−35 (26)	17 (49)	1.08	1
t355	69 (3.9)	23 (0–86)	+68 (99) −1 (1)	34 (50) 0 (0)	1.22	1
t437	69 (3.9)	33 (0–93)	−34 (49)	21 (62)	2.40	0.18
			−35 (51)	7 (20)	0.083	0.008
t032	61 (3.4)	52 (1–93)	+1 (2)	0 (0)		
			−60 (98)	23 (38)	0.38	0.03
t015	59 (3.3)	35 (0–93)	+0 (0)			
			58 (98)	22 (38)	0.85	1
t127	50 (2.8)	30 (0–98)	+5 (10)	3 (60)		
			−45 (90)	7 (16)	0.21	0.005
t223	52 (2.9)	16 (0–69)	+0 (0)			
			−51 (100)	18 (35)	0.69	0.96
t019	46 (2.6)	32 (0–76)	36 (86) 0 (0)	36 (86)	3.02	0.012
Other	827 (46.3)	32 (0–97)	+151 (18) −670 (81)	68 (45) 165 (25)		
All	1,788	30 (0–101)	630 1,158	353 (56) 318 (27)		

*Logistic regression model and a post-hoc analysis comparing the proportion of clinical infections. In the analysis types with less than 10 cases and the heterogeneous group "other" were excluded.

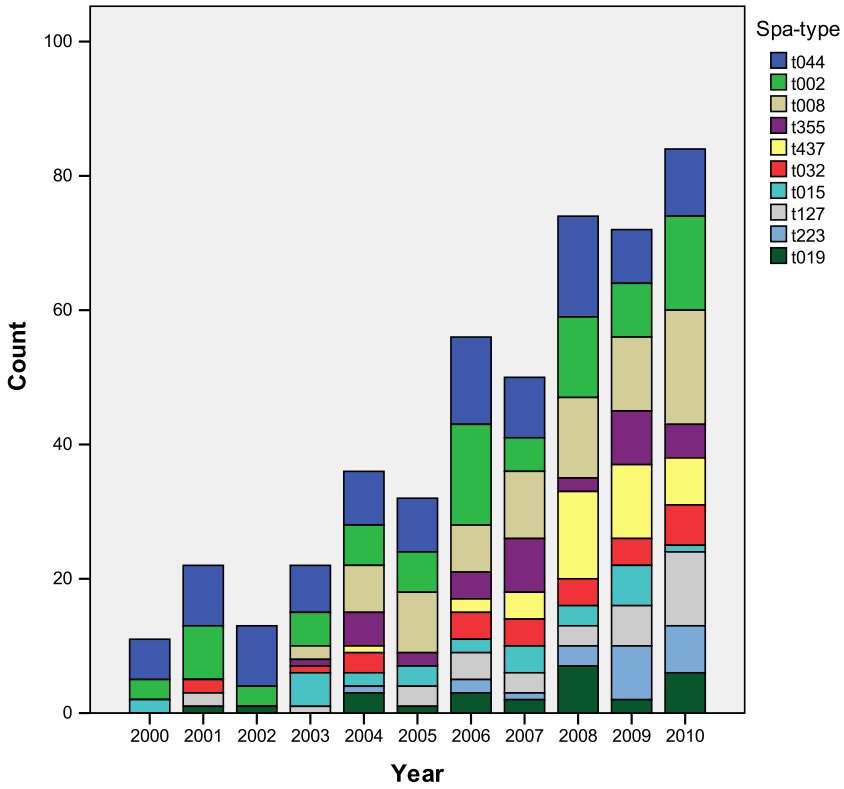

Fig. 2 Number of index MRSA cases with the 10 most common MRSA *spa* types in 2000–2010 in the Skåne region, Sweden

immigrants from the Middle East, whereas type t008 was most often acquired by persons of Swedish origin travelling abroad, to North America and other parts of Europe.

Of the patients originating from the "rest of Europe" 59 % acquired their MRSA in the "rest of Europe" and 22 % in Sweden. The patients from the Balkan states acquired their MRSA in Sweden in 40 % of the cases and in the Balkan states in 55 % of the cases. Of the patients originating from the Middle East, 46 % acquired their infection in Sweden and 42 % in the Middle East. The patients from Asia acquired their infection in Asia in 91 % and 9 % in Sweden and the patients from Africa 56 % in Africa and 29 % in Sweden. The patients of Swedish origin acquired their infection in Sweden in 58 % of the cases and in 42 % of the cases abroad.

Table 2 MRSA index cases with *spa* types and number community-acquired. Household contacts traced and number of MRSA positive

Spa	Frequency, *n* (%)	Community acquired, *n* (%)	Number of household contacts, mean	Number of household contacts traced for MRSA	Number of contacts positive for MRSA (%)*
t044	102 (10.5)	74 (73)	3.3	339	105 (31)
t002	85 (8.7)	44 (52)	2.7	227	100 (44)
t008	75 (7.7)	47 (63)	1.6	124	54 (44)
t355	35 (3.6)	21 (60)	2.9	102	34 (33)
t437	38 (3.9)	27 (79)	2.1	81	29 (36)
t032	28 (2.9)	10 (34)	1.4	38	13 (34)
t015	28 (2.9)	19 (68)	2.3	65	28 (43)
t127	33 (3.4)	6 (18)	1.8	61	24 (39)
t223	22 (2.3)	11 (50)	3.1	69	28 (41)
t019	26 (2.7)	16 (62)	1.8	47	19 (40)
Other	504 (51.4)	218 (44)	1.8	974	303 (31)
All	976	493 (51)	2.3	2,127	737 (35)

*A logistic regression model found significant differences between the proportions of family infections among different *spa* types (excluding "other", since this is a heterogeneous group by definition). Owing to observed over-dispersion, a quasibinomial model was used with estimated dispersion 1.68 (Fobs=4.48, denom.df=10, nom.df=353, $p<0.001$). Unfortunately, the post-hoc analysis with all pairwise comparisons failed to identify which *spa* types differed

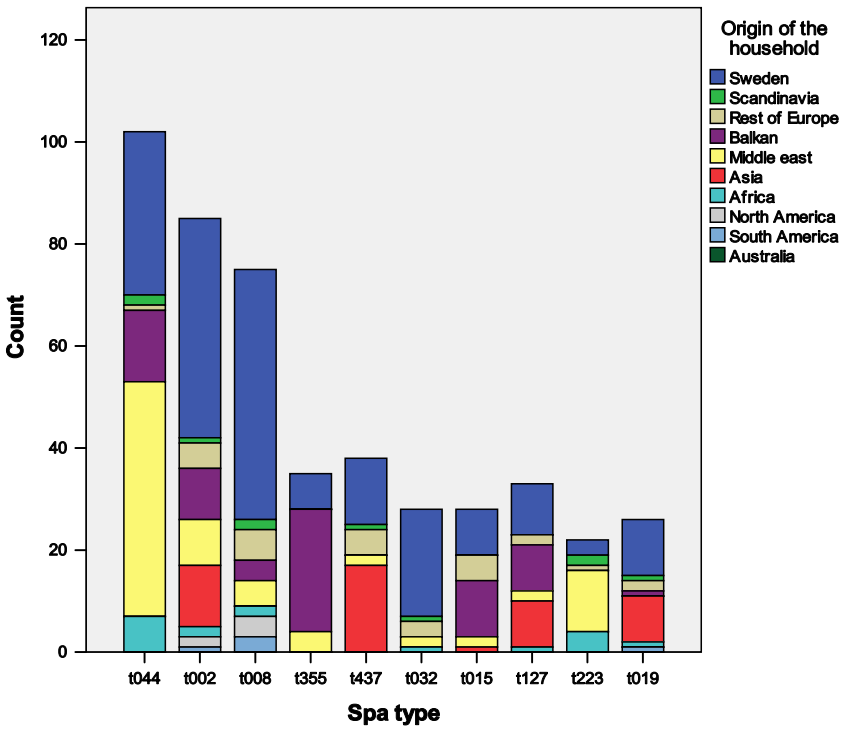

Fig. 3 The ten most frequent *spa* types. The origin of the household of the index cases

Of the household contacts of the MRSA index patients, 2,127 were screened for MRSA and 737 (35 %) were MRSA positive. For the MRSA positive household contacts, no specific *spa* type was significantly more prevalent than the others (Table 2).

Discussion

Although the prevalence of MRSA in Skåne county is very low from an international perspective, there was a 10-fold increase in the detected number of MRSA cases in the 11-

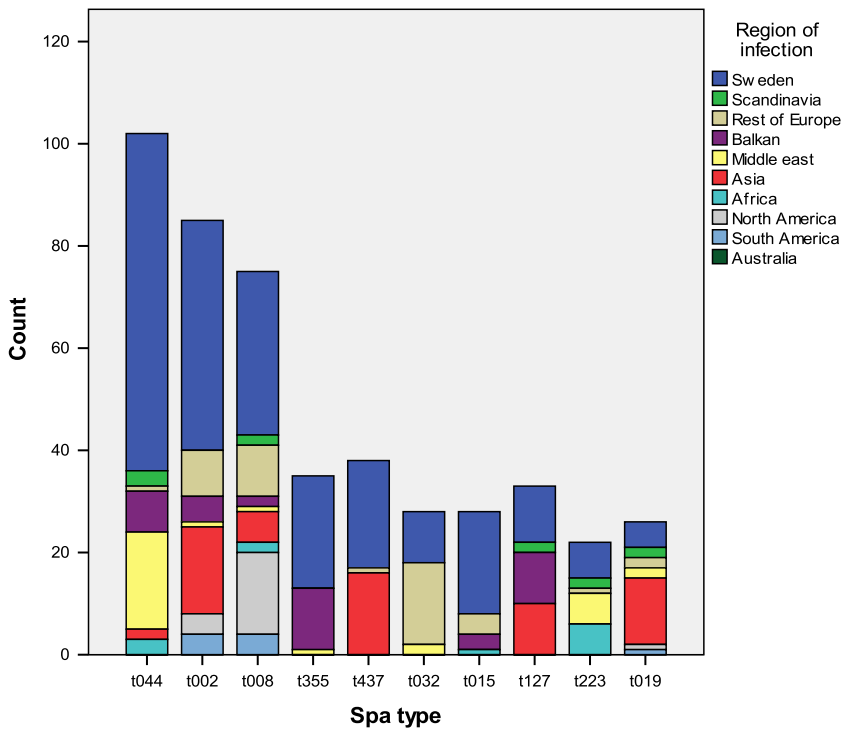

Fig. 4 The ten most frequent *spa* types. The region of acquisition of the index patients

year period from 2000 to 2010. Contrary to many other countries, the MRSA patients in our study were younger (median age 30 years) and more often had community-acquired infection [2]. During the years that were studied, only a few minor healthcare-associated MRSA outbreaks have occurred in Skåne County. The MRSA cases contracted abroad were mostly healthcare-associated, but the number of cases with MRSA acquired in the community abroad increased over time, probably reflecting the worldwide emerging epidemic of MRSA in the community [9]. In contrast to other countries the majority of our MRSA cases were asymptomatic carriers, detected by contact tracing of household- and healthcare contacts or by screening of patients and healthcare workers owing to health care contacts abroad. Only 36 % had an MRSA infection at the time of diagnosis, with another 10 % developing infection after the initial MRSA diagnosis. Fewer than 1 % had severe infections with positive blood culture.

A wide spectrum of MRSA strains with 233 different *spa* types was seen. There was a change in epidemiology over time, with some strains present at the beginning of the study period (*spa* types t044, t002, t032 and t015) and others emerging and increasing during the last years of the study (*spa* types t355, t437, t127, t223 and t019). *Spa* type t008 was first seen in 2003 and was the predominant type in 2010. *Spa* type t008 (USA 300) rapidly became the dominant community-associated clone in the USA [10] and in a recent study represented 40 % of the community-associated MRSA in Europe [11]. This reflects a dynamic spread of MRSA strains across the globe [12]. As seen in Denmark [13], Norway [14] and Germany [15], and also in this study, there was an association between acquisition of MRSA and a foreign origin or travelling and staying abroad. Only 231 (24 %) of the index cases were both of Swedish origin and had contracted their MRSA in Sweden, but many of the patients of Swedish origin (58 %) had acquired their MRSA in Sweden. The patients of foreign origin mostly contracted MRSA when travelling to their home countries, but acquisition in Sweden was also common, probably reflecting contact with fellow citizens that had recently been in their country of origin or with visitors to Sweden.

Stenhem et al. have shown that some MRSA strains are more prevalent in some parts of the world [16]. Similarly, our study showed a relation between different *spa* types and regions of MRSA acquisition. Sometimes changes in travel and immigration patterns might explain why certain *spa* types have become more common than others. Travel to and immigration from Asia has increased during the study period (TDB, Travel Data Base and SCB, Statistical Central Bureau) and may explain why *spa* types t437, t127 and t019, which in our study had a connection with Asia, increased. Immigration from the Middle East to Skåne County is common and increased from 1000 immigrants in year 2000 to more than 3,000 in 2008 and then declined to 2,000 immigrants in 2010 (SCB). This immigration pattern was obvious in that *spa* type t044 was strongly related to family origin from and acquisition in the Middle East. Similarly, the increase in *spa* types t355 and t223 could be explained by increased immigration from the Balkan states.

In an European study from 2007 [17] livestock-associated MRSA accounted for only a small proportion of MRSA isolates from humans, but was higher in some countries, the Netherlands, Belgium, Denmark and Austria. In our material only 14 MRSA cases (0.7 %) belonged to *spa* types associated with livestock.

It is recognized that MRSA can be shared among household contacts [18]. In one recent study [19], 23 % of the household contacts to children with a community-acquired infection were colonized in the nose. In an American study of 315 patients with *S. aureus* infection where 812 household contacts were cultured for *S. aureus* and MRSA [20] and 405 were found to be colonised with MRSA, *spa* type t008 showed the greatest potential for the household. This might be one of the reasons why *spa* type t008 has so successfully spread in the community around the world. In our study, 35 % of the screened household contacts were positive for MRSA with none of the *spa* types being significantly more prevalent. *Spa* type t032 is common in hospital outbreaks [21, 22] and did cause an outbreak in a long-term care facility in Skåne County during the study period. It is therefore recommended that contact tracing in health-care settings should be performed with stringency if a case with *spa* type t032 is found in a healthcare environment.

The PVL toxin is a well known virulence factor in *S. aureus* [23]. Similar to what has been reported in several other studies, the PVL-positive strains in our study caused more clinical infections than PVL-negative ones [23]. In particular, PVL-positive MRSA with *spa* types t008, t019 or t044 caused significantly more skin infections than other types. PVL-negative strains of some *spa* types (t032, t127, t002 and t437), caused significantly fewer clinical infections. This may support eradication treatment of patients being colonised with the infection-prone *spa* types. However, another European study concluded that *spa*-typing of MRSA isolates is unsuitable for predicting the likelihood of an infection with MRSA [24].

The limitation of this study is that it is retrospective. Some of the MRSA-colonised individuals could at some point have had a minor skin infection that was not reported and cultured. Furthermore, the number of positive household contacts could have been underestimated as some of them were only cultured once or twice. Although there was quite a large total number of MRSA cases, we found many different *spa* types, most of which were represented by only a few cases. Because of their limited number, it is not possible to draw any conclusions about these *spa* types and they were thus not analysed in relation to country of origin of the family or to the region of acquisition. A weakness in the statistical analysis of the ability to spread to household contacts is the absence of adjustments for important confounders such as size of living area, duration of contact and age distribution.

In conclusion, we saw a change in the epidemiology of MRSA in Skåne County during the study period (2000–2010). There was a strong association between MRSA acquisition and either a non-Swedish origin or travelling and staying abroad. This supports screening for MRSA in patients treated in health-care settings abroad and taking cultures from patients with skin infections contracted outside Sweden. Different *spa* types were seen in patients who had travelled to or originated from different regions of the world. This knowledge may give valuable clues in the process of contact tracing. In our study, 35 % of the household contacts were positive for MRSA, which supports continued contact tracing of household contacts. The PVL-positive strains with *spa* types t008, t019 or t044 caused significantly more skin infections compared with the other *spa* types. This fact may support eradication treatment of the infection-prone *spa* types.

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Conflict of Interest The authors declare that they have no conflict of interest.

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