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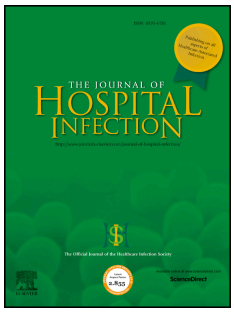

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Epidemiology and *spa*-type diversity of meticillin-resistant *Staphylococcus aureus* in the community and healthcare settings in Norway

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Running title: Diversity measures for MRSA epidemiology

Key words: MRSA epidemiology; diversity measures; *spa*-typing; Hill numbers; Incidence Rate; time trends.

Summary

Background There has been a marked increase in the incidence of MRSA during the past decade in Norway, a country with one of the lowest prevalence's and an active "search-and-destroy" policy applied to hospital settings.

Aim To characterize the trends of notification rates of community associated (CA) and healthcare associated (HA) MRSA in Norway and explore the diversity and circulation of MRSA *spa*-types within and outside healthcare settings.

Methods We conducted a registry-based study on notified MRSA infections and colonizations in Norway between 2006 and 2015. The diversity and abundance of CA- and HA-MRSA *spa*-types were compared using novel ecological diversity measures, Hill numbers.

Findings During the study period, the monthly notification rate increased 6.9-fold and 1.8-fold among CA- and HA-MRSA, respectively; the increase was steeper among colonizations than infections. In both settings the distribution of *spa*-types was uneven, with a few dominant *spa*-types and many singletons. The *spa*-type diversity of CA-MRSA was higher than HA-MRSA in terms of different types (685 vs. 481) and increased during the study period. However, the diversity associated with the dominant *spa*-types were similar and remained stable. A high overlap of *spa*-types was estimated between the settings; *spa*-t002, t019 and t008 were the most common.

Conclusion The present findings suggest a strong connection between CA- and HA-MRSA epidemiology in Norway. If the fast-growing trend of CA-MRSA continues, in the years to come, it may challenge current guidelines and infection control of MRSA in healthcare environments.

Key words: MRSA epidemiology; diversity measures; *spa*-typing; Hill numbers; Incidence Rate; time trends.

Introduction

In recent years, meticillin-resistant *staphylococcus aureus* (MRSA) has become increasingly common in community settings with a subsequent mixture of MRSA genotypes circulating in the community and in healthcare institutions. The rapid spread of MRSA among the general population is a major challenge for the public health systems[1],[2]. An increased transmission of MRSA in the community creates reservoirs, which may challenge the infection control in hospitals and other healthcare institutions[3]–[6].

Norway deploys an active "search and destroy" policy in healthcare settings and has one of the lowest prevalence's of invasive MRSA in the world (~1%)[7],[8]. However, the notification rate (NR) of MRSA infections has increased almost three-fold during the last ten years [9]. In Norway, all diagnosed MRSA cases are mandatorily notifiable, and the national registry data contain both demographic and molecular information allowing for comprehensive analyses of the circulation of MRSA genotypes within and outside healthcare settings.

Information about the numbers of different genotypes and their abundances in terms of evenness and dominance, are key aspects to understand MRSA epidemiology. Previous publications have characterized MRSA strains with the use of summary statistics, frequency tables of the most common *spa*-types and with the use of diversity indices, such as the Simpson or Shannon index[10]–[12]. However, each diversity index measures particular aspects of diversity and is insufficient to characterize the composition of a bacterial population in terms of their frequency. Further, diversity indices suffer from several important shortcomings; they are unitless and they are associated with diversity in a non-linear way, implying that if the diversity is doubled, the values of the indices are not. In this study, we introduce a novel measure, the Hill numbers, as a suitable diversity measure to analyse and, more importantly, compare diversity of MRSA in the community and healthcare setting[13]. Hill numbers are a unified family of diversity measures, related to diversity indices, that were recently reintroduced in ecology by L. Joust[14]. The approach is advantageous because it takes into account the full composition of diversity and does not suffer from the limitations described above for diversity indices.

The aim of this study is to investigate the characteristics and the time trends of MRSA *spa*-types derived in the community and healthcare setting, as well as the interaction between these reservoirs in Norway. The epidemiology is studied using *spa*-typing and detection of Panton-Valentine Leukocidin (PVL) genes[15].

Methods

Data

We analysed the national registry of all confirmed MRSA infections and colonizations notified to the Norwegian Surveillance System for Communicable Disease (MSIS) from January 2006 to December 2015. Patient characteristics and molecular information about MRSA *spa*-type and the presence of the PVL genes were available in the dataset (A.2 Text). The variables used in this study are: age, gender, county of residence, place of infection, the date when the sample was taken, the reason for MRSA discovery, MRSA *spa*-type, presence of the PVL genes, information about the hospitalization status at the time of the testing and information defining if the infected or colonized person was a healthcare worker.

Data from Akershus University Hospital, containing MRSA cases reported in South-Eastern Norway between 2006-2008, were merged to integrate part of the missing information in the MSIS dataset on MRSA *spa*-type (A.2 Text).

Definitions

Utilizing the information in the dataset, we defined:

- Healthcare associated (HA)-MRSA as all cases who were hospitalized or in nursing homes at the time of the testing, including MRSA cases occurring among healthcare workers.
- Community associated (CA)-MRSA as all cases who were not hospitalized or in nursing homes at the time of the testing, excluding healthcare workers.

These definitions represent a pragmatic way to define the association to community or healthcare settings, based on the place where MRSA is detected. We did not include molecular information to distinguish CA-MRSA and HA-MRSA. The definitions reflect those adopted in previous analyses of the Norwegian national registry, ensuring coherence in the interpretation of the results[7].

Statistical analysis

The diversity measures employed in the study are presented here. Additional information on methods is reported in the supplementary material.
The diversity of *spa*-types among CA-MRSA and HA-MRSA has been compared estimating the Hill numbers at different orders q, which are defined as

$$ {}^{q}D = \begin{cases} \left(\sum_i p_i^q \right)^{\frac{1}{1-q}}, & q \geq 0, q \neq 1 \\ \exp\left(-\sum_i p_i \log p_i \right), & q = 1 \end{cases} \qquad (1) $$

where p_i represents the proportion of the *spa*-type *i* in the sample. The values of the Hill numbers, D, are referred to as the effective number of *spa*-types, i.e. the number of equally abundant *spa*-types that would be needed to give the same value of a diversity measure. The parameter *q* determines the measure's sensitivity to the relative abundances of *spa*-types. Increasing *q,* more importance is given to the dominant *spa*-types. For *q*=0, all *spa*-types are weighted equally and ${}^0D$ is the count of the different *spa*-types (richness); for *q*=1, *spa*-types are weighted by their frequencies and ${}^1D$ is equal to the exponential of the Shannon-Wiener index, a diversity measure of common *spa*-types; for *q*=2, ${}^2D$ corresponds to the diversity associated with the Simpson's index, that is a diversity measure of the dominant *spa*-types. The diversity profile is obtained by plotting the Hill numbers as function of order *q*, with continuous values ranging from zero to infinity. The plot is usually visualized for $0 \leq q \leq 3$, since changes in ${}^qD$ beyond that range are minor. If the diversity profiles of two communities do not intersect, then the community with the highest Hill numbers is truly more diverse. If the communities have overlapping profiles, then only partial ranking can be concluded conditional on *q*.

The Hill numbers address the distribution but not the presence of specific *spa*-types in an environment. To study the overlap of the *spa*-types detected in the community and the healthcare setting, we used the Morisita-Horn index (MH),

$$\mathrm{MH} = 1 - \frac{\sum_i (p_{i1} - p_{i2})^2}{\sum_i (p_{i1}^2 + p_{i2}^2)} \qquad (2)$$

where p_{i1} and p_{i2} represent the relative abundance of the *spa*-type *i* within the community 1 and 2, respectively. The index's value varies from 0, no overlap, to 1, complete overlap.
To explore temporal and regional patterns of diversity, we repeated the analyses using sub-sets of the data. We also tested for potential effects of under-sampling by calculating adjusted Hill numbers (A.4 Text).

In additional analyses, we explored and compared the *spa*-types abundance distribution for CA-MRSA and HA-MRSA (plots of ranked *spa*-type abundances) by fitting different parametric models to the curves (A.4 Text). Multivariable logistic and LOESS regressions have been used to analyse the characteristics and the temporal trend of the monthly notification rates (NRs) of CA- and HA-MRSA, respectively (A.3 Text).

Results

Distributions, time trends and characteristics of reported MRSA

A total of 11461 MRSA infections and colonizations were notified in Norway from 2006 to 2015. Of those, 11080 (96.7%) could be classified into CA-MRSA (7433; 67.1%) and HA-MRSA (3647; 32.9%) and were considered in the analyses.

From 2006 through 2015 the mean NRs of CA-MRSA increased by a factor 6.9 (3.4 infections; 14.6 colonizations); for HA-MRSA the NR went up by a factor of 1.8. The NR of HA-MRSA only increased among colonizations, but remained stable among infections. Young age (0-19 years), acquired abroad, and presence of PVL genes were more common among CA-MRSA cases than among HA-MRSA cases. CA-MRSA found through contract tracing increased after 2009 (Supplementary data).

MRSA diversity profiles and *spa*-type ranking

Among the analysed MRSA cases, 10612 (95.8%) were *spa*-typed and 868 different *spa*-types were discerned. Figure 1 shows the diversity profiles of CA-MRSA and HA-MRSA *spa*-types, in terms of Hill numbers, ${}^{q}D$, as function of order q. The number of different *spa*-types (q=0) was larger in the community (685) than in healthcare settings (481). Both curves decrease steeply with increasing order of q, highlighting a highly uneven distribution with few dominant *spa*-types in both settings. For $q \geq 1$, the two curves overlap, indicating similar abundance patterns among common and dominant *spa*-types in the community and health-care environments.

The similarities were confirmed by plotting the CA- and HA-MRSA *spa*-type abundances as a function of their rank. In both settings, the shape of the abundance distribution was well described by power laws with comparable scaling exponents (Supplementary data). In total, 47.4% and 54.9% of the *spa*-types detected in the community and healthcare setting, respectively, were singletons. The ten most common *spa*-types accounted for almost 50% of the reported cases in both settings. Among singletons detected in the community, 25% were acquired in Norway, 37,5% imported from abroad and 37.5% had an unknown place of acquisition. For HA-MRSA singletons, 26.9% were domestic cases, 34.1% were imported and of 39.0% had an unknown place of acquisition.

CA- and HA-MRSA diversity increased during the second half of the study period, as indicated by higher Hill numbers, particularly numbers associated with low q-values, including *spa*-type richness ${}^{0}D$. The increase was smaller in the overlapping region of the CA- and HA-MRSA profiles, where more weight to abundant and dominant *spa*-types is given, and were negligible for HA-MRSA at q>2. Focusing on different geographic regions, the analyses revealed higher *spa*-type diversity and uneven distributions in the South-Eastern region, which is the most populated area in the country.

Finally, to check for potential bias associated with under-sampling, we estimated low-bias corrected diversity profiles using the full sample. The results suggest that s*pa*-type richness

may be underestimated (q=0), while no significant effects of under-sampling were found for more common *spa*-types (Supplementary data). We estimated a high overlap between the specific *spa*-types in the two settings, with a Morisita-Horn index of 0.93 (95% CI 0.91; 0.95). The overlap increased significantly during the study period and was high in all the Norwegian regions.

Spa-types t002 (1116 cases), t019 (921 cases) and t008 (810 cases) were the most common. The proportion of *spa*-t002 remained stable around 10% during the study period. A growth in the proportions of *spa*-t127 and *spa*-t223 was observed in 2015; the latter became the second most frequent *spa*-type by the end of the study period. *Spa*-t304 was frequent between 2006 and 2007, but reduced in subsequent years (supplementary data).

The rank of *spa*-types among MRSA infections, revealed that the first three among CA-MRSA; *spa*-t019, *spa*-t008 and *spa*-t002, were the same as HA-MRSA infections. *Spa*-t002 was also the most common *spa*-type among CA- and HA-MRSA colonizations. *Spa*-t019 and t008 were found to be predominantly PVL-positive, both among CA- and HA-MRSA. Contrary, s*pa*-t002 was mainly PVL-negative, even though similar proportions of PVL-positive and PVL-negative MRSA were found among CA-MRSA infections.

Discussion

Our analyses reveal that the major rise in MRSA notification rates in Norway between 2006 and 2015, is largely driven by an increase of cases detected in the community, predominantly colonizations. The rate of MRSA infections notified in healthcare institutions remained stable. Using a novel approach, the Hill numbers, a diversity measure derived from ecology, we were able to compare two different environments taking into consideration the entire distribution of *spa*-types, from singletons to the most abundant types. Our results highlight highly uneven abundance distributions in both community and healthcare settings, characterized by many different and rare *spa*-types and few abundant *spa*-types. A key finding in this study is that the diversity of singletons and less common *spa*-types was higher in the community compared with the healthcare institutions, while the diversity of common and dominating *spa*-types was similar. The diversity profiles also revealed that the recent surge in notified MRSA cases for the most part is accompanied by increasing diversity in less common *spa*-types. A single diversity index would have given only partial information on *spa*-types compositions. Using the Shannon or the Simpson index, for instance, we would have detected the similarity in the diversity of the common or dominant *spa*-types in the two settings, but not the significant differences observed in the number of less frequent *spa*-types.

With some exceptions, the common *spa*-types in the community were also frequently found in healthcare environments. This overlap observed between the two settings, which increased during the study period, suggests a high degree of connection between the epidemiology of CA- and HA-MRSA. The search-and-destroy policy has succeeded in keeping a low level of MRSA transmission in healthcare settings, as indicated by a low and constant notification rate of HA-MRSA infections. The similarity of the dominant *spa*-types observed in healthcare environments with the dominant CA-MRSA *spa*-types could be interpreted as the result of an import of cases from community, where the notification rate of infections is increasing.

The observed uneven distribution of MRSA, confirms the findings of previous studies in Norway and other countries, reporting a high variety of strains and only few frequent types[12],[16],[17]. The change in the epidemiology in Norway, defined by an increasing unevenness of the *spa*-types distribution, is comparable to the evolution observed in other countries, such as the UK where a few strains became dominant during the last two decades, reshaping the more uniform distribution observed before the 1990s[17].

In previous analyses our group has shown that import of MRSA through travelling and immigration plays an important role in the current epidemiology of MRSA in Norway[9]. The large number of singletons observed in this study, characterized by a high proportion of imported cases, represents additional evidence in support of our earlier findings.

The South-Eastern region was characterized by a more uneven distribution and a greater number of *spa*-types, compared to the other regions, suggesting a continuous import of MRSA. This area has a higher numbers of immigrants than in other parts of Norway and, consequently, a higher degree of connection with the rest of the world[18]. The larger diversity, comparable with the profiles obtained for the whole country, suggests a primary

role of this region in driving the introduction of new potential endemic (and/or epidemic) *spa*-types. There were small differences in the number of dominant *spa*-types among regions, also characterized by high degree of overlapping, suggesting that only few dominant *spa*-types have been able to establish their presence across Norway.

Our results, covering a period of 10 years, present a picture of the molecular epidemiology of MRSA that is constantly evolving, with a rising number of *spa*-types found among the Norwegian population. *Spa*-type t002, commonly reported in many European countries[10], was among the most frequent genotypes for the whole study period and was present in both community and healthcare settings. The majority of *spa*-t002s were PVL-negative. S*pa*-t019, s*pa*-type t657 (the Bengal Bay clone) and *spa*-t437, all primarily PVL-positive and found mostly among CA-MRSA infections, are common clones from Asia associated with the community[19-21]. The presence of these *spa*-types, as well as PVL-positive *spa*-t008, a common CA-MRSA *spa*-type in the USA, reflects the global spread of MRSA. *Spa*-t019 and s*pa*-t437 have also been observed among the most frequent types in neighbouring Sweden and Denmark[12, 22].

The recent emergence of *spa*-t223 (predominantly PVL-negative), which in 2015 became the second most frequent *spa*-type in Norway, was also reported in Sweden in 2000-2010[12]. This *spa*-type was observed in community and healthcare environments, primarily colonizations. The majority of the cases reported with *spa*-t223 had immigrant background (mainly connected to Russia, Syria and Afghanistan) contrary to the most frequent *spa*-types, such as t002, t019 and t008. *Spa*-t223, together with *spa*-t032, successfully spread in hospital environments in the United Kingdom and other European countries[10,17,23]. In Norway, s*pa*-t032 PVL-negative was more frequent among infections and colonizations in healthcare settings, confirming the results of previous studies[12,24,25]. A high number of *spa*-t304 PVL-negative was found among HA-MRSA colonizations. This *spa*-type was the cause of several outbreaks occurring in nursing homes in the Oslo area, in the first years of the study[16],[26],[27].

As highlighted in other studies analysing the Norwegian national registry[7], a limitation is related to our definition of HA-MRSA, which is exclusively based on the information available in the dataset and do not enable a precise identification of the setting of acquisition. However, continuity in the use of these definitions over time ensures coherence in the analyses of the national-registry, representing an important data source for MRSA surveillance. Part of CA-MRSA cases, particularly among carriers, could have been detected among outpatients tested during their hospital visits, who are not registered as hospitalized. Variations in outpatient screening would affect the number of notified CA-MRSA colonizations and thus the temporal trend of their NR; generally, the number of reported carriers is prone to detection bias, depending on the effort put into the screening activity that might change over time and among different regions.

In this study, we analysed the epidemiology of MRSA using *spa*-typing and information on the presence of the PVL-genes, being the typing information available in the national registry, an approach used in macroepidemiological studies[28]. Future surveillance of MRSA with whole genome sequencing[29], coupled with national registry data, might reveal which

strains are currently circulating and could help to improve our understanding of transmission patterns.

How to contain MRSA in the community represents a serious challenge for the Public health systems. The current infection control measures implemented in Norway are focused on preventing the spread of MRSA in healthcare settings. The link observed between healthcare and community environments, highlighted by the similar genotypes observed in these two settings, indicates that additional measures will be required to control the rise in MRSA prevalence outside hospitals to reduce the pressure in the healthcare institutions.

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Ethical approval

The study was approved by the Regional Committees for Medical and Health Research Ethics-South East Norway (project number 2011/2456).

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Figures

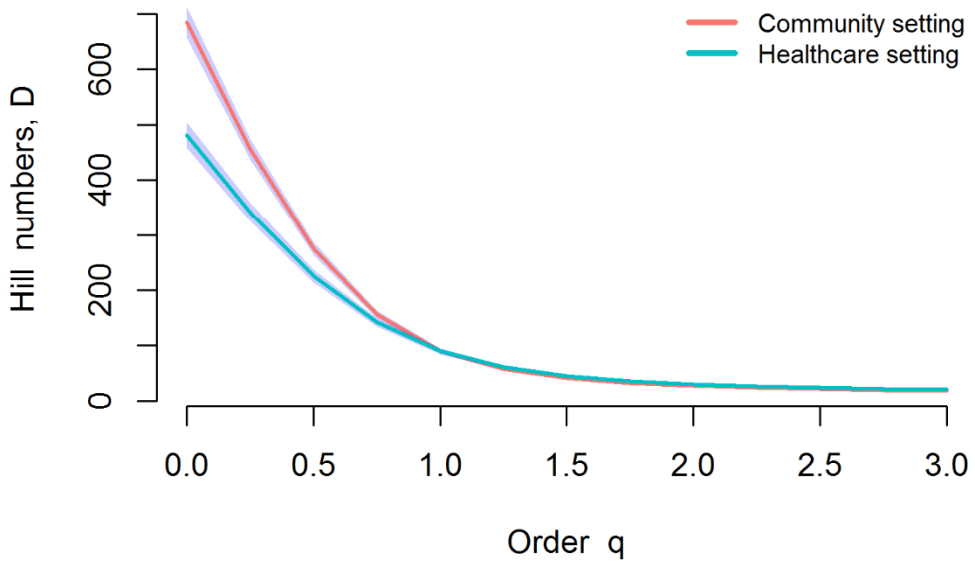

Figure 1: Profile of the Hill numbers. ${}^{q}D$, at different order q, for CA-MRSA (red line) and HA-MRSA (blue line). For q=0 the Hill number corresponds to the total number of *spa*-types present in the samples (*spa*-types richness). For q=1 the measure represents the diversity associated with the Shannon-Wiener's index, ${}^{1}D$=90.1 (95%CI 85.9; 94.3), for CA-MRSA, ${}^{1}D$=89.8 (95%CI 84.1; 95.6), for HA-MRSA. At q=2 the Hill number represents the diversity associated with the Simpson's index, ${}^{2}D$=27.0 (95%CI 25.8; 28.1), for CA-MRSA, ${}^{2}D$=30.2 (95%CI 27.9; 32.5), for HA-MRSA. A setting with equally abundant *spa*-types (even distribution) would be characterized by a flat diversity profile. The decreasing curves in the figure are the consequence of uneven distributions, with many rare *spa*-types and a smaller number of dominant types.