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ORIGINAL PAPER

The cost of resistance: incremental cost of methicillin-resistant *Staphylococcus aureus* (MRSA) in German hospitals

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Abstract Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant problem in many healthcare systems. In Germany, few data are available on its economic consequences and, so far, no study has been performed using a large sample of real-life data from several hospitals. We present a retrospective matched-pairs analysis of mortality, length of stay, and cost of MRSA patients based mainly on routine administrative data from 11 German hospitals. Our results show that MRSA patients stay in hospital 11 days longer, exhibit 7% higher mortality, are 7% more likely to undergo mechanical ventilation, and cause significantly higher total costs (€ 8,198).

Keywords Cost analysis · Length of stay · Mortality · MRSA · Outcome

JEL Classification I12 · I18 · C13 · C14

Introduction

According to data from the European Antimicrobial Resistance Surveillance System (EARSS), methicillin-resistant *Staphylococcus aureus* (MRSA) rates vary considerably throughout Europe, with Southern European countries, Ireland, and the United Kingdom showing the highest (>60% resistance in the case of Malta), Scandinavia showing the lowest levels (below 4%), and central European countries falling in between. In Germany, resistance increased from 12.5% in 2000 to more than 20% in 2005. Since then, rates seem to have receded slightly [7].

MRSA rates in intensive care units (ICUs) are often higher than in other departments [7]. From 1997 to 2003, resistance among nosocomial *S. aureus* infections in German ICUs increased from 8% to 30%, according to data from the German Nosocomial Infection Surveillance System (KISS) [9].

Among the main reasons cited for the spread of resistance is poor hand hygiene compliance [3, 21]. Further factors (explaining inter-country differences) are inappropriate use of antibiotics (especially in Southern Europe) and "search-and-destroy" tactics (as employed, e.g. in the Netherlands).

MRSA causes a variety of severe infections and is associated with increased mortality [3, 9, 11]. As a consequence of the high and prolonged morbidity of MRSA-infected patients, MRSA also represents an economic burden for hospitals/healthcare systems. Various publications have documented that MRSA colonisation or MRSA infection is associated with substantially higher cost when compared to methicillin-susceptible *S. aureus* (MSSA). The majority of such studies found a 1.3- to 2-fold increase in length of stay (LOS), costs, and mortality [4].

For the German healthcare system, few data are available on the economic consequences of MRSA. In 1996–1998, Geldner et al. [10] calculated the cost increment of

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MRSA-infected versus MRSA-non-infected patients in a German university hospital's surgical ICU as € 9,409. These costs were linked to diagnostics and treatment as well as an additional 5.8 days of in-hospital stay for MRSA, but also represented opportunity cost from beds blocked by isolation measures. However, the reimbursement system has changed since Geldner's study and figures are therefore not comparable with nowadays.

Herr et al. [13] estimated an additional € 9,261 for hygienic measures in a university hospital's surgical ward, most of which was caused by beds blocked due to isolation. This study does not take into account the effect of MRSA on LOS and associated hotelling and nursing costs, which, in another international analysis [18] accounted for the majority of the increased costs.

More recently, Greiner et al. [12] found average treatment costs for MRSA blood stream infections (BSI) in patients undergoing haemodialysis to be more than twice as high as those of MSSA BSI (€ 10,573 vs € 24,931).

The German Federal Government quotes an estimate from the Robert-Koch-Institute, according to which the incremental cost of each MRSA case varies between € 1,600 and € 10,000, depending on medical discipline and type of infection [20]. It is not clear, however, whether this comparison is against patients with MSSA infections or against uninfected patients.

So far, no study has been performed that uses a large sample with real-life data from several hospitals. Thus, the aim of this study was to assess the burden of MRSA using routine data, considering outcomes, resource use, and costs.

Methods

Our analysis is based on data collected in hospitals for the purpose of reimbursement within the German diagnosis-related groups system (G-DRG). This data is collected nationally and analysed by a dedicated institute called "InEK" to calculate the system's cost weights. InEK releases aggregate statistics but no individual case data so these had to be obtained directly from the hospitals; 11 hospitals agreed to participate.

MRSA can occur in different patient populations and in different hospital settings; the outcome and economic consequences of MRSA may vary according to hospital size and specialisation. Accordingly, we included in the sample a range of hospitals from small specialized clinics to large maximum care and university hospitals. All of these hospitals participate in the national cost calculation and thus apply the InEK's accounting rules with some degree of consistency.

The hospitals represented the following types:

- 2 university hospitals,
- 5 tertiary maximum care hospitals,
- 2 basic care hospitals,
- 2 specialized hospitals.

The hospitals provided a total of 395,217 cases,[1] which represents 100% of their in-patient stays for the year 2004. After filtering outpatients, cases with incomplete cost data and cases with missing information, 313,942 remaining cases (about 1.9% of all cases reported in German hospitals in 2004) were included in the study. All cases were grouped into DRG-classes using the G-DRG 2005 classification and 3M FileInspector 3.0 software.

Data quality considerations and selection of matching variables

From the literature, it is known that MRSA infection is confounded with other cost drivers such as advanced age and co-morbidity. In order to control for the influence of confounding and bias, MRSA cases were matched with non-MRSA controls. We controlled for variables that either influence the probability of an MRSA infection or that are independent cost drivers in their own right. Moreover, these variables/cost influencers should not be potential consequences of MRSA.

Unlike Noskin et al. [19], we therefore decided not to match on DRG, as the attribution of a case to a DRG is influenced not only by the underlying medical condition, but also in part by the consequences of additional complications such as MRSA.

Unfortunately, the routine data used in this study do not include time stamps for the individual variables such as diagnoses or measures of clinical complexity. This makes it difficult to distinguish cause and effect, i.e. whether a patient was severely ill before the MRSA infection or as a consequence of the MRSA infection. Whereas in the first case, matching would be appropriate to avoid overestimating the incremental cost, in the second case, it would actually remove some of the effect of MRSA. The reason for this is that patients suffering from the effects of an MRSA infection would be assigned to controls that are

[1] Our data set consists of hospital stays, not patients. In the G-DRG system, there are elaborate rules that result in two cases being merged into one if they occur within a short timeframe and are either likely to be caused by the same underlying condition or if the second is likely to be caused by complications incurred during the first stay. Cases that were merged according to these rules were excluded from the analysis to avoid contamination with this problem and because no 100% clear-cut length of stay can be determined. Thus, the remaining cases can be regarded as independent for the purpose of our analyses.

more severely ill than the MRSA cases were before their infection with resistant strains.

The following variables were used for matching:

- Hospital and admitting ward: the hospital and the specific ward a patient is admitted to, are the consequence of a large number of medical, organisational and economic factors including, but not limited to, the patient's morbidity at admittance. These factors affect the likelihood of an MRSA infection as well as the medical and financial outcome.
- Principal diagnosis: the principal diagnosis is the main reason why the patient had to be treated in hospital as coded in retrospect at discharge in ICD-10-GM [5]. From both a medical and an economic perspective, it is a key variable strongly influencing LOS, mortality, and cost. Only the first three digits of the diagnoses were used, as an earlier study [23] found that ICD-coding in German hospitals was unreliable beyond this level. Moreover, exact matching on the full code would reduce sample size as it yields fewer match partners.
- Age
- Mean clinical complexity level (CCL) of comorbidities: to obtain a summary measure of the severity of illness, the average CCL of the comorbidities was computed using the CCL scores provided by the G-DRG system. As MRSA patients are likely to be more thoroughly examined and thus also likely to be diagnosed with more comorbidities than other patients (diagnostic suspicion bias [15]), the readily available Patient Clinical Complexity Level (PCCL), which in essence is the (rounded) sum of individual CCLs, could be biassed. The averaging used in the construction of our measure takes this into account, reducing the potential bias to some extent.
- Risk factors/cost drivers: a number of comorbidities that cannot occur as a consequence of MRSA, but are either cost drivers in their own right or influence the likelihood of an MRSA infection or both (see Table 1). Similar to Noskin et al. [19], the relevant comorbidities were chosen from the 100 most frequent comorbidities of MRSA patients by an expert panel (structured Delphi panel process of ten certified physicians). The association of the comorbidities was then verified, comparing the prevalence in the MRSA vs the non-MRSA patients in the unmatched full dataset. The analysis shows that all risk factors/cost drivers are more frequent in MRSA as compared to non-MRSA patients ($P < 0.001$). Again, only three digits (or, in the case of cancer, which forms a full chapter in the ICD nomenclature, one digit) of the ICD codes were used.

Practical experience with the German DRG system suggests that comorbidities not relevant for reimbursement, like MRSA, are often underreported. Hence, we complemented standard DRG data with microbiology data (provided by the hospitals from separate databases) to identify all MRSA cases in our study population. This revealed that, in fact, hospitals reported MRSA status in their medical coding only in 32.1% (average)[2] of all identified cases. DRG coding for MRSA without the respective microbiology results, on the other hand, was rare (0.1%).[3] Positive MRSA lab findings could be collected for a total of 1,443 patients (0.46%)[4] It was not possible to differentiate between manifest infections and colonisation with MRSA.

Table 1 Cost drivers/risk factors used in matching procedure

ICD-10-GM[a]	Text
N18	Chronic renal failure
I50	Heart failure
I25	Chronic ischemic heart disease
E11	Non-insulin-dependent diabetes mellitus
I10	Essential (primary) hypertension
I48	Atrial fibrillation and flutter
D62	Acute post-haemorrhagic anaemia
J44	Other chronic obstructive pulmonary disease
Z95	Presence of cardiac and vascular implants and grafts
C	Cancer (malignant neoplasms)

[a] International Classification of Diseases—German Modification

Matching procedure and description of the matched datasets

To date, a number of different matching algorithms have been established [14]. Unfortunately, most of them are designed primarily for reducing bias of continuously scaled covariates and not of nominally scaled factors. If they have only a small number of values, nominal variables can be decomposed into binary dummies, and can then be used to construct a propensity score. In our case, this was not possible. Due mainly to the high number of different diagnoses in the ICD nomenclature, the large number of potential controls, and software limitations, we had to rely heavily on exact matching. Thus, we implemented the following simple procedure on the basis of an Microsoft Access database:

1. Step 1: Exact matching on the nominally scaled variables.

[2] This figure varied between 4.1 and 92.3% across the surveyed hospitals.

[3] The maximum proportion of U80.0!-codes without a positive laboratory result was 0.3%.

[4] This figure is slightly lower than the 0.56% that can be computed from data supplied by the National Reference Centre for the Surveillance of Nosocomial Infections based on reports from 65 hospitals [17].

Table 2 Variables used for matching.

	Matching 1	Matching 2
Hospital	Exact	Exact
Admitting ward	Exact	Exact
Principal diagnosis (first three digits of ICD code)	Exact	Exact
Age	±10 years	±10 years
Mean CCL of comorbidities	±0.6	Not used
Risk factors/cost drivers	Number ±1	Exact

CCL Clinical complexity level, *ICD* International Classification of Diseases

2. Step 2: From the controls selected in the first step, match partners were chosen who, on the continuously scaled variables, showed a value within a specified tolerance around the value of their MRSA case (e.g. ±10 years of age).
3. Step 3: If still more than one match partner was found (which happened only for about 2% of cases), the one with the smallest Euclidean distance to his counterpart on the continuous variables was chosen (if more than one control still remained eligible, one was picked at random).

Using this procedure, we matched on two different sets of variables. These sets are summarised in Table 2 as "Matching 1" and "Matching 2". They differ only with respect to the way the two variables CCL and risk factors were used in the matching procedure:

- In Matching 1, it was decided that the risk factors/cost drivers should not be matched exactly. Instead, the number of risk factors for each case was used. This matching was designed to minimise the loss of cases. At the same time, it is clear that this goal was reached at the expense of accuracy of matching as merely using the number of risk factors inevitably results in loss of clinical information.
- Thus, in Matching 2, we used exact matching on these variables, but did not use CCL as a matching criterion.

These matchings were then evaluated with regard to the following criteria:

- Minimisation of cases lost in matching
- Reduction of variance of the covariates
- Amount of bias reduction on the covariates/balance achieved. As bias cannot be measured, except in simulation studies, we used the mean difference as a proxy.[5]

Table 3 Comparison of unmatched and matched datasets with respect to mean and standard deviation in the methicillin-resistant *Staphylococcus aureus* (MRSA) group, mean difference between MRSA and control group on the covariates used for matching (as a proxy for bias), and the degree to which the matching has eliminated the mean difference/bias

	Unmatched	Matching 1	Matching 2
n (number of MRSA cases/pairs)	1,443 cases	1,026 pairs	549 pairs
Mean/standard deviation (MRSA)			
Age (years)	68.7/15.5	69.4/14.7	65.9/17.8
Mean CCL of comorbidities (CCL points)	1.3/0.6	1.2/0.6	1.1/0.7
Number of risk factors/cost drivers	2.0/1.6	1.9/1.5	1.1/1.1
Mean difference (bias)			
Age (years)	16.6	0.11	0.15
Mean CCL of comorbidities (CCL points)	0.8	0.04	0.33
Number of risk factors/cost drivers[a]	1.1	0.08	0
Reduction of mean difference/bias			
Age		99.3%	99.1%
Mean CCL of comorbidities		94.8%	56.8%
Number of risk factors/cost drivers[a]		92.8%	100%

[a] As listed in Table 1

- Difference in the percentage of bias reduction achieved for the individual covariates.[6]

In Table 3, we present the results for both matchings and compare the datasets to the MRSA cases in the unmatched dataset.

Cochran's [2] rule of thumb states that means of treatment and control groups should differ by less than a quarter standard deviation on any given variable. This rule is fulfilled for all variables in matching 1 but not for the mean CCL in matching 2 (where it was not used as a matching variable). Matching 2 also contains considerably fewer cases and exhibits a higher standard deviation than the original data with regard to age and the mean CCL of comorbidities. According to its matching criteria, matching 2 requires more similarity between cases and controls. Given the nature of our data, this does not necessarily lead to a more appropriate matching procedure or even to results

[5] Apart from the mean difference, we also looked at boxplots of the distributions, and compared the distributions using the Kolmogorov–Smirnov and the Mann–Whitney *U* Tests. These results pointed in the same direction and are thus not reproduced here.

[6] The percentage of bias reduction should be as equal as possible over the covariates, as otherwise bias may be increased for some function of these covariates, even if univariate bias has been reduced for each of them. This property is known as "equal percentage bias reducing" or EPBR [22].

that could be considered more valid. Data from both matching procedures are presented to demonstrate the robustness of our analysis.[7]

Results

Principal diagnoses and DRGs

Table 4 shows the principal diagnoses and base DRGs of pairs and controls. While principal diagnoses on the 3-digit level are identical (as they were used for matching), the DRGs of the MRSA cases already reveal the high prevalence of long-term artificial respiration among this patient group.

LOS, mechanical ventilation, and mortality

MRSA patients stay in hospital for an average of 25.8 days (cf. Table 5). This is 1.8 times as long (mean difference 11.2 days, $P < 0.001$, paired sample t test) as the average LOS of controls (14.6 days). The second matching shows very similar results with 11 days mean difference (1.9 times the LOS of the control group).

MRSA patients are more than 7% more likely to undergo mechanical ventilation (matching 1: 32.6 vs 25.1%; Table 5). The lower values found in the second matched dataset reflect the better overall health status of its patients (27.7 vs 21.5%) and the estimated difference is diminished slightly (to approximately 6%). However, in both datasets, cases are more likely to undergo mechanical ventilation (odds ratios 3.2 in matching 1 and 3.8 in matching 2) and the differences found in both datasets are highly significant (paired sample McNemar test, $P < 0.001$).

In matching 1, of the MRSA patients, 18.3% die in hospital (Table 5), while among controls in-hospital mortality is only 10.9% (odds ratio: 2.1). Again, the results of the second matched dataset reflect the overall better health status and lower average age of this sample: both cases and controls are less likely to die (14.0 vs 4.9%) compared to the situation in matching 1. However, the difference in mortality (7.4 vs 9.1%) and the odds ratio (3.9) is even higher in sample two, and is highly significant (paired sample McNemar test, $P<0.001$) in both datasets.

Cost differences

In the unmatched dataset, the 1,443 MRSA patients make up only 0.46% of the patient population, but account for 2.32% of the total cost (€ 25,483,497 out of € 1,124,991,013). This already indicates that MRSA is potentially associated with considerably higher costs.

In matching 1, MRSA patients cost, on average, € 16,024 per stay, and are thus more than twice as expensive as non-MRSA patients (mean difference € 8,198, $P < 0.001$, paired sample t test). In the second sample, all estimates are slightly smaller, but the ratio remains roughly the same, and the difference (€ 7,257) is still significant ($P < 0.001$). However, there is a large range of cost differences even in the larger matching 1 sample (from −€ 90,519.83 to € 177,450.01).

The higher cost of MRSA patients can be attributed either to longer stays in hospital or to higher cost per day, or both. While LOS is increased for MRSA patients, the cost per day is only marginally higher (Table 6).

We further analysed subgroups with regards to mechanical ventilation (MV):[8] The cost difference was highly significant, both when case and control had undergone the procedure ($n = 223$, mean difference € 15,114) and when neither had been subjected to the treatment. However, in the latter case, the mean difference was only one-fifth of the former ($n = 657$, mean difference: € 3,010).[9]

[7] Here, we are at odds with Ho et al. [14], who claim that the choice of the matching algorithm is merely a mechanical decision of picking the one with the lowest bias (i.e. the best balance). This would require knowledge of which variables best represent the universe of the relevant pretreatment covariates—known to be measured or not. Also, there is more than one criterion for assessing the quality of the matching, and these do not always point in the same direction. The outcome, it is claimed, has no part to play in the decision as this could lead to "stacking the deck". While this danger is real, in our view the decision for one matching algorithm will always involve some judgment—even with regard to the plausibility of the estimated effects. Here, we present the results of different datasets to make the influence of our decision on the reported results as transparent as possible.

[8] We have chosen to carry out this subgroup analysis because MV is generously reimbursed in the G-DRG system. As reimbursement is based on average cost across the German hospital system, we decided that this subgroup merits closer analysis. MV is potentially associated with higher costs in a number of ways:

(1) MV increases length of stay.

(2) MV is an indicator of a more severe course of disease and is thus potentially associated with increased LOS and higher treatment costs.

(3) MV is a potential cause of nosocomial infection and its associated costs.

(4) According to G-DRG cost accounting regulations, some cost (nurses and medical technology) are apportioned to patients with mechanical ventilation using a much higher weighting factor for hours (e.g. 1.71) as compared to treatment (e.g. 1) or monitoring hours (e.g. 0.57) [6].

Unfortunately, in our retrospective study, we can neither determine the relative importance of these influences nor the direction of causation.

[9] Subgroups were analysed only in matching 1 for reasons of sample size. Also, we deem these results more accurate and thus present results from the second matching only to demonstrate the robustness of our overall results.

Table 4 Top 20 principal diagnoses and base diagnosis-related groups (DRGs) (matching 1)

Rank	Pairs				MRSA				Non-MRSA			
	ICD 3	Diagnosis	Percent	Cumulative percent	Base DRG	DRG name	Percent	Cumulative percent	Base DRG	DRG name	Percent	Cumulative percent
1	I70	Diseases of arteries, arterioles and capillaries	9.8	9.8	E77	Other infections and inflammations of the respiratory organs	4.9	4.9	E77	Other infections and inflammations of the respiratory organs	6.2	6.2
2	E10	Diabetes mellitus	6.7	16.6	A13	Artificial respiration >95 and <250 h	4.9	9.7	K60	Severe nutritional disturbance or diabetes	3.0	9.3
3	I60	Cerebrovascular diseases	5.2	21.7	A09	Artificial respiration >499 and <1,000 h	4.7	14.4	A13	Artificial respiration >95 and <250 h	2.8	12.1
4	C15	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue: digestive organs	5.0	26.7	A11	Artificial respiration >249 and <500 h	3.8	18.2	B70	Stroke	2.8	14.9
5	J10	Influenza and pneumonia	4.8	31.5	F21	Other circulatory system-related OR-procedures	3.4	21.6	T60	Septicaemia	2.6	17.5
6	A30	Other bacterial diseases	4.6	36.1	K01	Diverse OR-procedures with diabetes mellitus, with complications, without early rehabilitation, without early multidisciplinary geriatric rehabilitation	2.8	24.5	F59	Moderately complex vascular procedures without pump	2.5	20.1
7	I30	Other forms of heart disease	4.5	40.5	L63	Kidney and urinary tract infections	2.4	26.9	F62	Heart failure and shock	2.3	22.4
8	T80	Complications of surgical and medical care, not elsewhere classified	4.2	44.7	F62	Heart failure and shock	2.1	29.0	L63	Kidney and urinary tract infections	2.2	24.7
9	I20	Ischaemic heart disease	4.2	48.9	B70	Stroke	1.9	31.0	K01	Diverse OR-procedures with diabetes mellitus, with complications, without early rehabilitation, without early multidisciplinary geriatric rehabilitation	2.1	26.8

Table 4 continued

Rank	Pairs				MRSA				Non-MRSA			
	ICD 3	Diagnosis	Percent	Cumulative percent	Base DRG	DRG name	Percent	Cumulative percent	Base DRG	DRG name	Percent	Cumulative percent
10	K55	Other diseases of intestines	3.4	52.3	F28	Amputation in the case of vascular diseases, other than upper limb and toes, without vascular surgery, with severe or catastrophic CC	1.7	32.7	L60	Renal failure with dialysis	2.0	28.8
11	N17	Renal failure	3.0	55.4	J64	Cellulitis, erysipelas or other inflammation of the skin	1.6	34.2	A11	Artificial respiration >249 and <500 h	1.9	30.8
12	L80	Other disorders of the skin and subcutaneous tissue	2.6	58.0	T60	Septicaemia	1.6	35.8	J64	Cellulitis, erysipelas or other inflammation of the skin	1.9	32.7
13	K80	Disorders of gallbladder, biliary tract and pancreas	2.5	60.5	T01	OR-procedures with infectious or parasitic diseases	1.4	37.1	B02	Craniotomy	1.9	34.6
14	N30	Other diseases of urinary system	2.5	63.1	L60	Renal failure with dialysis	1.4	38.5	F21	Other circulatory system related OR-procedures	1.8	36.4
15	J60	Lung diseases due to external agents	2.1	65.2	K60	Severe nutritional disturbance or diabetes	1.3	39.8	F65	Peripheral vascular disorders	1.7	38.0
16	I80	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	1.9	67.2	E65	COPD	1.3	41.0	F54	Vascular procedures other than major reconstructive, without pump, without complicating procedures, without revision with catastrophic CC	1.6	39.6
17	S00	Injuries to the head	1.7	68.8	A07	Artificial respiration >999 and <1,800 h	1.3	42.3	G18	Digestive system OR-procedures	1.4	40.9
18	L00	Infections of the skin and subcutaneous tissue	1.5	70.3	G46	Gastroscopy with major digestive disease	1.3	43.6	E65	COPD	1.4	42.3
19	S70	Injuries to the hip and thigh	1.5	71.7	F34	Other major reconstructive vascular procedure without pump with catastrophic CC	1.2	44.7	G46	Gastroscopy with major digestive disease	1.4	43.7

Table 4 continued

Rank	Pairs				MRSA				Non-MRSA			
	ICD 3	Diagnosis	Percent	Cumulative percent	Base DRG	DRG name	Percent	Cumulative percent	Base DRG	DRG name	Percent	Cumulative percent
20	C30	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue: respiratory and intrathoracic organs	1.4	73.1	G18	Digestive system OR-procedures	1.2	45.9	G60	Digestive malignancy	1.3	44.9

CC Complications and comorbidities, *OR* operating room, *COPD* chronic obstructive pulmonary disease

Table 5 Comparison of rates of mechanical ventilation (%) and mortality (%) (by matching procedure)

	Matching1		Matching 2	
	MRSA		MRSA	
	Yes	No	Yes	No
Mechanical ventilation (%)	32.6	25.1	27.7	21.5
Deceased (%)	18.3	10.9	14.0	4.9

Table 6 Means and mean differences for length of stay, cost, and hours of ventilation for MRSA patients and respective controls (by matching)

Paired sample differences						
	MRSA		Paired differences		*N*	Significance (2-tailed)
	Yes Mean	No Mean	Mean	SD		
Matching 1						
Length of stay	26	15	11	25	1,026	0.000
Total cost	16,024	7,825	8,198	19,403	1,026	0.000
Cost per day	583	556	28	482	1,026	0.066
Hours of ventilation	86	26	60	242	1,026	0.000
Matching 2						
Length of stay	23	12	11	23	549	0.000
Total cost	13,762	6,505	7,257	17,572	549	0.000
Cost per day	563	550	12	586	549	0.623
Hours of ventilation	65	22	43	207	549	0.000

Similarly, MRSA was associated with longer average stays in hospital. This effect, too, was more pronounced for the pairs requiring MV (mean difference: 19 days) than for those not requiring the procedure (7 days).

Discussion

Our analysis based on secondary data showed that MRSA is associated with significantly higher LOS, mortality, and total costs even when controlling for a number of medical and organisational influences. The exact figures vary across hospitals, but the results remain substantially the same. Within the framework of the DRG data, the increased total cost for an MRSA versus a non-MRSA patient could be attributed to prolonged stay in hospital, whereas costs per day are not increased significantly.

Another significant cost driver associated with MRSA is mechanical ventilation (MV). MRSA cases are more likely to undergo this costly procedure and, on average, for longer

hours. When MV is present, the differences in LOS and total cost between treated and controls are greater.

How valid are these findings? The quality of our results is dependent on (1) the quality of the hospitals' data, and (2) the degree to which the matching procedure has reduced bias and controlled for confounding.

Regarding (1), the quality of the data, it should be noted that German hospitals do not use real cost unit accounting. A large part of the costs are apportioned using a common set of methodologies that aim at comparability but still leave some room for hospital-specific differences [6]. Although direct costs that exceed a certain amount, such as expensive antibiotics, are allocated directly to the patient, others are not. Nursing costs and inexpensive drugs on regular wards, for instance, are allocated using a measure called 'PPR-minutes', an indicator of nursing time and nursing effort. The system effectively caps the maximum attributable cost for any given patient. Costs for doctors on a regular ward and indirect costs are apportioned according to the LOS and the cost of intensive care according to the hours in intensive care. As a consequence, intensive resource use allocated to MRSA patients may not be exhaustively reflected within the framework of the G-DRG system.

In our view, these data quality problems do not invalidate our primary finding that MRSA patients suffer from worse outcomes and cause substantially higher costs. The above mentioned problems do, however, make it difficult to estimate the exact cost increment and to discern the causes. For the reasons outlined, we take our results to be conservative estimates, but acknowledge that true numbers may be substantially higher.

Also, as there are no time stamps for diagnoses in the data, MRSA cannot be considered as the sole cause of the prolonged LOS and ventilation time. There are multiple plausible causal connections between the three variables that can be clarified definitively only in a prospective study.

It is sometimes also claimed that hospitals incur opportunity costs because isolated MRSA patients block two-bed rooms [10]. This cost cannot be reflected in our data as the datasets used—by definition—contain only the cost of cases that were actually treated, not reimbursements that could have been acquired by treating more patients.

Moreover, our data do not allow discrimination between manifest infections or "simple" colonisation. This will have a diluting effect on the analysis of manifest MRSA infections. The strength of this effect will, however, differ for different dimensions of outcome: colonisation might already lead to costly eradication and isolation procedures and an increase in LOS. Thus, the cost difference between colonisation and infection may be low. The difference in mortality, in comparison, can be expected to be higher, and our estimate may thus have been reduced considerably.

Regarding problem (2), the validity of the results is critically linked to the question of whether bias and confounding could be adequately controlled by matching. Firstly, as mentioned above, matching can control for bias/confounding only if confounding variables are measured. Empirically, Austin et al. [1] have shown that matching using administrative data does not necessarily balance unmeasured clinical variables. As a consequence, treatment effects in this analysis were exaggerated. The same mechanism could potentially lead to an inflation of the differences found between MRSA and control, if missing information led to MRSA patients being matched with healthier controls.

Secondly, matching could be inadequate in some other way, by assigning overly ill or less afflicted controls to MRSA cases. This could both inflate or reduce the impact of bias in the analysis. In particular, the mean CCL value will in part be influenced by an MRSA infection. Consequently, by using the mean CCL of co-morbidities, a patient will be assigned to a match partner who is more severely ill than the patient was before the MRSA infection. However, it is noteworthy that even though the CCL-bias is higher in the second matched dataset, the cost difference is not.

Still, it cannot be ruled out entirely that the two approaches to control for bias (or sources of additional bias) have altered the results somewhat. However, the two tendencies discussed above might plausibly have worked in opposite directions, balancing each other. Furthermore, and more importantly, it is worth pointing out the robustness of the results achieved by using two different approaches to matching.

Conclusions and recommendations

We have demonstrated that MRSA patients stay in hospital longer, show higher mortality, are more likely to undergo MV and, if they do, for longer hours. MRSA patients also cause substantially and significantly higher costs.

Our results are in line with earlier studies, e.g. [10, 12, 13, 18]. In particular, the increments of LOS, total costs, and mortality are all within the 1.3- to 2-fold range identified by the majority of other studies [4]. The German Government's cost estimate based on information from the Robert-Koch-Institute (€ 1,600–10,000) is also consistent with our findings [20]. The increase in absolute mortality risk of about 7.4% is slightly higher than Noskin et al.'s [19] estimates of, on average, 3.4–4.0% (depending on the method). To validate the exact estimates and the underlying causes, a prospective study recording time stamps for diagnoses and a detailed collection of resources used and costs incurred is necessary.

Table 7 Projection of total costs caused by MRSA infections in German hospitals based on epidemiological data (prevalence) and results from our study (costs)

Total number of hospital cases 2004[a]	16,627,206
Prevalence of MRSA 2004[b]	0.56%
Estimated number of MRSA cases in population	92,891
Incremental cost per MRSA case	€ 8,198
Estimated total cost increment from MRSA	€ 761,516,569

[a] Inpatients with LOS 1 day and over; source: federal health monitoring

[b] Authors' calculation based on [17]

Based on our results, the total burden for German hospitals can be estimated at around € 761.5 million annually (Table 7). As our sample is not representative of the population of German hospital cases, this must be considered a rough estimate.

Until recently, the G-DRG system did not reimburse hospitals for their costs associated with MRSA. With recent changes to the system, this information and this cost will now be relevant for the reimbursement of hospital cases.

In Germany, several actions to reduce infections and costs similar to the Dutch "Search and Destroy" model are currently being discussed or have already been implemented. There is evidence that preventative screenings of high-risk patients tend to be less expensive than treatment of MRSA infections and their consequences [3, 8, 13, 16, 24, 25]. Given the consequences of MRSA infections in terms of mortality and morbidity, both prevention of MRSA as well as the best available treatment of MRSA-infected patients are necessary.

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