Surveillance and outbreak report

Incidence of invasive meticillin-resistant *Staphylococcus aureus* infections in Germany, 2010 to 2014

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Voluntary surveillance systems in Germany suggest a recent decline in the incidence of infections (subsequent to at least 2010) with meticillin-resistant *Staphylococcus aureus* (MRSA) from various types of specimens and settings. We asked whether this decline is reflected by data from the mandatory national surveillance system for invasive MRSA infections. Our analysis is based on the population in Germany in 2010 to 2014. Cases were identified from passive reporting by microbiological laboratories of the diagnosis of MRSA from blood culture or cerebrospinal fluid. Respective clinical data were subsequently added to the notification. We calculated risk ratios (RR) between consecutive years, stratifying cases by sex, age and federal state of residence. The national incidence increased from 4.6 episodes per 100,000 persons in 2010 to 5.6 in 2012 (2011 vs 2010: RR: 1.13, 95% confidence interval (CI): 1.08–1.18; 2012 vs 2011: RR: 1.08, 95% CI: 1.04–1.13). It stagnated at 5.4 per 100,000 in 2013 (RR: 0.97, 95% CI: 0.93–1.01) before declining to 4.8 in 2014 (RR: 0.88, 95% CI: 0.84–0.91). This trend was observed in most, but not all federal states and strata of sex and age groups. Only 204 of 20,679 (1%) episodes of infection were notified as belonging to an outbreak. Our analysis corroborates previous findings that the incidence of invasive MRSA infections in Germany may be declining.

Introduction

In 2013, 12.8% (95% confidence interval (CI): 12–14) of *Staphylococcus aureus* isolates from blood culture in Germany were found to be resistant to meticillin in laboratories submitting data to the European antibiotic resistance surveillance network (EARS-Net), placing Germany below the European average of 18% [1]. The prevalence of meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia is now within the middle lower range of those reported in Europe.

MRSA infections in Germany are thought to be mainly healthcare-associated (HA) with only a small proportion, which are community-associated or livestock-associated [2]. HA-MRSA especially affects persons above the age of ca 50 years. Due to unknown reasons, the prevalence of HA-MRSA is higher among men than women as well as in the northern than southern states of Germany [3,4]. In addition, livestock-associated MRSA may account for ca 8% of MRSA isolated from blood cultures in regions with a high density of swine farming [5].

Analyses from voluntary laboratory- and hospital-based sentinel surveillance networks for different types of specimens and settings suggest a decline in the incidence of MRSA infections in Germany, subsequent to at least 2010 [1,2,6,7]. These networks are not part of the mandatory reporting system and are not representative for all of Germany. Many of them, such as the EARS-Net, report data solely on the proportion of meticillin resistance among all tested *S. aureus* isolates, which are difficult to translate to incidences. We therefore asked whether or not a similar decline could be seen in the statutory surveillance system for invasive MRSA infections, which was introduced in 2009 and allows the direct estimation of incidences [8].

Methods

Study design

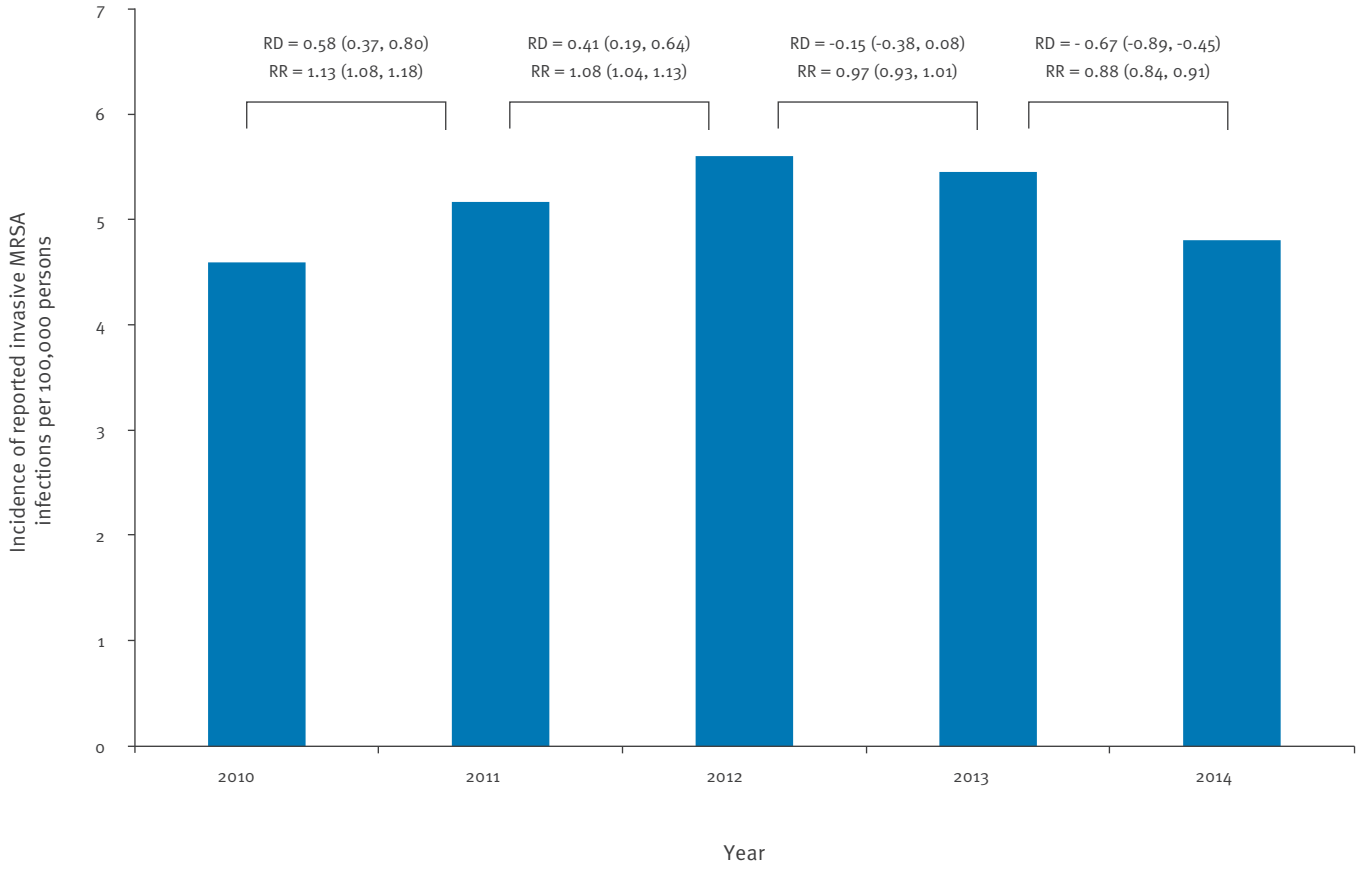
We conducted a retrospective cohort study including the total of the population in Germany. Cases were identified by the mandatory notification system for invasive MRSA infections, which was introduced in 2009. We limited the analysis to the period from 2010 to 2014, since 2010 was the first year with a full year of data collection [8]. As possible confounders or effect modifiers we included sex, age and area of cases' residences.

Case notifications

Microbiological laboratories are required to notify patients with MRSA positive blood culture or samples from cerebrospinal fluid (CSF) to the local health authorities. Valid tests included in the case definition

Figure 1

Annual incidence of episodes of invasive meticillin-resistant *Staphylococcus aureus*, Germany, 2010–2014 (n=20,679)



MRSA: meticillin-resistant *Staphylococcus aureus*; RD: risk difference; RR: risk ratio.

The numbers in parentheses indicate 95% confidence intervals. Only notifications marked as fulfilling the reference definition are included.

and reference definition (used for this analysis) are culture combined with meticillin sensitivity testing or with detection of the *MecA* gene, e.g. by polymerase chain reaction (PCR). The local health authorities subsequently add respective clinical data to these notifications and transmit them via the state office to the national surveillance database, which is maintained at the Robert Koch Institute. The German Protection against Infection Act mandates transmission to this database within two working days after diagnosis. To avoid multiple notifications of the same patient, subsequent notifications are excluded if reported within two weeks [9].

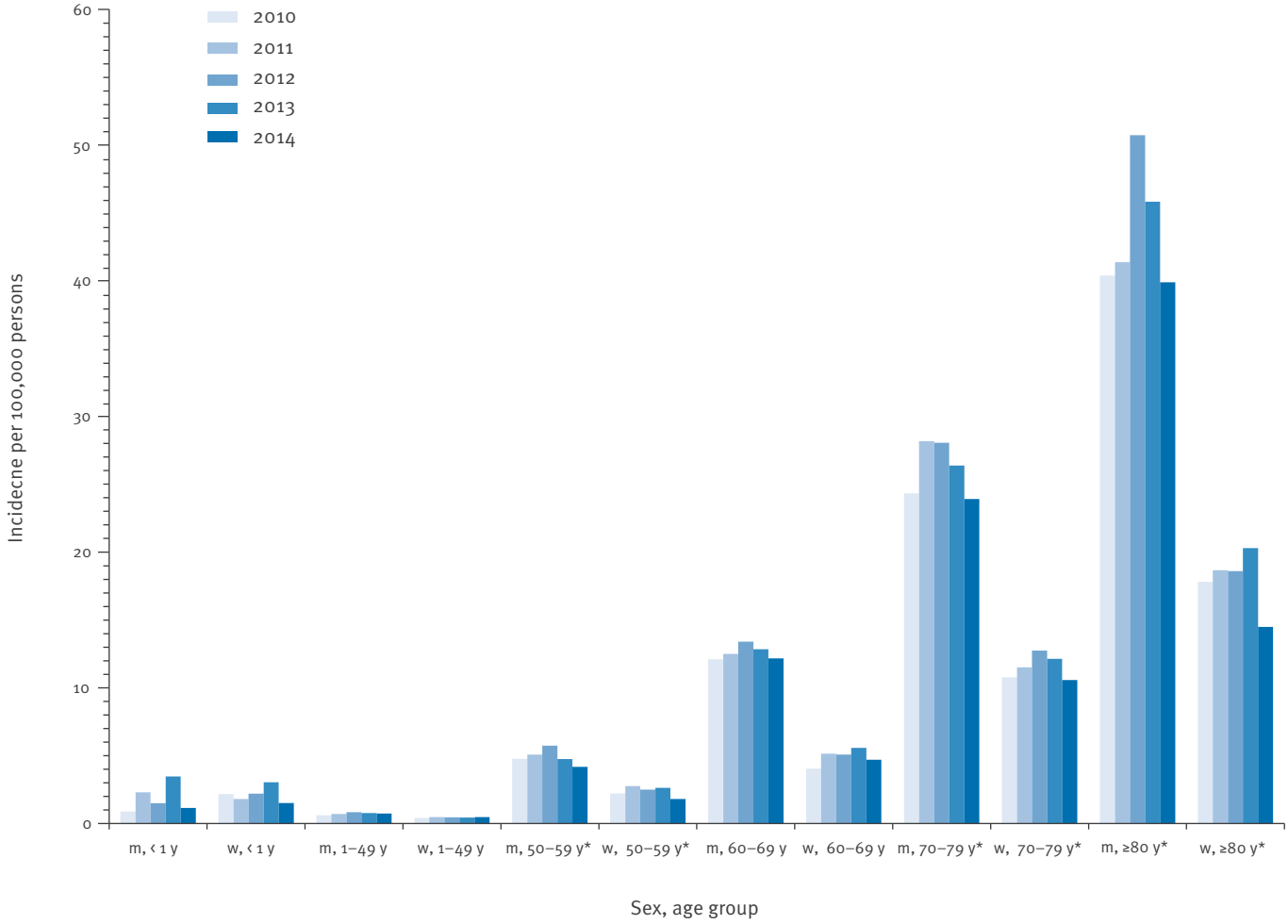
Data on the following case characteristics are transmitted to the Robert Koch Institute: sex, month and year of birth, the district of the patient's home address, the place of possible exposure, the date of the notification, the date of disease onset, the laboratory methods used for diagnosis (type of specimen and test used), whether or not the case fulfils the reference definition (independently of other variables), clinical symptoms, date of death and whether or not the death is due to an MRSA-infection, hospitalisation dates, whether or not the case is connected to an outbreak. The clinical case definition for invasive MRSA infections, as used by the German surveillance system, requires the patient to have at least one of the following symptoms: fever (≥38.5°C), signs of endocarditis, meningitis, meningoencephalitis, meningomyelitis, pneumonia or sepsis. However, the presence or absence of clinical characteristics does not change the necessity to notify this case to the authorities.

Since August 2011, information on HA infection outbreaks of epidemiologically-linked nosocomial (symptomatic) infections are additionally transmitted from local public health authorities to federal states and from there to the Robert Koch Institute [8,10]. In contrast to the notification of invasive MRSA infections, these notifications include information on the number of all affected patients; thus cases with non-invasive MRSA infection such as colonised cases are also included.

Data of notifications of invasive MRSA infections were extracted from the national surveillance database at

Figure 2

Incidence of notified episodes of invasive meticillin-resistant *Staphylococcus aureus* infections per 100,000 persons stratified by age, sex and year of notification in Germany, 2010–2014 (n=20,667) [a]



M: men; w: women; y: years-old.

The asterisk marks significant differences ($p < 0.05$) between 2012 and 2014. Only notifications marked as fulfilling the reference definition are included.

[a] 12 cases of 20,679 were excluded due to missing data for sex or age.

the Robert Koch Institute (SurvNet3@RKI) as collected up to 1 March 2015.

Population denominator

Aggregated population data in strata of age, sex, German federal state and calendar year (31 December of the preceding year, i.e. 2009 to 2013) were downloaded from the national institute of statistics (www.destatis.de) on 7 October 2014.

Statistics

We used chi-squared tests to compare categorical variables and Kruskal-Wallis tests to compare continuous variables between years. To calculate the annual incidence of invasive MRSA infections we categorised infections by the year of notification based on the epidemiological week number rather than calendar years. We then divided their number by the population at risk, i.e. the population on 31 December of the preceding year. We used chi-squared statistics to calculate confidence intervals around risk differences and risk ratios (RR) and to test for differences in incidence between years. We classified age in the categories shown based on the age distribution of the cases. We chose German federal state as the geographic level for analysis since a finer break down would have resulted in many empty or sparsely populated cells. For the differentiation in rural and urban areas we relied on the official German categorisation in urban ('kreisfreie Stadt') or rural districts ('Landkreis'). Some districts are excluded, since they comprised urban areas together with the surrounding rural area. For notifications with several places of a possible exposure we only included one in the analysis, prioritising foreign countries over Germany and other German states over those that equalled the notifying state. Since earlier software

products automatically set the place of exposure to the notifying state, the answer 'unknown' and 'same state as notification' were grouped together as one category. To assess the presence of effect modification we used the Mantel-Haenszel test for homogeneity. Throughout the analysis, tests were considered significant if the p-value was below 0.05.

We analysed the data with Stata SE13 (College Station, Texas, US). Maps were produced by Regiograph Planing Version 13 (GFK GeoMarketing GmbH, Germany).

Reporting

We followed the recommendations given in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [11].

Ethics

The study was based on the statutory case notifications as mandated by the German Protection against Infection Act. These data were available in anonymised form at national level. Ethical approval for analysis of such surveillance data are not required according to the Medical Association's professional code of conduct.

Results

Case characteristics

Between 2010 and 2014 there were 20,764 notifications of invasive MRSA infections in Germany. Eighty-five (0.4%) of them were excluded, since the reference definition was not fulfilled, resulting in a final study population of 20,679 notifications.

The characteristics of the included cases by year of notification are shown in Table 1 and 2. While the age distribution of the notified cases remained remarkably stable over the years, there were a number of other small but statistically significant changes. These include changes in the distribution of cases between the sexes, the German federal states, rural and urban areas, the type of specimen used for diagnosis, the proportion fulfilling the clinical case definition, several clinical symptoms, the proportion hospitalised, those with dates on disease onset and hospitalisation, those with a hospital onset of the infection, the mortality and case fatality ratios. Notable is an increase in the proportion and absolute numbers of patients with clinical signs of sepsis between 2010 and 2013, as well as those with sepsis due to a central vein catheter or other invasive access. The absolute numbers in both categories of cases however declined again in 2014 as compared with 2013.

Only few notifications of invasive MRSA infections were marked as being associated with a nosocomial outbreak (such notifications are independent of the transmission of data on nosocomial outbreaks as introduced in 2011). These amounted to a total of 204 of 20,679 (1%) for the whole study period, 37 of 3,754 (1%) for 2010, 37 of 4,227 (1%) for 2011, 31 of 4,485 (1%) for 2012, 40 of 4,372 (1%) for 2013, and 59 of 3,841 (2%) for 2014 ($p = 0.002$).

Remarkably, in patients with known disease onset and hospitalisation dates, few episodes (39%) of illnesses due to invasive MRSA occurred while patients were within the hospital. HA-MRSA infection was defined as disease onset later than the second day of hospitalisation but before or on the day of discharge.

The case fatality rate was 8%, with small but significant variations between the years. The cases with known dates of death and disease onset appeared to have a relatively short time between illness onset and death, with a median of seven days (interquartile range: 3 to 18). This short period can be explained by an underreporting of later deaths due to an undefined time point for follow-up by the public health department.

Possibility of recurrent infections

Even though unique personal identifiers are not included in the final dataset, we tried to assess the frequency of persons with repeated episodes of MRSA infections per year. We analysed the dataset for repetitions of the same combination of birth month and year, sex, district and notification year in the dataset. Over all five years (n=20,679 cases), we found 490 (2%) of these repetitions per year, suggesting that more than one episode of invasive MRSA infection in the same patient was rare. Of note, 71 (14%) of the repeated notifications were within two weeks of a previous notification, allowing for the possibility of double entries of the same episode.

Trends in the incidence of invasive meticillin-resistant *Staphylococcus aureus* infections

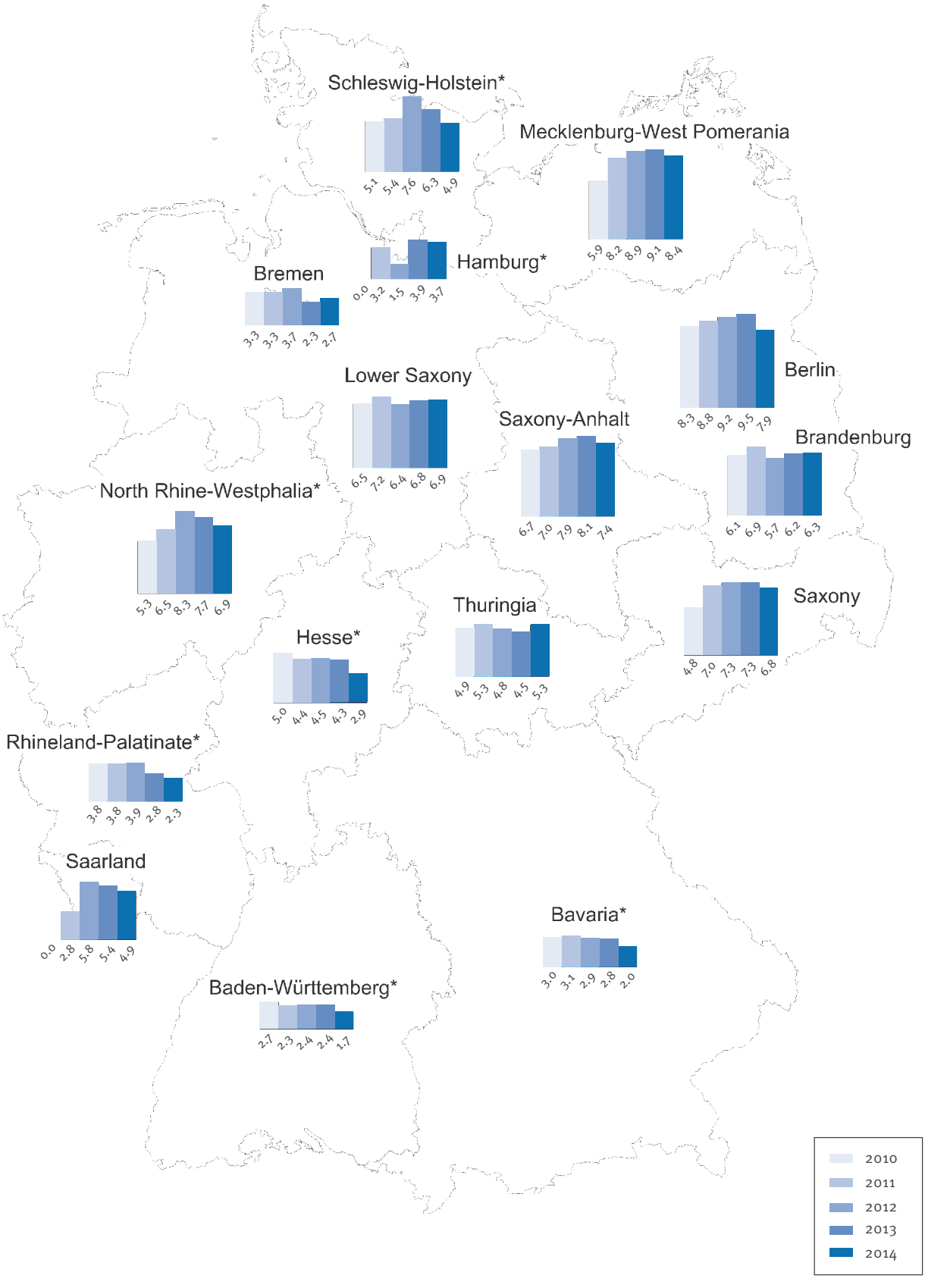
The incidence of invasive MRSA infections in Germany increased from 4.6 episodes per 100,000 persons in 2010 to 5.6 per 100,000 persons in 2012. With 5.4 episodes per 100,000 persons, it remained high in 2013, before dropping to 4.8 episodes per 100,000 persons in 2014. The risk difference and risk ratios (RR) between consecutive years are significant, with the exception of the years 2012 and 2013 (Figure 1). Results did not change appreciably when including all notified cases regardless of reference definition or when restricted to those specifying the origin of the sample as either blood or CSF (data not shown).

The effect of age, sex, state, and urban vs rural areas

The incidence is increasing with age, starting at ca 50 years of age (Figure 2). It was nearly double among men compared with women (RR: 1.79, 95% CI: 1.74–1.85), with the exception of children and adults below 50 years of age. It differed by a factor of ca four between federal states, with generally higher incidences in northern states (Figure 3) as well as in urban vs rural areas (Figure 4).

Figure 3

Incidence of notified episodes of invasive meticillin-resistant *Staphylococcus aureus* infections per 100,000 persons by federal state and year of notification, Germany, 2010–2014 (n=20,674)[a]

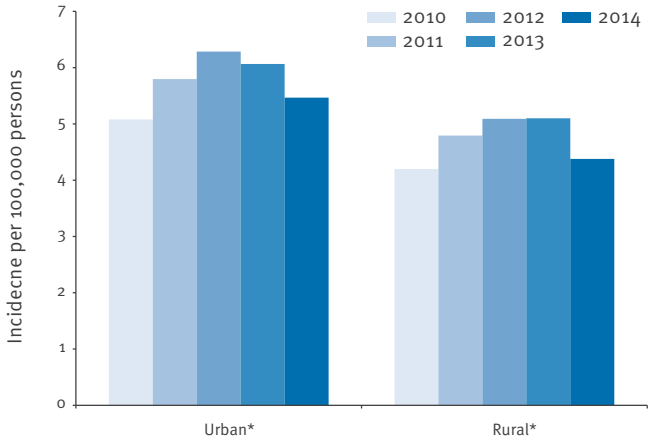


The asterisk marks significant differences ($p<0.05$) between 2012 and 2014. Only notifications marked as fulfilling the reference definition are included.

[a] Five cases of 20,679 were excluded due to missing data.

Figure 4

Incidence of notified episodes of invasive meticillin-resistant *Staphylococcus aureus* infections per 100,000 persons according to year of notification and urban or rural area, Germany, 2010–2014 (n=20,035)[a]



The asterisk marks significant differences ($p<0.05$) between 2012 and 2014. Only notifications marked as fulfilling the reference definition are included.

[a] 644 cases of 20,679 could not be attributed to either rural or urban areas.

A decline in the MRSA incidence between 2012 and 2014 is found for most but not all strata of age, sex, and state, as well as for rural and urban areas (Figure 2 to 4). For example the decrease in incidence from 2013 to 2014 is seen in all strata of age and sex, except for women between 1 to 50 years of age (test for homogeneity: $p=0.01$). Similarly, some states had even an increase in incidence in 2014 (Brandenburg, Bremen, Lower Saxony, Thuringia) or in 2013 (Brandenburg, Berlin, Hamburg, Lower Saxony, Mecklenburg-West Pomerania, Saxony-Anhalt) as compared with the preceding year (test for homogeneity for 2014 vs 2013: $p=0.005$; for 2013 vs 2012: $p=0.003$). These differences are not due to confounding since the age structure in Germany remained relatively stable during the time of the analysis and since the stratified and crude Mantel-Haenszel estimates were similar.

Outbreaks

As part of the notification for HA outbreaks, which are independent of the notification of invasive MRSA infections, a total of 95 outbreaks of MRSA were reported for the years 2012 to 2014. These comprise colonisation and all types of MRSA-infections, not only invasive infections. In 2012 there were 27 outbreaks comprising 120 cases (among those 98 infected, 20 colonised und 2 unspecified), 30 outbreaks with 143 cases (71 infected, 54 colonised and 18 unspecified) in 2013 and 38 outbreaks with 209 cases (79 infected, 103 colonised and 27 unspecified) in 2014.

Discussion

This is the first trend analysis of the incidence of invasive MRSA infections including the complete population in Germany. We found that the annual incidence of notified invasive MRSA infections increased from 2010 until its peak in 2012 to 2013 before declining again in 2014. We additionally observed statistically different trends between German federal states and to a lesser extent between some categories of age and sex, suggesting different trends at local level and possibly for certain patient groups.

As with all passive surveillance systems, underreporting and effects due to changes in the reporting compliance cannot be excluded. Especially during the first years after the inclusion of MRSA in the national surveillance system underreporting and the number of data errors may have been high due to a lack of training and due to technical problems [12]. We therefore think that the increase in 2011, and possibly in 2012 may in part be due to a surveillance artefact and it may also explain changes in clinical symptoms, such as the increase of clinical sepsis. However, given an assumed stabilisation of the surveillance system we believe that the decline in 2014, even though small, is likely to be real. The decline in 2014 includes cases with clinical sepsis as well as those with sepsis and central vein catheter or other invasive access, which further corroborates this interpretation.

Germany has done much to control its MRSA epidemic. This includes the implementation of a national antibiotic resistance strategy (DART, 2008 updated 2015) (www.bmg.bund.de), the establishment of regional networks to combat multiresistant bacteria (since 2004 with the support of the Robert Koch Institute) [13], the conduction of various screening programmes [14-16], the adaption of respective clinical guidelines (http://www.awmf.org), the development of antibiotic stewardship programmes, additional legislation on federal state levels, recommendations by the Robert Koch Institute concerning hospital hygiene (www.rki.de) and the establishment of various surveillance systems such as the mandatory reporting for invasive MRSA infections in 2009 and the antibiotic resistance surveillance (ARS) in 2007 [7]. It is therefore tempting to think that these interventions had some effect on the incidence of invasive MRSA infections. However, surveillance data are rarely suitable to prove causal links. We cannot exclude other causes, such as changes in the frequency of testing and biological mechanisms [17]. For example with additional testing, which is likely to have occurred due to an increased awareness of the possibility of antibiotic resistance, the number of detected and reported cases is likely to increase [18]. A biological factor possibly contributing to the decrease of MRSA in Germany is the reduction of epidemic clones throughout central Europe [19], as well as shifts of epidemic strains found within Germany [20].

The decline in the incidence of invasive MRSA infections reported here is smaller and occurred later than that suggested by other German surveillance systems. For example, in the laboratory-based ARS network the

Table 1

Demographic characteristics of patients with invasive meticillin-resistant *Staphylococcus aureus* infection in Germany by year of notification, 2010–2014 (n=20,679)

Characteristics	Total	2010	2011	2012	2013	2014	P-value
N	20,679	3,754	4,227	4,485	4,372	3,841	–
Female n (%)	7,595 (37)	1,392 (37)	1,573 (37)	1,608 (36)	1,668 (38)	1,354 (35)	0.05
Median age in years (IQR)	74 (64, 80)	73 (65, 80)	73 (64, 80)	73 (64, 80)	74 (64, 80)	74 (64, 80)	0.47
Age group in years, n (%)							
<1	67 (0)	10 (0)	14 (0)	12 (0)	22 (1)	9 (0)	0.23
1 to 49	1,392 (7)	245 (7)	285 (7)	304 (7)	279 (6)	279 (7)	
50 to 59	2,159 (10)	400 (11)	458 (11)	485 (11)	445 (10)	371 (10)	
60 to 69	3,877 (19)	731 (19)	788 (19)	803 (18)	809 (19)	748 (19)	
70 to 79	7,508 (36)	1,321 (35)	1,554 (37)	1,641 (37)	1,569 (36)	1,423 (37)	
≥80	5,673 (27)	1,047 (28)	1,127 (27)	1,242 (28)	1,247 (29)	1,010 (26)	
Federal state of residence, n (%)							
Baden-Württemberg	1,234 (6)	292 (8)	248 (6)	253 (6)	255 (6)	186 (5)	<0.001
Bavaria	1,730 (8)	378 (10)	385 (9)	358 (8)	356 (8)	253 (7)	
Berlin	1,486 (7)	285 (8)	304 (7)	306 (7)	321 (7)	270 (7)	
Brandenburg	772 (4)	152 (4)	173 (4)	139 (3)	153 (4)	155 (4)	
Bremen	101 (0)	22 (1)	22 (1)	24 (1)	15 (0)	18 (0)	
Hamburg	214 (1)	0 (0)	57 (1)	26 (1)	67 (2)	64 (2)	
Hesse	1,274 (6)	302 (8)	266 (6)	271 (6)	257 (6)	178 (5)	
Mecklenburg-West Pomerania	653 (3)	97 (3)	134 (3)	143 (3)	145 (3)	134 (3)	
Lower Saxony	2,655 (13)	514 (14)	571 (14)	498 (11)	531 (12)	541 (14)	
North Rhine-Westphalia	6,123 (30)	944 (25)	1,160 (27)	1,457 (33)	1,354 (31)	1,208 (31)	
Rhineland-Palatinate	664 (3)	154 (4)	153 (4)	156 (3)	110 (3)	91 (2)	
Saarland	189 (1)	0 (0)	28 (1)	58 (1)	54 (1)	49 (1)	
Saxony	1,359 (7)	202 (5)	290 (7)	296 (7)	295 (7)	276 (7)	
Saxony-Anhalt	849 (4)	157 (4)	164 (4)	179 (4)	182 (4)	167 (4)	
Schleswig-Holstein	824 (4)	144 (4)	153 (4)	213 (5)	177 (4)	137 (4)	
Thuringia	547 (3)	111 (3)	119 (3)	105 (2)	98 (2)	114 (3)	
Type of area, n (%)							
Rural	12,649 (61)	2,278 (61)	2,596 (61)	2,715 (61)	2,723 (62)	2,337 (61)	<0.001
Urban	7,386 (36)	1,310 (35)	1,506 (36)	1,604 (36)	1,560 (36)	1,406 (37)	
Undefined	644 (3)	166 (4)	125 (3)	166 (4)	89 (2)	98 (3)	
Place of possible exposure, n (%)							
Other federal state than state of notification	275 (1)	39 (1)	55 (1)	64 (1)	55 (1)	62 (2)	0.26
Outside of Germany	40 (0)	4 (0)	5 (0)	11 (0)	10 (0)	10 (0)	0.34

IQR: interquartile range.

Only notifications marked as fulfilling the reference definition are included. Missing data were less than 0.1%, except for the exposure place, where the exact number could not be identified due to technical reasons.

percentage of oxacillin resistance in blood culture collected from inpatients declined from a peak of 24% (95% CI: 22.5–27.0) in 2010 to 18.4% (95% CI: 16.5–20.3) in 2011 [7] and is currently at 13% (www.ars.rki.de). The EARS-net reported a decline in the proportion of MRSA among *S. aureus* isolates for Germany from 20.9% in 2010 to 12.8% in 2013 [1], the triennial survey by the Paul Ehrlich Institute found a decline from 30.3% in 2007 to 16.7% in 2010 [21] and data from the hospital infections surveillance system (KISS) suggest a decline from 33% in 2007 to 27% in 2012 among nosocomial *S. aureus* infections [6]. This may in part be explained by the different indicators used and the possible non-representativeness of these voluntary systems, but more probably is due to the underreporting in the national reporting system in the first years. Thus a definite conclusion concerning the start of the decline cannot be made.

Despite the decrease in 2014, the incidence of 4.8 invasive MRSA infections per 100,000 persons in Germany is still higher than that in some neighbouring countries, such as Denmark (1 case of MRSA bacteraemia per 100,000 in 2014) [22], western Sweden (one case of community onset MRSA blood stream infection between 2004 and 2008 for a catchment population of 256,000) [23] and England, where, after intensification of control mechanisms, a recent decline was reported

Table 2

Clinical characteristics of patients with invasive meticillin-resistant *Staphylococcus aureus* infection in Germany by year of notification, 2010–2014 (n=20,679)

Characteristics	Total	2010	2011	2012	2013	2014	P-value
N	20,679	3,754	4,227	4,485	4,372	3,841	–
Type of specimen for diagnosis, n (%)							
Blood	19,318 (93)	3,587 (96)	3,837 (91)	4,156 (93)	4,126 (94)	3,612 (94)	<0.001
CSF	117 (1)	24 (0)	13 (0)	37 (1)	25 (1)	18 (0)	
CSF and blood	17 (0)	2 (0)	5 (0)	1 (0)	3 (0)	6 (0)	
Not indicated	1,227 (6)	141 (4)	372 (9)	291 (6)	218 (5)	205 (5)	
Clinical case definition fulfilled, n (%)							
Yes	18,775 (91)	3,343 (89)	3,855 (91)	4,133 (92)	3,967 (91)	3,477 (91)	<0.001
No	1,245 (6)	195 (5)	308 (7)	260 (6)	302 (7)	180 (5)	
Unknown	659 (3)	216 (6)	64 (2)	92 (2)	103 (2)	184 (5)	
Patients with available data on clinical symptoms, n (%)							
With data	18,268 (88)	3,329 (89)	3,609 (85)	3,978 (89)	3,890 (89)	3,462 (90)	<0.001
Clinical symptoms among those with available data (N=18,268), n (%)[a]							
Fever	13,697 (75)	2,444 (73)	2,739 (76)	3,036 (76)	2,876 (74)	2,602 (75)	0.02
Signs of meningitis, meningoencephalitis or meningomyelitis	1,813 (10)	44 (1)	493 (14)	494 (12)	457 (12)	325 (9)	<0.001
Pneumonia	3,494 (19)	588 (18)	681 (19)	778 (20)	760 (20)	687 (20)	0.15
Endocarditis	428 (2)	67 (2)	79 (2)	99 (2)	89 (2)	94 (3)	0.35
Lesion, skin abscess or ulcer	269 (1)	0 (0)	0 (0)	1 (0)	68 (2)	200 (6)	<0.001
Screening examination	304 (2)	0 (0)	0 (0)	0 (0)	64 (2)	240 (7)	<0.001
Sepsis	12,086 (66)	1,682 (51)	1,866 (52)	2,678 (67)	3,135 (81)	2,725 (79)	<0.001
Characteristics among patients with sepsis (N=12,086), n (%)[a]							
Central vein catheter or other invasive access	4,324 (36)	511 (30)	675 (36)	979 (37)	1,105 (35)	1,054 (39)	<0.001
Other foreign object associated infection	594 (5)	50 (3)	69 (4)	124 (5)	190 (6)	161 (6)	<0.001
MRSA infection of known focus	5,425 (45)	12 (1)	622 (33)	1,298 (48)	1,846 (59)	1,647 (58)	<0.001
Characteristics among MRSA infections of known focus (N=5,425), n (%)[a]							
Urinary tract	1,031 (19)	5 (42)	124 (20)	226 (17)	358 (19)	318 (19)	0.15
Abdomen (e.g. after operation)	267 (5)	1 (8)	35 (6)	75 (6)	90 (5)	66 (4)	0.20
Respiratory tract	1,777 (33)	1 (8)	208 (33)	438 (34)	587 (32)	534 (33)	0.31
Skin or soft tissue	2,291 (42)	4 (33)	265 (43)	576 (44)	781 (42)	665 (40)	0.27
Bones or joints	399 (7)	0 (0)	41 (7)	82 (6)	150 (8)	126 (8)	0.25
Other	596 (11)	2 (17)	67 (11)	140 (11)	217 (12)	170 (10)	0.67
Hospitalisation, n (%)							
Yes	18,423 (89)	3,281 (87)	3,753 (89)	4,065 (91)	3,897 (89)	3,427 (89)	<0.001
No	1,675 (8)	437 (12)	417 (10)	357 (8)	315 (7)	149 (4)	
Unknown	581 (3)	36 (1)	57 (1)	63 (1)	160 (4)	265(7)	
Date of onset of symptoms and of hospitalisation known, n (%)	11,273 (55)	1,774 (47)	2,163 (51)	2,490 (56)	2,510 (57)	2,336 (61)	<0.001
Among these, symptom onset while in hospital n (%)[b]	4,412 (39)	646 (36)	818 (38)	993 (40)	1,036 (41)	928 (40)	0.01
Vital status							
Vital status known n (%)	20,293 (98)	3,694 (98)	4,151 (98)	4,433 (99)	4,353 (100)	3,662 (95)	<0.001
Mortality among those with vital status known (N=20,293)							
All-cause mortality n (%)	1,973 (10)	320 (9)	366 (9)	437 (10)	396 (9)	454 (12)	<0.001
Case fatality rate n (%)[c]	1,580 (8)	319 (9)	354 (9)	359 (8)	293 (7)	255 (7)	<0.001
Time from symptom onset to death, median days (IQR)[d]	7 (3, 18)	9 (3, 20)	6 (3, 18)	8 (4, 21)	7 (3, 17)	6 (2, 15)	0.04

CSF: cerebrospinal fluid; IQR: interquartile range; MRSA: meticillin-resistant *Staphylococcus aureus*.

Only notifications marked as fulfilling the reference definition are included. Missing data were less than 1% or are as indicated.

[a] Several categories could apply simultaneously. Thus the total may tally to more than 100%.

[b] Onset > 2 days after hospitalisation and before or on discharge.

[c] MRSA infection identified as a cause of death.

[d] Based on patients with available data: n=187 in 2010, 252 in 2011, 295 in 2012, 289 in 2013, 335 in 2014.

in 2014 (with an incidence of 1.6 case of MRSA bacteraemia per 100,000 in that year) [24]. This indicates that still more needs to be done in Germany as well. Finally, a decline in invasive MRSA infections does not necessarily mean that other forms, such as livestock-associated and community-associated MRSA infections, are also declining. These forms are not properly captured by the surveillance system analysed here. However, data from the voluntary ARS system indicate declines in various forms of MRSA infections (https://ars.rki.de/).

A possible focus for further interventions should include the MRSA management in ambulatory settings and a more rigorous detection of outbreaks. Similar to data from various other countries [23,25], 61% of the patients with available hospitalisation and disease onset dates, had an onset before day three of hospitalisation, indicating that colonisation and infections may occur before hospitalisation possibly in the community. Furthermore, only 1% of cases were associated with outbreaks. While it is unclear, which proportion of MRSA infections is expected to be caused by outbreaks, we think that the notified number is a large underestimation, especially given the fact that only invasive infections are to be notified and detection of MRSA at other body sites is much more frequent. The increase in the number of reported outbreaks from 27 in 2012 to 38 in 2014 with a simultaneous decrease of the number of infected persons and an increase of colonised persons is however a promising sign, that more outbreaks are being detected and reported.

The mortality and case fatality rate of respectively 10% and 8% observed in this study were lower than those reported in the literature [26-28]. For example one study reported a case fatality rate of 22% for community-onset MRSA bacteraemia [28] and a multicentre prospective study in 13 European hospitals found a mortality for MRSA bloodstream infection of 36% [26]. We believe this to be due to the lack of a defined follow-up period in the German surveillance system. There are no strict rules for when the public health department should collect patient information including the treatment outcome. Therefore, the values presented here are likely to be underestimations.

The causes for the higher incidence among men are not clear, even though previously shown by other surveillance systems in Germany [4] and elsewhere [24]. In our data a difference according to sex becomes only apparent among older patients suggesting medical or behavioural factors in this age group as the key driver. More studies are however needed to better understand the underlying causes for this association. Similarly, studies are needed to investigate the causes for the higher incidence in the north of Germany.

The study has further limitations in addition to those already mentioned above. These include the absence of federal validation processes of the notification system, since communicable disease management is in the responsibility of the German federal states. A limitation is also the notification by patients' home addresses, which may not be the place of exposure. This may especially lead to an underestimation of the incidence in urban areas, if many patients from surrounding districts are treated in a nearby urban centre, but are notified for their home address. Finally, the number of software packages and versions available for the local public health office may result in different implementation of some variables, such as the clinical symptoms, which are difficult to understand retrospectively at the national level. Thus trends over time in some variables may be biased due to delayed updates of software or changes in the proportion of various software packages over time. Finally, the absence of a personal identifier does not allow identifying recurrent infections with certainty.

In summary, data from the national surveillance system corroborate previous reports that the incidence of MRSA infections in Germany may be declining. However, additional studies are needed to better understand its causes and to accelerate this still modest downward trend.

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Conflict of interest

None declared.

Authors' contributions

Design of the study: JH, MAS, SH, TE, JW. Analysis: JW, SH, HPB. Writing of the first draft: JW.

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