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Increasing trend of antimicrobial resistance among methicillin-resistant *Staphylococcus aureus* strains in Southwest Finland, 2007–2016: An analysis of shifting strain dynamics and emerging risk factors

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ABSTRACT

Objective: Substantial rise in the annual incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in Southwest Finland (12.4–24.9/100,000 people) between 2007 and 2016. To understand the implications of these changes to the management of MRSA, we sought to analyse the antimicrobial resistance (AMR) trends of MRSA in relation with patient characteristics.

Methods: Antimicrobial susceptibility was determined for 10 clinically relevant antimicrobials. Strains with resistance to ≥2 antimicrobials were defined multi-resistant. The isolates were spa-typed and clustered. AMR trends and risk factors were identified by associating resistant phenotypes with patient demographics.

Results: A total of 983 new MRSA cases were identified between 2007 and 2016. After 2011, significant increasing trends were observed in the proportion of isolates resistant to clindamycin (13.9%–31.5%, $P < 0.001$), erythromycin (19.4%–35.4%, $P < 0.001$) and tetracycline (16.7%–32%, $P < 0.001$). The proportion of multi-resistant isolates more than doubled from 14.8% to 39.2%. The increasing AMR trend was reflected in the increase of new strain types and the decrease of previously dominant, non-multi-resistant strains. Patient risk factors associated with ($P < 0.001$) the acquisition of multi-resistant strains included community acquisition, livestock contact, hospital care abroad and immigrant status.

Conclusions: Notable increasing AMR trends among MRSA isolates were observed in Southwest Finland, 2007–2016. The shift in patient demographics to younger age groups and community acquisition contributed to the increase in multi-resistant strains. Immigration, contact with hospital environment abroad and contact with livestock were identified as essential risk factors of multi-resistance. The increased level of co-resistance has persisted after 2016.

1. Introduction

The spread of methicillin-resistant *Staphylococcus aureus* (MRSA) is a global public health threat causing a significant burden of disease [1]. Especially in healthcare-associated cases, broad-spectrum antimicrobial resistance (AMR) can result in suboptimal treatment outcomes and increased mortality [2,3].

Differences in antimicrobial susceptibility between MRSA strains reflect the clonal nature of successful lineages as well as differences in the selective pressure due to regional differences in antimicrobial policy and use [4,5]. In Southwest Finland, where invasive MRSA infections are rare, current recommendations for empiric antimicrobial treatment of *S. aureus* infection include beta-lactams, *i.e.,* cloxacillin, while for a suspected MRSA case an infectious disease specialist consultation is suggested [6]. On the

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national level, the reported MRSA co-resistance is generally low, although slight increases in the proportion of strains resistant to erythromycin and clindamycin have been reported recently [7]. To date, vancomycin-resistant MRSA has not been reported in Finland.

While the proportion of MRSA among invasive *S. aureus* cases has remained low in Southwest Finland, a substantial increase in the overall MRSA incidence was reported (from 12.4 to 24.9/100,000 people per year) between 2007 and 2016 [8]. Although non-β-lactam antimicrobial agents are routinely used for treating MRSA infections, the level of putative MRSA co-resistance must be critically considered in clinical decision-making before antimicrobial susceptibility test (AST) results are available [9]. No in-depth analyses of the co-resistance patterns or risk factors for multi-resistance in MRSA strains in Southwest Finland have been reported to date.

While the general AMR of MRSA strains is well documented on the national level, specific understanding on the local resistance pattern and risk factors of co-resistance are lacking. The aim of this study was to characterize the AMR patterns and trends of MRSA strains in Southwest Finland accompanying the rising incidence in 2007–2016. We also aimed to determine demographic risk factors associated with MRSA co-resistance and to identify the circulating strain types contributing to resistance. Understanding resistance patterns and risk factor profiles provide valuable insights to inform more effective clinical practices in treatment and prevention of MRSA infections.

2. Material and methods

2.1. Study material and definitions

All new MRSA cases between 2007 and 2016 in the Hospital District of Southwest Finland (HD) were identified through our previous retrospective, population-based study [8]. One MRSA isolate per patient was recorded in the study material. For each patient, the relevant demographic background information and possible risk factor information were obtained as previously described: age, sex, specimen type (screening or clinical), healthcare association (HA-MRSA, including healthcare workers, infants under 28 d of age, hospitalization within 2 y), community association (CA-MRSA), long-term care, immigrant status (including persons who were asylum seekers, refugees, residents of another country or other immigrants) and hospital care abroad within 2 y or livestock contact. Household and healthcare outbreaks were defined as 2 or more cases epidemiologically linked in the same family/hospital cluster.

Clinical specimens were inoculated, and *S. aureus* was identified as part of routine diagnostics using standard methods (coagulase tests, Vitek 2 and MALDI-TOF from 2011 onward) [8]. MRSA was identified by resistance to cefoxitin in both clinical and screening specimens, where selective enrichment broth (2008 onward) and chromogenic MRSA agars were used. The presence of *mecA* (2014 onward also *mecC*) was confirmed using a commercial molecular method throughout the study period (Evigene MRSA kit, Statens Serum Institut, Copenhagen, Denmark until 2010, Xpert MRSA kits, Cepheid, Sunnyvale, CA, USA until 2016). Antimicrobial susceptibility was determined by disk diffusion (Oxoid, Thermo Fisher Scientific, Waltham, MA, USA) for cefoxitin, clindamycin (CLI), erythromycin (ERY), fusidic acid (FUS), gentamicin (GEN), levofloxacin (LVX), rifampicin (RIF), tetracycline (TET) and trimethoprim/sulfamethoxazole (SXT) or by the E-test (bioMérieux, Marcy-l'Étoile, France) for vancomycin (VAN) according to the CLSI and EUCAST (2011 onward) guidelines. CLSI and EUCAST-affiliated quality control strains (S. aureus ATCC-29213) were used throughout the study, the distribution of inhibition zone diameters of cefoxitin being constantly at the level determined by EUCAST (target 27 mm, range 24–30 mm).

Due to the known rarity of extensively drug-resistant phenotype in our material and the recommendation to consider MRSA a multidrug-resistant organism by virtue, we defined the resistance phenotypes in two categories: non-multi-resistant or multi-resistant MRSA when resistance was detected for one or $\geq$2 of the tested non-β-lactam antibiotics, respectively [10]. Isolates assigned to the EUCAST category 'susceptible, increased exposure' were interpreted as susceptible in the statistical analysis.

All the isolates were *spa*-typed [8,11]. Typing was routinely performed for all new MRSA isolates by the Finnish Institute for Health and Welfare (THL) from 2009 onward, while isolates from 2007 to 2008 were typed at the University of Turku Research Laboratory for this study. Clonally related *spa* types were clustered into groups (spa-CCs) using the based-upon-repeat pattern (BURP) algorithm [12]. Spa-CCs were named according to the *spa* type with the highest founder score according to BURP analysis. Strains with cost values of less than or equal to four were assigned to the same spa-CC, and *spa* types shorter than five repeats were excluded from BURP clustering.

2.2. Statistical analysis

Trends in the annual proportions of resistant isolates to each antimicrobial and multi-resistant phenotype were analysed using the Cochran-Armitage test for trend. The presence of a trend was evaluated separately for periods 2007–2010 and 2011–2016 because of the change in AST guidelines. Fisher's exact test was used when comparing demographic variables, and the Mann–Whitney *U* test was used for non-normally distributed outcomes. A two-tailed *P*-value of <0.05 indicated statistical significance.

3. Results

3.1. Changes in AMR

In total, 971 MRSA isolates were included. Before 2011, increasing trends were observed in the proportion of isolates resistant to TET (5.2%–16.7%, $P = 0.005$) and SXT (1.7%–11.1%, $P = 0.03$). However, the proportion of multi-resistant MRSA remained between 14.8% and 23.6% before 2011 (Fig. 1). After 2011, the increasing trend of TET resistance continued (16.7%–32%, $P < 0.001$) and additional increasing trends were observed in the proportion of isolates resistant to CLI (13.9%–31.5%, $P < 0.001$) and ERY (19.4%–35.4%, $P < 0.001$). The proportion of multi-resistant MRSA more than doubled from 2011 to 2016 (15.1%–39.2%, $P < 0.001$). The proportion SXT resistant isolates peaked in 2015 (15.7%), decreasing notably in 2016 (2.4%). LVX resistance peaked in 2014 (26.0%) and decreased until 2016 (13.8%), resulting in a decreasing trend ($P = 0.02$).

No significant increases or decreases in the levels of resistance to GEN, RIF or FUS were detected. The annual proportion of isolates resistant to GEN remained between 2.0% and 10.9% (mean 4.7%). The level of RIF resistance was overall low (mean 2.1%), including two consecutive years (2009–2010) without a single resistant finding. The proportion of isolates resistant to FUS remained between 7.0% and 14.8% (mean 10.5%). Resistance to VAN was not detected.

3.2. Resistance across strain types

All 971 MRSA isolates were *spa*-typed, resulting in 173 different *spa* types, while 17 isolates remained nontypeable [4]. Ten or more isolates were found from 15 *spa* types, representing 71.2% of all isolates (Table S1). Among 59 *spa* types, two to eight were found in each, representing 18.6% of all isolates; and 99 *spa* types were singletons, representing 10.2% of all isolates.

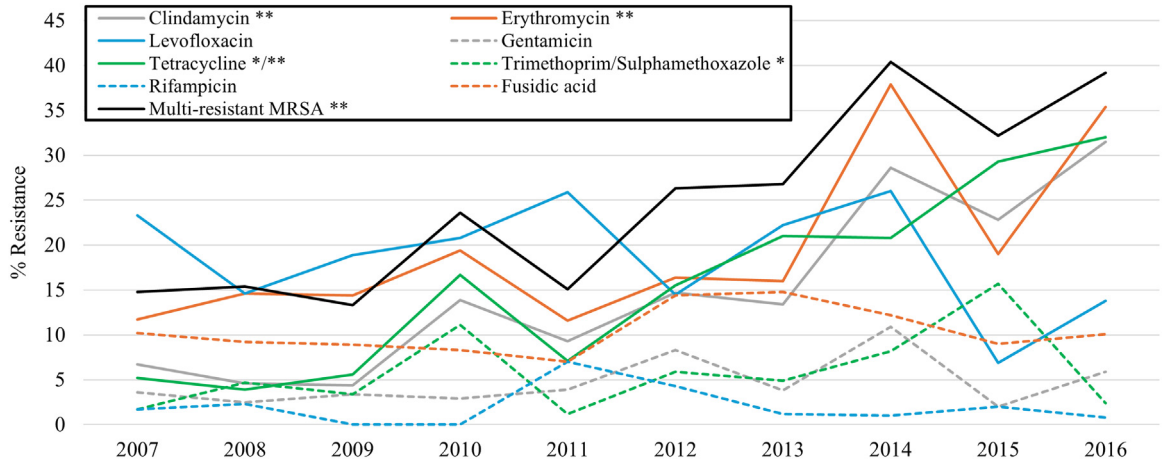

Fig. 1. Annual percentage of antimicrobial resistance among MRSA isolates (n = 971) in the Hospital District of Southwest Finland, 2007–2016. Significant increasing linear trends before (*) and after (**) 2011 are indicated with asterisks (P < 0.05, Cochran-Armitage test for trend).

Table 1
Proportion of antimicrobial resistance and most frequently associated *spa* types, MRSA isolates (n = 971), Hospital District of Southwest Finland, 2007–2016.

Antimicrobial	Resistant isolates (%)	*spa* types: total	*spa* type (frequency)[a]
Clindamycin	152 (15.6)	47	t034 (18), t437 (13), t002 (12), t127 (11), t386 (8), t008 (7), t688 (7), t044 (4), t005 (4), t189 (4), t037 (4)
Erythromycin	196 (20.2)	66	t008 (18), t437 (13), t002 (13), t127 (13), t386 (12), t044 (6), t304 (6), t688 (5), t189 (5), t223 (5)
Fusidic acid	101 (10.4)	34	t044 (24), t002 (24), t127 (9), t172 (6), t688 (4)
Gentamycin	44 (4.5)	24	t008 (6), t037 (4), t189 (4), t127 (3), t005 (3), t345 (3)
Levofloxacin	171 (17.6)	52	t032 (39), t008 (24), t067 (14), t002 (7), t037 (4), t189 (4), t005 (4), t020 (4)
Rifampicin	20 (2.1)	13	t037 (3), t002 (2), t008 (2), t064 (2), t172 (2), t127 (2)
Tetracycline	155 (16.0)	47	t044 (23), t034 (18), t127 (13), t688 (9), t386 (8), t172 (7), t223 (6), t437 (6), t002 (5), t008 (5)
Trimethoprim/ sulfamethoxazole	57 (5.9)	31	t223 (11), t034 (4), t019 (4), t172 (3), t064 (3)
Multi-resistant MRSA[b]	248 (25.5)	71	t044 (23), t008 (22), t034 (18), t127 (16), t002 (14), t437 (13), t386 (12), t688 (7), t223 (6), t189 (5), t032 (5), t304 (5)

[a] Complete data are shown in Table S1.
[b] Resistance to ≥2 of the tested antimicrobials.

The distribution of AMR was investigated across *spa* types. Among all isolates, those resistant to ERY, CLI, LVX and TET were the most frequent (Table 1). A multi-resistant phenotype was detected in 248 (25.5%) isolates across 71 *spa* types. The most abundant *spa* types exhibiting a multi-resistant phenotype were t044 (23 isolates), t008 (22 isolates) and t034 (18 isolates). The exhibited multi-resistant phenotypes were different between the strain types: Among the *spa* type t044 isolates, FUS/TET resistance was the most common phenotype, while among t008 isolates, ERY/LVX resistance was the most common phenotype. Among t034 isolates, CLI/TET resistance was the most common phenotype.

3.3. Changing strain types

The relative proportions of strain types changed over the study period, resulting in an increased strain type diversity towards the end of the study period, as reported previously by Junnila et al. [8]. To better understand these changes, related *spa* types were clustered with the BURP algorithm, resulting in 13 spa-CC clusters and 13 singletons (Table S1). Spa-CC 172 was the largest cluster and included 273 isolates from 12 different *spa* types, followed by spa-CCs 002 (n = 143, 25 different *spa* types) and 790 (n = 122, 25 different *spa* types). The six largest spa-CCs (172, 002, 790, 008, 012 and 4173/267) collectively accounted for 81.9% of the isolates. Thirty-seven isolates were excluded from the BURP clustering (*spa* types shorter than five repeats), and 17 isolates remained nontypeable. The changing strain type scheme was reflected in the decreasing proportion of spa-CCs 172 and 002, while the proportions of 012, 4173/267 and singletons were increasing (Fig. 2).

3.4. Risk factors for AMR

To identify risk factors for AMR among MRSA isolates, resistant phenotypes were associated with patient demographics. Each antimicrobial and multi-resistant phenotype was analysed individually.

Risk factors for detecting a multi-resistant MRSA phenotype included community acquisition, immigrant status, hospital care abroad and livestock contact (Table 2). Healthcare acquisition, screening specimen type, long-term care residency and hospital outbreaks were associated with non-multi-resistant phenotypes. Multi-resistant MRSA cases were associated with a younger median age than non-multi-resistant MRSA cases. No differences between the groups were detected in terms of sex, healthcare worker status or association with a household cluster.

In the analysis of each antimicrobial agent individually (Table S2), several risk factors for the detection of a resistant phenotype were identified. Similar to the multi-resistant isolates, CLI, ERY, TET and FUS-resistant isolates were each individually associated with patients of younger median age than patients with susceptible strains. For LVX, the median age of patients with resistant isolates was greater than that of patients with susceptible isolates. Immigrant status was identified as an individual risk factor for CLI, ERY, TET and GEN resistance. ERY and LVX resistance were associated with clinical specimen type. Livestock contact was identified as a risk factor for CLI, TET and SXT resistance. Patient sex was not associated with any resistant phenotype.

ERY, TET and FUS resistance was associated with community acquisition, while LVX resistance was associated with healthcare

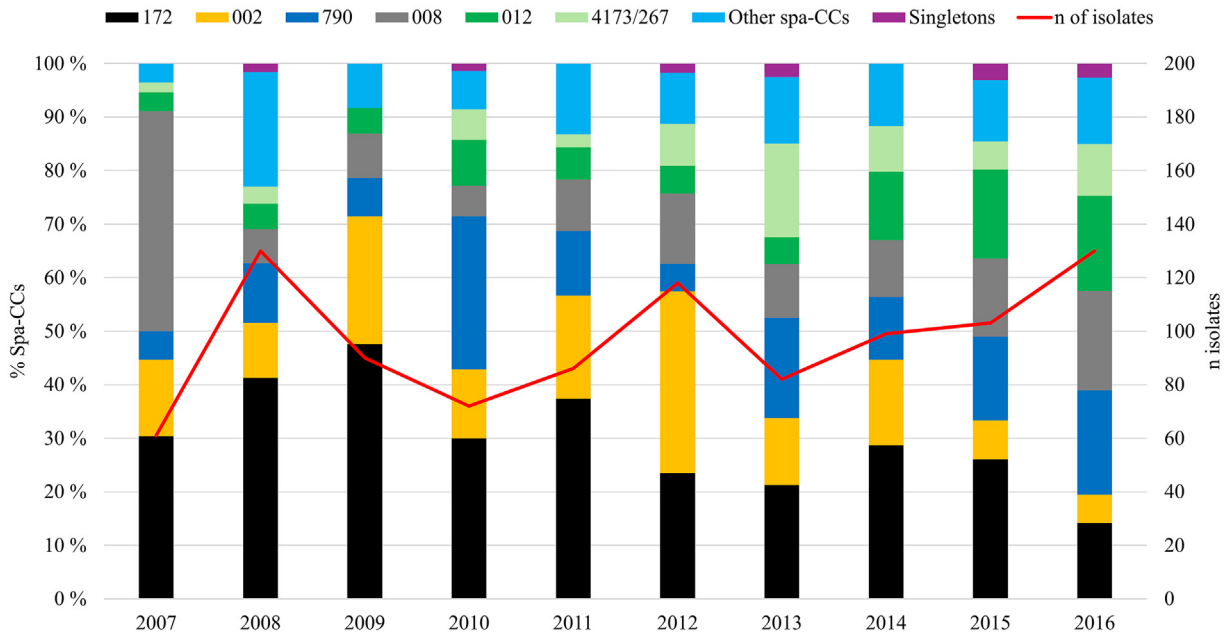

Fig. 2. Annual distribution of spa-CC clusters and number of isolates (secondary axis), Hospital District of Southwest Finland, 2007–2016. Seven minor spa-CCs combined in the other spa-CCs category (Table S1).

Table 2
Demographic risk factors for the multi-resistant MRSA phenotype, Hospital District of Southwest Finland 2007–2016.

	Multi-resistant MRSA[a] *n* (%)	MRSA *n* (%)	*P*[b]
Case count	248	723	–
Male sex	119 (48.0)	321 (44.4)	0.337
Median age, IQR	34.0 (32.7)	48.5 (51.2)	**<0.001**
Screening sample	166 (66.9)	532 (73.6)	**0.049**
Immigrant status	88 (35.5)	119 (16.5)	**<0.001**
Hospital care abroad	70 (28.2)	85 (11.8)	**<0.001**
Livestock contact	20 (8.1)	2 (0.3)	**<0.001**
CA-MRSA[c]	94 (37.9)	211 (29.2)	**0.011**
Household cluster	82 (33.1)	239 (33.1)	1.000
HA-MRSA[c]	154 (62.1)	512 (70.8)	**0.011**
Long-term care	11 (4.4)	161 (22.3)	**<0.001**
Healthcare worker status	22 (8.9)	47 (6.5)	0.251
Hospital outbreak	10 (4.0)	210 (29.0)	**<0.001**

[a] Resistance to ≥2 non-β-lactam antimicrobials.
[b] Fisher's exact test or Mann–Whitney *U* test (median age, IQR), significance level two-tailed $P < 0.05$, significant values bolded.
[c] Community-associated (CA-MRSA), healthcare-associated MRSA (HA-MRSA).

acquisition. Transmission within household clusters was identified as a risk factor for FUS resistance; otherwise, neither hospital nor household clusters were identified as risk factors. Hospital care abroad was identified as a risk factor for CLI, ERY, TET, LVX, SXT, GEN and RIF resistance. Long-term care resident status was not a risk factor for resistance but was rather associated with the susceptible phenotype (CLI, ERY, TET, LVX, FUS and GEN). Healthcare worker status was identified as a risk factor for LVX and SXT resistance.

4. Discussion

In this study, we characterized the changing AMR trend of new MRSA cases in Southwest Finland in the years 2007–2016. A notable increasing trend after 2011 was observed in the proportion of isolates resistant to CLI, ERY and TET. Interestingly, the prevalence of multi-resistant MRSA phenotypes increased significantly, reaching almost 40% of the isolates in 2016 (Fig. 1). We identified emerging multi-resistant MRSA *spa* types and were able to detect several risk factors for resistance, reflecting the further shift in MRSA transmission dynamics towards the community [8]. As was reported recently (2019–2022) by the Clinical Microbiology Laboratory of Turku University Hospital, CLI, ERY and TET resistance among MRSA isolates has remained at the same or higher level (34, 52 and 47%, respectively) as observed in our study, suggesting the persistence of the multi-resistant phenotype [13].

The proportion of spa-CC 008 isolates peaked in 2007 due to a healthcare ward outbreak caused by *spa* types t008 and t919 (Fig. 2). After the outbreak, the proportion of spa-CC 008 cases increased steadily from 2008 to 2016 (6.2%–16.2%). Simultaneously, the proportion of spa-CC 002 decreased. Within spa-CCs 008 and 002, the main *spa* types were t008, t304, t688 and t002 (Table S1). Types t008 and t002 are commonly reported among successful CA-MRSA lineages internationally, such as USA300/CC8 and CC5, respectively, and represent multiple successful subclones in which the AMR pattern can vary substantially [5,14]. While *spa* types t008 and t002 were the second and third most abundant *spa* types (73 and 51 isolates, respectively) overall, only 30.1% and 27.5% of the strains with these *spa* types were respectively multi-resistant, suggesting genetic diversity within these strains. As for the t304 and t688 types, both of them have been previously detected elsewhere in Northern Europe, and for t304, a linkage with migration from the Middle East has been proposed [15,16].

Similarly, in spa-CC 790, where t032 and t223 were the main *spa* types, the proportion of the multi-resistant phenotype was low (12.5% and 15.8%, respectively). However, t032, t008 and t067 were identified as the most common LVX-resistant strains (Table 1). Type t032 has been previously linked to healthcare environments and clinical specimen types, while the t067 strain caused a long-lasting outbreak involving multiple healthcare institutions in the Pirkanmaa area, 2001–2014, neighbouring our hospital district in the northeast [8,17]. The use of fluoroquinolones in the hospital patient population is a known risk factor driving fluoroquinolone resistance and contributing to the persistence of resistant clones [18,19].

Previously, the decline of the major *spa* type t172 was reported accompanying the increase in strain type diversity in the latter half of the study period [8,20]. In this study, we observed a low frequency of co-resistance among the t172 MRSA isolates, and a declining proportion of additional related strains was confirmed in spa-CC 172 (Fig. 2). The linkage of t172 cases with long-term care and household clusters indicates local transmission chains and, in relation to the increasing AMR trend, suggests the influx of new more resistant strains in the community, replacing the t172 type [20].

The risk factors for the multi-resistant MRSA phenotype included community acquisition, immigrant status, hospital care abroad and livestock contact (Table 2). Prevalent multi-resistant *spa* types t044 and t223 have been previously associated with CA-MRSA and immigrant status, suggesting the introduction of these types via immigration [8]. Types t044 and t223 have also been reported in Danish hospital outbreaks and in southern Sweden, where their acquisition was strongly linked with patients originating from both the Balkan area and the Middle East [21,22]. Other *spa* types linked with immigration, t304 and t386, were also frequently multi-resistant in this study [15]. All of these strains (t044, t223, t304 and t386) have been isolated among refugees and asylum seekers from the Middle East upon admission to Helsinki University Hospital, which neighbours our hospital district in the southeast, between 2010 and 2017 [23]. The multi-resistance of these *spa* types arises from distinct AMR patterns including resistance to FUS, ERY, TET and SXT, which can be acquired or chromosomal, reflecting the dynamics of antimicrobial selection in the bacterial source population [24].

Livestock-associated MRSA (ST398) in Finland predominantly represents *spa* type t034, which was also frequently multi-resistant in this study [7,8,15]. Livestock contact is a known risk factor for TET resistance in *S. aureus* infections, following host adaptation and veterinary application of antimicrobials [25–27]. In our study, both TET and CLI resistance were abundant among the t034 isolates (Table 1), which indicates the presence of genetic elements contributing to both CLI and TET resistance described previously in this clone [28]. Similar findings have been reported in Germany, where an increase in the non-susceptibility of MRSA isolates to tetracyclines was observed in an outpatient setting from 2010 to 2015 [29].

Limitations of this study include the fact that our results are specific to Southwest Finland, 2007–2016, meaning they may not be generalized as such to other regions and AMR pattern of MRSA has evolved since. However, changes in the AMR pattern of MRSA isolates elsewhere in low-endemicity settings can be explained by similar epidemiological phenomena, as indicated by the influx of multi-resistant MRSA strains [30]. The strengths of this study include the comprehensive availability of patient risk factor data and the use of large, uniform AST material. *spa* types prevalent with the multi-resistant phenotype in this study (such as t008, t034, t304 and t127) have been increasingly detected in Finland during recent years [7]. Nonetheless, more data regarding genetic factors contributing to the observed changes in AMR and strain type patterns are crucial in the future.

In conclusion, we characterized patient-related risk factors for consideration when developing treatment regimens for suspected MRSA infections in a low-endemicity setting such as Southwest Finland. Importantly, information about migration, livestock contact and hospital care abroad should be accounted for when considering the treatment options. In the hospitalized patient population, LVX resistance is probably more prevalent.

Author contributions

All the authors contributed to the study conception and design. Jenna Junnila, Tiina Hirvioja and Jaakko Silvola collected the material. Jaakko Silvola completed the analyses with contributions from Jaana Vuopio, Kirsi Gröndahl-Yli-Hannuksela, Kari Auranen and Kaisu Rantakokko-Jalava. Jaakko Silvola wrote the manuscript with significant input from all the authors, who reviewed the manuscript and discussed the results.

Declaration of competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Data availability

The datasets generated during the current study are not publicly available as they contain health-related data, but limited datasets (without any identifiable, person-related data) are available from the corresponding author upon reasonable request.

Ethical approval

The study was approved by the Hospital District of Southwest Finland (T162/2016; J28/21) and the Finnish Institute for Health and Welfare (THL336/6.02.00/2016; THL/319/5.05.00/2020). According to the Finnish Medical Research Act (488/1999), the Act of the Medical Use of Human Organs, Tissues and Cells (101/2001) and the Biobank Act (688/2012), which were amended and confirmed by the Hospital District of Southwest Finland Research Ethics Committee, no ethics committee approval or informed consent was needed for this retrospective, register-based study.

Other statements

Some of these results were presented in the e-flash poster session of the 33rd ECCMID conference in Copenhagen, 2023.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2024.11.015.

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