



Decrease of methicillin resistance in *Staphylococcus aureus* in nosocomial infections in Germany—a prospective analysis over 10 years

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SUMMARY

Objectives: Methicillin resistant *Staphylococcus aureus* (MRSA) remains an important cause of healthcare-associated infections. Here, we describe the development of methicillin-resistant isolates among nosocomial *Staphylococcus aureus* (SA) infections in Germany between 2007 and 2016.

Methods: We analyzed data from the voluntary German national nosocomial Infection Surveillance System. Data on bloodstream infections (BSI) and lower respiratory tract infections (LRTI) were derived from intensive care units (ICU), whereas data on surgical site infections (SSI) were collected from surgical departments (SD). Univariate analysis was performed on trend of proportion, while multivariable logistic regression was performed to identify risk factors for MRSA-infections.

Results: Data of 1218 ICU and 1,556 SD were included. Overall, a decrease in the proportion of MRSA among all nosocomial SA-infections from 32.8% to 20.0% was noted. MRSA decreased from 37.1% to 21.8% ($p = 0.01$) for BSI, from 38.7% to 19.2% for LTRI ($p < 0.01$) and from 21.1% to 7.4% ($p < 0.01$) in SSI. Logistic regression revealed that SA-infections in Mecklenburg Western-Pomerania were more likely caused by MRSA (Odds ratio (OR): 2.5; 95% CI: 1.7, 3.6).

Conclusion: We observed a significant reduction of the proportion of nosocomial *Staphylococcus aureus* infections due to MRSA in Germany over the course of the last 10 years.

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Introduction

Methicillin resistant *Staphylococcus aureus* (MRSA) is the most common multidrug resistant gram-positive organism causing healthcare-associated infections (HAI). Therefore, MRSA remains an important target for infection control and prevention measures. Despite introduction of effective treatment options, HAI due to MRSA are still a significant cause for morbidity and mortality.¹ Regional differences in Europe regarding the proportion of HAI due to MRSA have been described previously² and in some countries a decrease has been observed. The surveillance report of the European Antimicrobial Resistance Network (EARS-Net) in 2016 described an EU/EEA population-weighted mean MRSA percentage of 13.7% in invasive isolates with large differences ranging from 1.2% to 50.5% for different countries. However, more than one-third of countries that continuously participated reported a significant

decreasing trend regarding MRSA. Those developments were true for countries with initially high as well as low MRSA prevalence.

The objective of this study was to describe the development of different HAIs caused by MRSA in Germany and to identify risk factors for MRSA infections by using data from the large German national nosocomial infection surveillance system (“KISS”) from 2007–2016.

Methods

Data from two surveillance components of KISS were analyzed for the period between 2007 and 2016. KISS is a voluntary national system for the surveillance of HAI. Participation in a module of KISS is determined and infections are recorded by the infection-control and -prevention team of the participating institution based on clinical and microbiological data following predefined criteria.³ In the intensive care component of KISS (ICU-KISS) data on nosocomial blood stream-infections (BSI), nosocomial lower respiratory tract infections (LRTI) and nosocomial urinary tract-infections (UTI) are recorded,⁴ while data on surgical site infections (SSI) is recorded from surgical departments (SD) (OP-KISS).⁵

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Table 1a
ICU and surgical departments providing MRSA infection data for 2007–16 per 2 years from the German national nosocomial infection surveillance system (KISS).

	2007/08	2009/10	2011/12	2013/14	2015/16	Total	p-Werte
Number of intensive care units	465	533	645	856	985	1218	
Number of surgical wards	432	558	681	972	1139	1556	
Number of nosocomial SA-infections	2654	2727	2856	3177	2994	14,408	<0.0001
Number of MRSA-infections (%)	870 (32.8)	836 (30.7)	753 (26.4)	800 (25.2)	598 (16.7)	3857	
Number of SA-infections in intensive care units	1913	1965	2072	2246	2441	10,637	<0.0001
Number of MRSA-infections in intensive care units (%)	719 (37.6)	679 (34.6)	627 (30.3)	657 (29.3)	547 (22.4)	3229	
Number of nosocomial SA-infections in surgical departments	741	762	784	931	553	3771	<0.0001
Number of nosocomial MRSA-infections in surgical departments (%)	151 (20.4)	157 (20.6)	126 (16.1)	143 (15.4)	51 (9.2)	628	

ICU, intensive care unit; MRSA, methicillin resistant *Staphylococcus aureus*; # Total number of different ICU/surgical departments that reported data for at least 6 month in any year

Ethics and data protection

According to the German Protection against Infection Act §23 surveillance of HAI is mandatory for all healthcare institutions. Here, we analyzed aggregated and anonymized surveillance data. Therefore, ethical approval by an institutional board was not required.

Statistical analysis

Data recorded in ICU-KISS and OP-KISS was pooled. We analyzed the yearly proportion of MRSA in infections caused by *Staphylococcus aureus* (SA). For each type of infection (BSI, UTI, LRTI and SSI) the proportion of MRSA (MRSA rate) were calculated as number infection caused by MRSA divided by number of infections caused by *Staphylococcus aureus* (SA) and multiplied by 100. Univariate testing was performed for a yearly linear trend by using Cochran-Armitage-test.⁶

For the years 2015 and 2016 we investigated differences in the MRSA proportions between the 16 German federal states. In a multivariable logistic regression analysis we calculate adjusted Odds ratios with 95% confidence intervals for MRSA proportions for the German federal states adjusted by the following confounders: year, gender, age group (0–50, 51–65, 66–70 and 71–120 years), type of hospital (university hospital, other hospital), season, type of ICU or SD, and hospital size (<400 beds and ≥400 beds). All variables were dummy-coded. Stepwise forward-backward selection was used to derive the final logistic regression model. Parameters were entered into the model at a significance level of $P \leq 0.05$ and were removed at $P > 0.05$. Odds Ratios (OR) with 95% CIs were calculated.

Since not all hospitals reported data for the entire study period, we conducted a sensitivity analysis in which only hospitals were included that had reported data annually from 2007–2016 (“core group”) and provided data on nosocomial infections for at least 6 months per year. p -values ≤ 0.05 were considered statistically significant.

All analyses were performed with R 3.4.3 [R Core Team (2013); R Foundation for statistical computing, Vienna, Austria] and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 1218 ICU and 1556 SD that participated in the surveillance system for at least 6 month in one year were included in the analysis. During the study period, the number of participating ICU as well the number of SD increased from 465 and 432 in 2007 to 985 and 1139 in 2016, respectively. A total of 14,408 HAI due to SA were recorded during the observational period. Of those 10,637 were recorded in ICU-KISS and 3771 were recorded in OP-KISS. Overall the proportion of infections caused by MRSA decreased over time from 37.4% in 2007 to 22.4% in 2016 in ICU and

from 20.4% to 9.4% in SD (Table 1a). This was also true if only sites that continuously provided data throughout the entire study period were included even though the absolute number of SA-infections decreased over time (“core group”, Table 1b). ICU and SD of that group detected 4.4 and 1.1 SA-infections on average per year that met the definitions.

In the time trend analysis, the proportion of MRSA in BSI caused by SA decreased statistically significant from 37.1% to 21.8% ($p = 0.01$) and in LRTI from 38.7% to 19.2% ($p < 0.01$; supplementary Table 1a). The proportion of MRSA in SSI caused by SA also decreased statistically significant from 21.1% to 7.4% ($p < 0.001$) (Fig. 1). A similar trend was also present in the core group (supplementary Table 1b, Fig. 2). In UTI, no statistically significant trend was identified; however, number of urinary tract infections with SA were small (supplementary Table 1a & 1b).

Regarding regional differences in HAI due to MRSA among German federal states (Fig. 3), logistic regression revealed that in 2015/2016 nosocomial infections due to SA in Mecklenburg Western Pomerania were more likely to be caused by MRSA when compared with the most populous federal state of Germany, North Rhine Westphalia (Odds ratio (OR): 2.5; 95% CI: 1.7, 3.6 Table 2). In the federal states of Baden-Wuerttemberg, Bavaria, Hamburg, Hesse, Rhineland Palatinate and Saxony-Anhalt infections with SA were less likely to be caused by MRSA (Table 2). Another factor that increased the chance for a nosocomial SA-infection to be caused by MRSA was medical ICU (OR: 1.8; 95% CI: 1.3, 2.4). Factors that decreased the chance that a nosocomial SA-infection is due to MRSA were younger age (≤ 50 years (OR: 0.6; 95% CI: 0.4, 0.7) and in between 51–65 years (OR: 0.7; 95% CI: 0.6, 0.9), nosocomial SA-infection during treatment in a university hospital (OR: 0.6; 95% CI: 0.5, 0.8) or a nosocomial SA-infection in a hospital with ≥ 400 beds (OR: 0.8; 95% CI: 0.7, 0.9) and nosocomial SA-infection acquired in a surgical department (OR: 0.5; 95% CI: 0.4, 0.6) (Table 2) were less likely to be caused by MRSA.

Discussion

We were able to show a significant decrease of nosocomial infections caused by MRSA in Germany over a time period of 10 years. This decrease was observed in blood stream infections, lower respiratory tract infections as well as in surgical site infections. Similar findings have been reported by others in the recent past. For example, Dantes et al. reported an overall decrease in the incidence rate of MRSA-infections for the United States of America between 2005 and 2011.⁷ In the UK, a decline of MRSA-infections has been observed since 2006 which was possibly influenced by the introduction of a mandatory surveillance and feedback system for BSI due to MRSA in 2001.⁸ In Germany, the voluntary laboratory based national surveillance system for development of antimicrobial resistance (ARS) also reported a decline in the rates of MRSA derived from different types of clinical specimens in the past years.⁹ This was not only observed in samples derived from

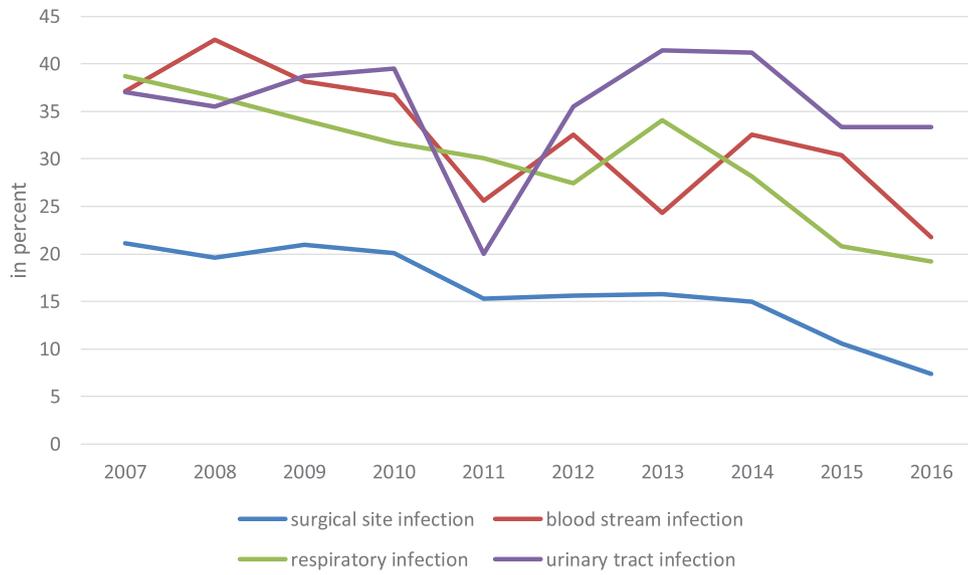


Fig. 1. Time trend for percentage of nosocomial methicillin resistant *Staphylococcus aureus* (MRSA) infections. Data from the German national nosocomial infection surveillance system (KISS), 2007–2016.

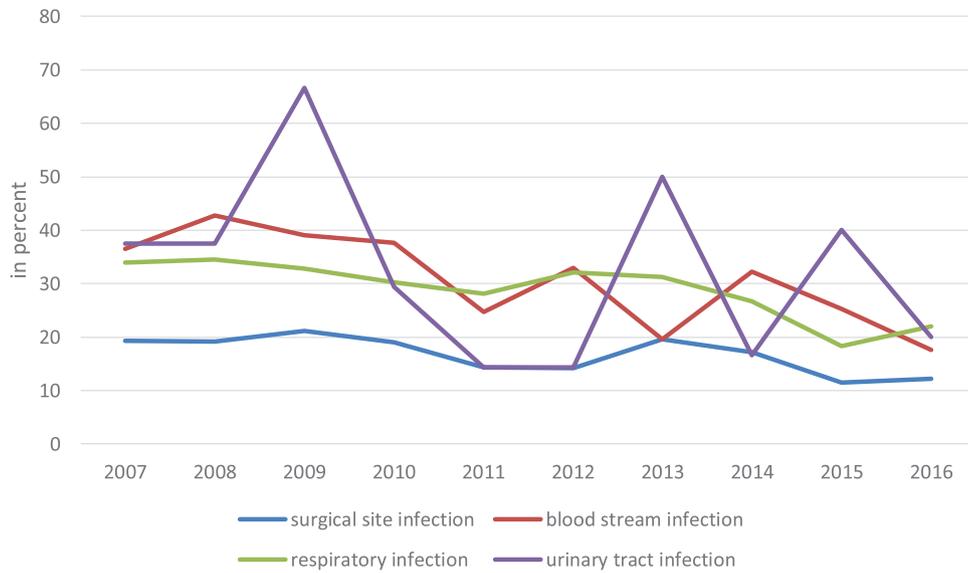


Fig. 2. Time trend for percentage of methicillin resistant *Staphylococcus aureus* (MRSA) infections according to the German national nosocomial infection surveillance system (KISS), by infection type. Data from wards that participated continuously from 2007–2016 (“core group”).

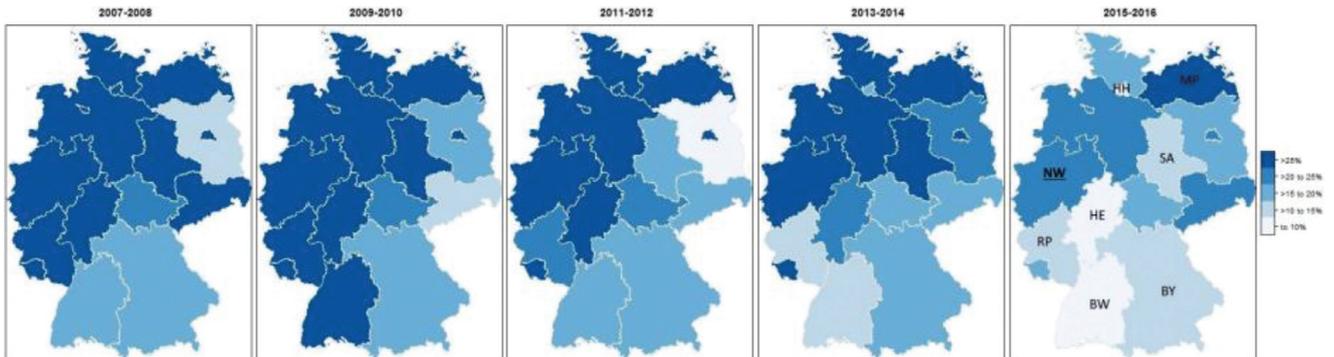


Fig. 3. Distribution of the proportion of methicillin resistant *Staphylococcus aureus* (MRSA) infections among German federal states according to data from the German national nosocomial infection surveillance system (KISS) 2007–2016. (NW = North Rhine Westphalia, reference, RP = Rhineland Palatinate, BW = Baden Württemberg, BY = Bavaria, HE = Hesse, SA = Saxony Anhalt, HH = Hamburg, MP = Mecklenburg Western Pomerania).

Table 1b

ICU and surgical departments continuously providing MRSA infection data for 2007–16 per 2 years (“core group”) from the German national nosocomial infection surveillance system (KISS).

	2007/08	2009/10	2011/12	2013/14	2015/16	Total	p-value
Number of intensive care units	240	240	240	240	240	240	
Number of surgical departments	174	174	174	174	174	174	
Number of nosocomial SA-infections	1693	1503	1180	1070	1005	6451	<0.0001
Number of MRSA-infections (%)	525 (26.3)	449 (28.9)	295 (25.0)	269 (25.1)	178 (17.7)	1716	
Number of SA- infections in intensive care units	1247	1111	836	752	667	4613	<0.0001
Number of MRSA-infections in intensive care units (%)	439 (35.2)	370 (33.3)	246 (29.4)	210 (27.9)	138 (20.7)	3229	
Number of nosocomial SA-infections in surgical departments	446	392	344	318	338	1838	0.0069
Number of nosocomial MRSA-infections in surgical departments (%)	86 (19.3)	79 (20.2)	49 (14.2)	59 (18.6)	40 (11.8)	313	

ICU, intensive care unit; MRSA, methicillin resistant *Staphylococcus aureus*; # Total number of ICU/surgical departments that reported data for at least 6 month in any year

Table 2

Logistic regression of risk factors associated with any SA-HAI due to MRSA. Data from the German national nosocomial infection surveillance system (KISS), 2007–2016.

Group of variables	Risk factors	Odds-ratio	[95% CI]	p-value
Age	≤50 years	0.6	[0.42, 0.74]	<0.0001
	51–65 years	0.7	[0.58, 0.88]	0.0016
Type of hospital	University hospital	0.6	[0.47, 0.82]	0.0009
Size of hospital	>400 beds	0.8	[0.65, 0.94]	0.0098
Type of ward	Interdisciplinary ICU	Reference		
	Surgical department	0.5	[0.38, 0.58]	<0.0001
	Medical ICU	1.8	[1.32, 2.43]	0.0002
Federal state	North-Rhine-Westfalia	Reference		
	Baden-Württemberg	0.3	[0.19, 0.49]	0.0003
	Bavaria	0.4	[0.31, 0.59]	0.0018
	Hamburg	0.3	[0.12, 0.62]	0.0191
	Hesse	0.3	[0.18, 0.53]	0.0018
	Mecklenburg Western Pomerania	2.5	[1.65, 3.6]	<0.0001
	Rhineland Palatinate	0.6	[0.40, 0.90]	0.5182
Saxony-Anhalt	0.6	[0.36, 0.88]	0.3804	

hospital but also from the outpatient setting^{10,11}. Data derived from an independent voluntary surveillance system monitoring antibiotic consumption and development of resistance rate on ICUs in German hospitals (SARI) also show a decrease of MRSA.¹²

The reasons for this decrease are thought to be multifactorial and might have been influenced by the following factors:

- (i) In Germany, a multitude of infection control measures were introduced in the past, which might have influenced this development. In addition, specific legislation on infection prevention and –control was introduced and updated regularly. One key point of these measures was to optimize identification of patients at risk for MRSA and initiate decolonization of patients that were found to be MRSA positive. MRSA colonization upon admission to an ICU was identified as an important factor for the occurrence of nosocomial MRSA cases.¹³ Decreasing colonization rates of MRSA from hospitals participating in a voluntary MRSA-Surveillance module in KISS were reported, when looking at admission screening from 2006–2015.¹⁴
- (ii) The distribution of MRSA strains in Germany might have changed and led to the occurrence of less transmissible or less invasive strains.^{15,16} The German national reference center on Staphylococci recently reported that isolates from hospitals belonged to certain clonal lineage like ST22 or ST225 and that lines like ST8, ST45 and ST228 were identified less frequently than in the past.¹⁷

Interestingly, we found regional differences in MRSA-rates between German federal states. Differences in Germany for MRSA have previously been reported⁹ but reasons for it remain unclear. In Switzerland, regional differences regarding MRSA-rates were thought to occur upon the influence of the approach of neighboring country.¹⁸ In Germany, infection prevention measures

were implemented nationwide and regional differences were not observed¹⁹; however, this does not rule out the possibility that declining MRSA-rates of neighboring countries might well have contributed to our findings.

Another reason for the differences might be attributable to nosocomial infections derived from colonization with livestock associated MRSA (LA-MRSA). Even though the transmissibility of LA-MRSA appears to be lower than for other MRSA²⁰, nosocomial transmission of LA-MRSA have been reported,^{21,22} especially in regions with a high density of livestock farming even if no direct contact was described²³; despite its high density of livestock farming, low prevalence of LA-MRSA in Mecklenburg Western Pomerania were previously reported²⁴ while federal states with high density of livestock farming like Lower-Saxony and North Rhine-Westfalia²⁵ showed a decrease of MRSA in our data; therefore, this explanation seems at least doubtful.

Limitations

- (i) The data used in this study was retrieved from a voluntary hospital infection surveillance system, therefore selection bias cannot be ruled out. For example, university hospitals might have a higher rate of microbiological sampling (blood cultures) which might lead to an underestimation of MRSA cases.^{26,27} (ii) Although more than 60% of all German ICU are participating in KISS³ it is unclear whether the data are representative for Germany as a whole; however, it is unlikely that the overall development will strongly deviate from our findings. (iii) Quality of surveillance is highly dependent of the individual center; however, validation and quality assurance of KISS is achieved by regular training modules in which participating hospitals are trained in the respective surveillance method.²⁸ (iv) The criteria used for the surveillance of infections are highly specific which might have led to

underreporting²⁹; however, the advantage of using proportions of MRSA is that they are independent from the frequency of microbiological examinations.

Conclusion

MRSA still remain a relevant part of healthcare associated infections due to *Staphylococcus aureus* in Germany. Nonetheless, a significant decrease of its proportion occurred over the course of the past 10 years. This development was true for healthcare institutions in almost all federal states and was possibly influenced by changes in legislation, surveillance and implementation of infection prevention measures, and biological changes. The reasons for the regional differences remain unclear.

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Transparency declarations

Declarations of interest: none

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jinf.2018.12.005](https://doi.org/10.1016/j.jinf.2018.12.005).

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