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# Consumption of anti-meticillin-resistant *Staphylococcus aureus* antibiotics in Swiss hospitals is associated with antibiotic stewardship measures

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SUMMARY

***Background:*** Consumption of antibiotics active against meticillin-resistant *Staphylococcus aureus* (MRSA) has been described in numerous European studies. However, the underlying predictors of consumption are still poorly understood.

***Aim:*** To describe the consumption of anti-MRSA antibiotics (daptomycin, intravenous glycopeptides, linezolid) in Switzerland over time and to identify underlying predictor variables.

***Methods:*** A retrospective observational multi-centre study was conducted in 21 Swiss hospitals over a period of 11 years (2009–2019). Multiple linear regression models were built to identify regional and hospital-specific predictor variables affecting the consumption of anti-MRSA antibiotics.

***Findings:*** Consumption of anti-MRSA antibiotics increased between 2009 and 2019 from 12.7 to 24.5 defined daily doses per 1000 bed-days (+93%). In the first model presented, which includes data of the whole study period, the following variables were associated with higher anti-MRSA antibiotic consumption: number of MRSA cases ($P < 0.01$), year ($P < 0.01$), hospital type (tertiary care university hospitals vs others, $P < 0.01$), hospital department (intensive care unit vs others, $P < 0.01$) and linguistic region (French vs German and German vs Italian, $P < 0.01$). In a second model including data from a query on hospital policies in place in 2019, the presence of an antibiotic stewardship group ($P < 0.01$) and prescription restrictions ($P < 0.01$) were associated with consumption of anti-MRSA antibiotics.

***Conclusion:*** Our study shows that both the presence of an antibiotic stewardship group and the implementation of prescription restrictions, i.e. factors that can be controlled by the hospital itself, were associated with a lower consumption of anti-MRSA antibiotics.



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## Introduction

*Staphylococcus aureus* was reported to be the second most frequent micro-organism causing healthcare-associated infections in Europe in 2017, causing sepsis, cardiac valve infection, and joint, bone, wound, and soft tissue infections [1]. Approximately 50% of the population are nasal carriers, and they are widely disseminated [2]. Infections with meticillin-resistant *Staphylococcus aureus* (MRSA), resistant against all classical β-lactams, including combinations with β-lactam inhibitors, represent a high risk, especially for seriously ill and immunocompromised patients, and are therefore a serious threat in hospitals worldwide. Despite decreasing MRSA rates, deaths attributable to MRSA infections increased by a factor of 1.38–6810 yearly deaths in Europe between 2007 and 2015 [3]. By causing 32.6 disability-adjusted life-years (DALYs) per 100,000 individuals, MRSA ranked second of all DALYs attributed to infections with antimicrobial-resistant bacteria in the European Union (EU) and European Economic Area (EEA) and ranked third in Switzerland (8.9 DALYs per 100,000 individuals [4]). For different linguistic regions in Switzerland, both decreasing and slightly increasing MRSA rates were described [5]. In 2019, the MRSA rate in Switzerland was 3.4%, with slightly higher rates in southern and western Switzerland [6].

The emergence and spread of antimicrobial resistance are favoured by antibiotic therapy through evolutionary pressure [7–9]. Surveillance of antibiotic consumption is a crucial element in 'antibiotic stewardship', and it has been shown that optimizing the use of antibiotics may prevent the spread of resistant bacteria [10].

Daptomycin, glycopeptides (vancomycin and teicoplanin), linezolid, tigecycline, clindamycin, trimethoprim–sulfamethoxazole, fosfomycin, ceftobiprole, and ceftaroline are known to be biologically active against MRSA [11,12]. However, intravenous glycopeptides and the reserve antibiotics daptomycin and linezolid are the only effective options for the treatment of MRSA bacteraemia. While intravenous glycopeptides are mainly used against MRSA, daptomycin and linezolid may also be used against vancomycin-resistant enterococci (VRE). Due to these properties, we restrict our analysis to the glycopeptides daptomycin and linezolid, referred to hereinafter as 'anti-MRSA antibiotics'.

Therapy with intravenous glycopeptides, which are known for their relatively complex handling and toxicity, was the only effective treatment against MRSA bacteraemia until the introduction of linezolid in Switzerland in 2001. The introduction of daptomycin followed in 2007. Daptomycin and linezolid are comparable in their effectiveness, whereas the incidence of thrombocytopenia is higher under linezolid [13,14]. The potential effect of the introduction of daptomycin on the consumption of glycopeptides and linezolid has not yet been studied in Switzerland.

For different European countries, both increasing and decreasing trends in consumption of anti-MRSA antibiotics have been described for the period from 2010 to 2019 [15]. However, to the best of our knowledge, the underlying predictors of these long-term processes have only been studied to a limited extent for glycopeptides.

The aims of this study were: (i) to describe the consumption of anti-MRSA antibiotics in 21 Swiss hospitals from 2009 to 2019; (ii) to identify underlying predicting parameters; and (iii) to include hospital policy-dependent predictors such as antibiotic stewardship policies in a second model for 2019 only.

## Methods

### Design and study population

A retrospective observational multi-centre study was conducted with data from 21 Swiss hospitals over a period of 11 years (2009–2019). To homogenize the dataset, analysis was restricted to hospitals with more than 200 beds and data availability for at least two years within the study period.

### Data collection and processing

Antibiotic consumption and resistance data were obtained from the Swiss Centre for Antibiotic Resistance (ANRESIS) database. ANRESIS is a representative surveillance system that continuously collects national data on antibiotic use and antibiotic resistance.

Yearly antibiotic consumption was described in defined daily doses (DDD) per 1000 bed-days (BD) and reflects the amount of antibiotics delivered from the hospital pharmacy to individual departments [16].

MRSA was defined as *Staphylococcus aureus* non-susceptible to at least one of the following antibiotics: meticillin, oxacillin, flucloxacillin, or cefoxitin. VRE was defined as *Enterococcus faecalis* or *Enterococcus faecium* non-susceptible to vancomycin. Analyses were restricted to isolates from sterile sites, surrogating invasive infections. Isolates obtained within 30 days after the first positive result for the same patient at the same hospital were considered duplicate and were excluded. Incidence is given by the number of invasive infections per 1000 bed-days. To obtain data on the 2019 hospital policies (i.e. availability of guidelines for the treatment of MRSA infections and restrictions for the use of daptomycin, glycopeptides and linezolid), a short online questionnaire (Survs®, https://survs.com/) was sent to the infectious diseases specialists at participating hospitals).

### Statistical models

A multiple linear regression model was developed to identify predictor variables contributing to the consumption of anti-MRSA antibiotics (DDD/1000 BD) from 2009 to 2019 ('model 1'). The following predictor variables were included in the initial model: MRSA incidence, VRE incidence, time (i.e. the years), hospital type (university vs non-university hospital), linguistic region (see details below) and intensive care unit (ICU) vs non-ICU department. The initial model, which included all predictor variables, was transformed logarithmically to meet the assumptions for linear regression. The likelihood ratio test ($\chi^2$ statistics) was then used in a backwards elimination process ($P < 0.05$ to retain) to select the set of independent variables for the final model.

The German-speaking region was used as a reference in comparisons of the three-level factor linguistic region. To analyse differences between the French- and Italian-speaking regions, the French-speaking region was additionally used as a reference.

### *Analysis of hospital policies in 2019*

To improve the regression model, we included parameters of the hospital policies into an additional model ('model 2'). Data for this model were restricted to the year 2019, as data on hospital policies were available for this year only. Additional dichotomous ('yes'/'no') predictor variables included in this model were the presence of an antibiotic stewardship group (ABS group), meeting at least three times yearly, availability of internal guidelines for treatment of MRSA infections, pre-existing written restrictions in prescription of anti-MRSA antibiotics, recommendation of glycopeptides as the first choice for empirical treatment of severe skin and soft-tissue infections, and routine testing of daptomycin resistance. The questions which led to these variables where added to the supplement (Survey Questions for Analysis 2019). The initial model, which included all predictor variables, was transformed logarithmically to meet the assumptions for linear regression. The likelihood ratio test ($\chi^2$ statistics) was then used in a backwards elimination process ($P < 0.05$ to retain) to select the set of independent variables for the final model.

All analyses and visualizations were performed with R software (version 3.6.1, R Core Team, Vienna, Austria).

## Results

### *Temporal and regional patterns from 2009 to 2019*

Total consumption of anti-MRSA antibiotics increased significantly ($P < 0.01$) from 2009 to 2019 in Switzerland (Table I). Consumption increased from 12.7 to 24.5 DDD/1000 BD (+93%) between 2009 and 2019, with the highest increase observed between 2009 and 2013 (up to 22.2 DDD/1000 BD, +75%). Increases were observed for all anti-MRSA antibiotics (glycopeptides 11.2 to 16.9 (+51%), daptomycin 1.4 to 7.9 (+400%), and linezolid 0.51 to 0.67 DDD/1000 BD (+31%)) (Figure 1). The percentage of daptomycin in the total consumption of anti-MRSA antibiotics increased from 9% in 2009 to 28% in 2019, whereas the proportion of glycopeptides decreased from 87% to 70% and that of linezolid decreased slightly from 4% to 2.7%.

The results of model 1 showed that the number of MRSA infections was positively associated with the consumption of anti-MRSA antibiotics ($P < 0.01$, Table I). Consumption was significantly higher in ICU departments than in non-ICU departments ($P < 0.01$, Figure 2). Conversely, the effect of MRSA incidence on consumption was lower in ICU departments than in non-ICU departments ($P < 0.01$). Further predictor variables were hospital type ($P < 0.01$) and linguistic region ($P < 0.01$). VRE incidence was not associated with the consumption of anti-MRSA antibiotics.

Consumption increased in all settings over time, with the exception of French-speaking university hospitals (Supplementary Table A1, Figure 2).

MRSA incidence decreased from 0.085 to 0.076 invasive infections/1000 BD (−11%) between 2009 and 2019, with the largest decrease between 2009 and 2013 (−22%). Remarkably, the incidence of MRSA decreased in university hospitals in the French-speaking region only (from 0.26 to 0.11 invasive infections/1000 BD, −58%), whereas increasing incidences were observed in the other linguistic-hospital type combinations (Supplementary Table A2, Figure 2). In ICU departments, MRSA incidence was consistently higher than that in non-ICU departments.

**Table I**
Predictor variables of a model describing the consumption of anti-MRSA antibiotics [$\log_{10}$(DDD/1000 BD)] in Switzerland from 2009 to 2019

| Variable | Estimate[a] | 95% CI | *P*-value |
|---|---|---|---|
| Year | 0.04 | (0.02, 0.05) | <0.001 |
| MRSA incidence | 1.02 | (0.89, 1.16) | <0.001 |
| ICU vs non-ICU | 0.68 | (0.51, 0.84) | <0.001 |
| University vs non-university hospital | 0.39 | (0.25, 0.53) | <0.001 |
| French vs German | 1.34 | (1.21, 1.46) | <0.001 |
| Italian vs German | 2.22 | (0.88, 3.55) | 0.001 |
| MRSA and ICU interaction | −0.78 | (−1.01, −0.55) | <0.001 |
| University and French interaction | −1.88 | (−3.2, −0.55) | 0.006 |
| VRE incidence | No association[b] | | |
| $R^2$/adjusted $R^2$ | 0.731/0.725 | | |
| *F*-statistic | 130.2 | | <1 E-15 |

MRSA, meticillin-resistant *Staphylococcus aureus*; DDD, defined daily doses; BD, bed-days; CI, confidence interval; ICU, intensive care unit; VRE, vancomycin-resistant enterococci.
[a] Negative sign indicates a negative association.
[b] Variable does not improve the model (likelihood ratio $\chi^2$-statistic, $P > 0.05$).

### *Survey results for hospital policies in 2019*

Nineteen out of 21 hospitals sent consumption data for 2019; 15 (79%) responded to the 2019 survey on hospital policies (11/13 from the German-, 4/4 from the French- and 0/2 from the Italian-speaking region). An infectious disease (ID) specialist was on-site at each participating hospital, and antibiotic stewardship groups who met at least three times yearly existed in eight (53%) of all hospitals. Guidelines concerning antibiotics in general were available in 14 out of 15 (93%) hospitals, whereas specific guidelines on MRSA and VRE

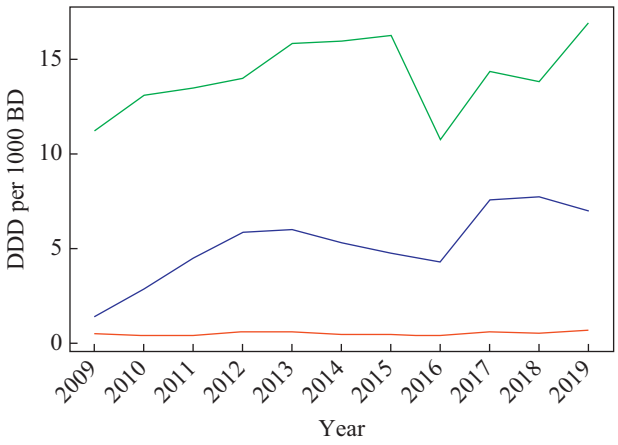


**Figure 1.** Consumption of the anti-MRSA antibiotics (defined daily doses (DDD) per 1000 bed-days) daptomycin (blue), glycopeptides (intravenous vancomycin, teicoplanin, green) and linezolid (red) in 21 Swiss hospitals between 2009 and 2019.

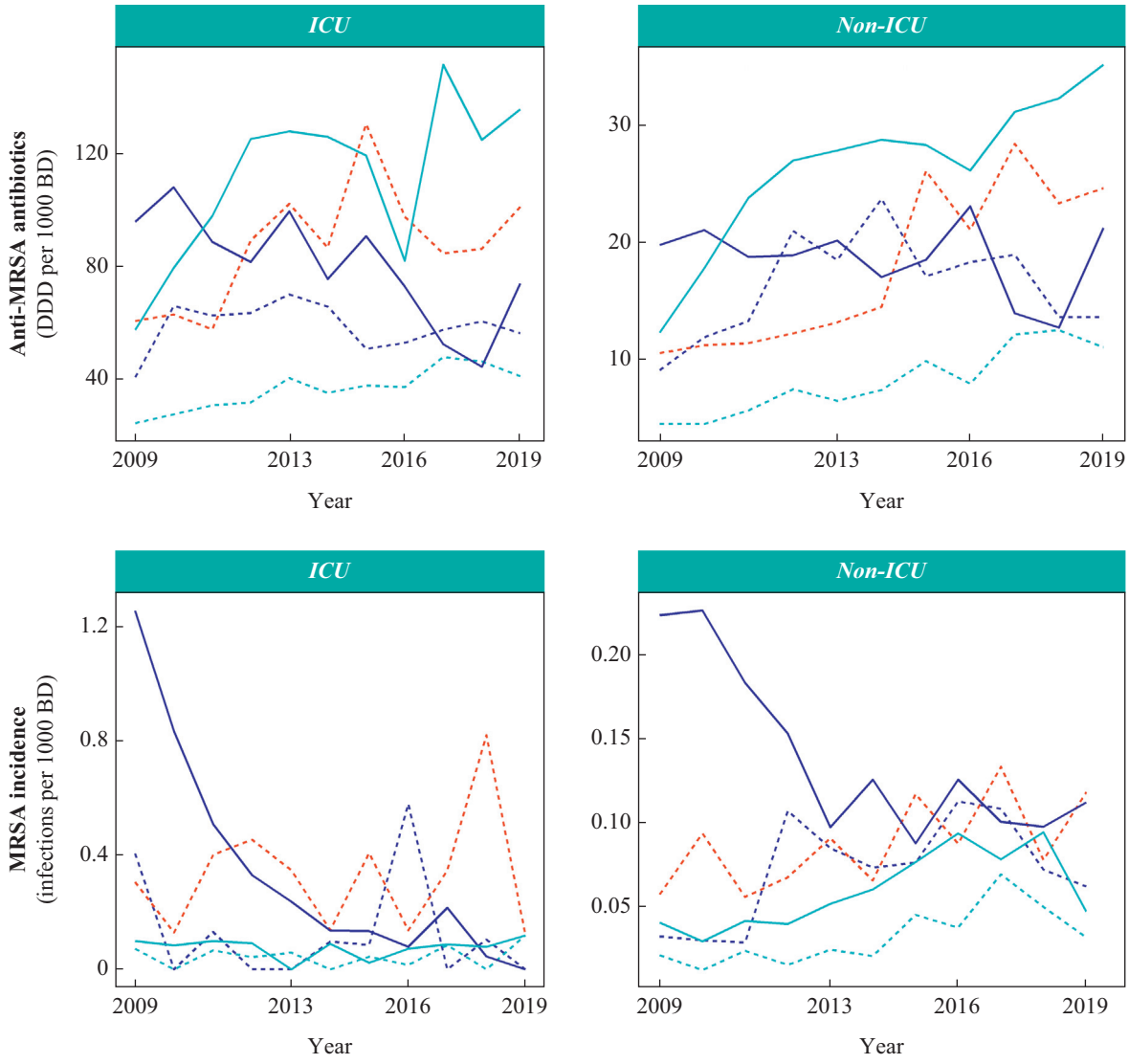


**Figure 2.** Median consumption of anti-MRSA antibiotics (defined daily doses (DDD) per 1000 bed-days (BD), upper panels) and MRSA incidence (invasive infections per 1000 bed-days, lower panels) in university (solid line) and non-university (dashed line) hospitals of the French-speaking (dark blue), German-speaking (light blue) and Italian-speaking (red) regions of Switzerland between 2009 and 2019 in intensive care unit (ICU) (left panels) and non-ICU departments (right panels).

treatments were available in eight (53%) and four (27%) of all hospitals, respectively. However, in four out of 11 (36%) hospitals without MRSA/VRE guidelines, a consultation from an ID specialist was automatically triggered after an MRSA or VRE infection. In one out of 15 hospitals (7%) a limitation in treatment days for intravenous glycopeptides was in place. More hospitals had restrictions on prescriptions for daptomycin (87%) than on those for linezolid (80%) or glycopeptides (27%). Common restrictions included an obligation to consult an ID specialist or the chief physician before prescription of anti-MRSA antibiotics or automatic limitation of the treatment duration. Other restrictions were the consultation of an ID specialist or validation by a clinical pharmacist. The recommended daily daptomycin doses for the treatment of skin and soft tissue infections ranged between 4 and 10 mg/kg body weight (BW). The recommended dosage in university hospitals was higher, with a median of 8 mg/kg BW (interquartile range: 6–8 mg/kg BW), than that in non-university hospitals, with a median of 6 mg/kg BW (interquartile range: 4.5–6 mg/kg BW).

The hospital policy-dependent predictor variables, namely, existing antibiotic stewardship group meeting at least three times yearly and pre-defined restrictions on prescriptions, were significantly (each $P < 0.01$) associated with lower consumption of anti-MRSA antibiotics in 2019 (Table II, Figure 3). Overall, the hospital policy-dependent factors explained 44% of the variability explained by this model.

All hospitals had either an existing antibiotic stewardship group, restrictions in prescription of anti-MRSA antibiotics, or both. Restrictions could not be specified further due to multicollinearity of different restriction types.

Except for hospital type and ICU vs non-ICU department, none of the predictors included in the initial model, including linguistic regions and MRSA incidence, were significantly associated with consumption of anti-MRSA antibiotics (Table II).

**Table II**
Predictor variables, including hospital policies, of a model describing the consumption of anti-MRSA antibiotics [$\log_{10}$(DDD/1000 BD)] in Switzerland in 2019

| Variable | Estimate[a] | 95% CI | *P*-value |
|---|---|---|---|
| University vs non-university hospital | 1.15 | (0.71, 1.6) | <0.001 |
| ICU vs non-ICU | 1.01 | (0.62, 1.4) | <0.001 |
| ABS group vs none | −0.71 | (−1.15, −0.26) | 0.003 |
| Restrictions[b] vs none | −0.97 | (−1.59, −0.36) | 0.003 |
| French vs German | No association[c] | | |
| MRSA incidence | No association[c] | | |
| VRE incidence | No association[c] | | |
| Internal MRSA guidelines vs none | No association[c] | | |
| Daptomycin resistance testing routinely vs not | No association[c] | | |
| First choice for empirical therapy[d] (yes vs no) | No association[c] | | |
| Physicians in hospital hygiene/500 beds | No association[c] | | |
| $R^2$/adjusted $R^2$ | 0.73/0.687 | | |
| *F*-statistic | 16.93 | | <1 E-06 |

MRSA, meticillin-resistant *Staphylococcus aureus*; DDD, defined daily doses; BD, bed-days; CI, confidence interval; ICU, intensive care unit; VRE, vancomycin-resistant enterococci.
ABS group: antibiotic stewardship group present with regular meetings (>3 times a year).
[a] Negative sign indicates a negative association.
[b] Restrictions on the prescription of anti-MRSA antibiotics.
[c] Variable does not improve the model (likelihood ratio $\chi^2$-statistic, $P > 0.05$).
[d] Glycopeptides as the first choice for empirical therapy of skin and soft-tissue infections.

## Discussion

Increasing consumption was observed for all anti-MRSA antibiotics, despite decreasing MRSA incidences in Switzerland between 2009 and 2019. Remarkably, the use of daptomycin, which was introduced in 2007, did not replace the use of glycopeptides (Figure 1). This finding is in contrast to observations from France and Italy, where decreased glycopeptides consumption was observed after the introduction of daptomycin [17]. Similar trends as in Switzerland, i.e. no reduction in glycopeptides consumption despite increasing consumption of new MRSA antibiotics (daptomycin, linezolid) and stable MRSA rates, were described in Spain between 2007 and 2012 [18]. However, according to stratified Swiss data, the overall decrease in MRSA incidence was caused solely by French-speaking university hospitals, in which consumption of anti-MRSA antibiotics was stable. In other regions, both the MRSA incidence and consumption of anti-MRSA antibiotics increased.

The finding that the consumption of anti-MRSA antibiotics in the French- and Italian speaking parts of Switzerland was higher than that in German-speaking regions may be explained by socio-cultural factors and by higher MRSA rates in neighbouring countries (2019: Italy 35.6%, France 11.6%, Germany 6.7%), as patients and medical staff exchange across the national borders [19–21]. Different MRSA rates, as well as different background of treating physicians, both influence prescription of anti-MRSA antibiotics which always is a balance between avoiding risks for the patient and avoiding resistance development. Development and advertisement of own national guidelines could help to further reduce these differences. Similar consumption patterns within Switzerland were described by Plüss-Suard *et al.* for vancomycin between 2004 and 2008 [22].

The consumption of anti-MRSA antibiotics in university hospitals was higher than that in non-university hospitals. In addition to the higher MRSA rates observed in French university hospitals only, the higher consumption in university hospitals is probably caused by the more severe and complex cases accommodated in higher-level-of-care hospitals, assuming that critically ill patients are more likely to be treated with anti-MRSA antibiotics [23]. This also holds true for the higher consumption in Swiss ICU compared to non-ICU departments observed in our study. These findings are consistent with those of previous studies in Germany, which described higher glycopeptide consumption in ICU compared to non-ICU departments and in university compared to non-university hospitals [24,25].

Our data reveal large variations in both MRSA incidence and consumption of anti-MRSA antibiotics at the regional, hospital, and even departmental levels (Supplementary Figure A1). Seventy-three percent of the variance in consumption was explained by different predictor variables, including MRSA incidence and the interaction between MRSA incidence and department. An analogous positive association between MRSA incidence and consumption of glycopeptides was observed in France during a single year in 2002, but the interaction between MRSA incidence and department type was not analysed [26].

In our study, the effect of the number of MRSA infections on the consumption of anti-MRSA antibiotics was more pronounced in non-ICU departments than in ICU departments. This could be explained by the early transfer of patients to the non-ICU department for prolonged antibiotic therapy after initial stabilization in the ICU. Further considering the critical condition of ICU patients, it is likely that they more frequently receive anti-MRSA antibiotics while awaiting microbiological results.

The VRE incidence in Switzerland is low. The absence of a significant association between VRE incidence and the consumption of anti-MRSA antibiotics should therefore be interpreted with care.

Since our data still showed considerable differences in the consumption of anti-MRSA antibiotics within otherwise comparable hospitals, we developed an advanced model including data on hospital policies. This model was restricted to data from 2019, as hospital policy data were available for this year only. In this model, 44% of the explained variability in consumption was due to prescription restrictions and the establishment of regular meetings of an antibiotic stewardship group. This positive effect is in line with the findings of Borde *et al.*, who reported a decline and optimization in the use of daptomycin after starting an antibiotic stewardship

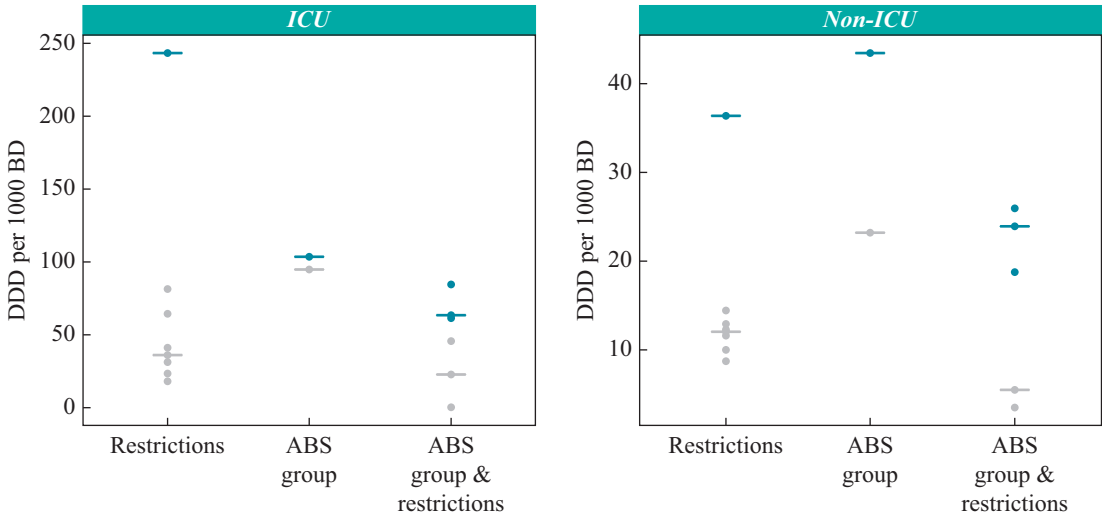


**Figure 3.** Association of antibiotic stewardship group (ABS), restrictions on the prescription of anti-MRSA antibiotics (Restrictions) or both (ABS group & Restrictions) with the consumption of anti-MRSA antibiotics (defined daily doses (DDD) per 1000 bed-days) in 15 Swiss university (turquoise) and non-university (grey) hospitals in 2019. Both individual data points and group medians (lines) are shown. Consumption data were grouped per intensive care unit (ICU) (left panel) and non-ICU department (right panel).

programme [27]. In our study, we did not analyse the effects of the optimized use of anti-MRSA antibiotics, but, as suggested by other studies, these interventions may not only reduce resistance rates but also decrease patient harm due to side-effects, mortality, and costs [27,28].

In contrast to the whole study period, variability in consumption of anti-MRSA antibiotics between hospitals was not explained by MRSA incidence in 2019. This may be explained by lower MRSA incidence and especially lower variance in MRSA incidence but comparable variance in consumption of anti-MRSA antibiotics compared to the whole study period. In addition, in model 1 the difference to the previous year was considered by the variable time (year) which could not be considered in model 2. Further, the statistical power was weaker in model 2, due to smaller dataset.

Our study has several limitations. First, the two models are not directly comparable, as only data from 2019 could be included in model 2. However, both models fit well ($R^2 = 0.73$ each), and we assume that continuous surveillance of hospital policies could even improve our model. Second, data were grouped by department level. The inclusion of patient-specific data could essentially improve these models. With the introduction of electronic prescriptions, such an analysis will be possible in the future. Third, MRSA cases were not confirmed by a central laboratory; however, all participating laboratories use Clinical and Laboratory Standards Institute or European Committee on Antimicrobial Susceptibility Testing guidelines and are accredited by the Swiss government.

The main strength of our study is the extensive data collection, covering 11 years and all university and tertiary hospitals in Switzerland. In addition, Switzerland uniquely allows stratification into different linguistic and socio-cultural regions within a single country. To the best of our knowledge, this is the first multi-centre study investigating hospital policy-dependent predictors for the use of anti-MRSA antibiotics.

In conclusion, we found that daptomycin, when introduced, did not replace glycopeptides, since consumption of all anti-MRSA antibiotics examined in this study increased in Switzerland. It can also be concluded that, in addition to MRSA incidence, both regional factors and hospital type affect anti-MRSA antibiotic consumption, as significantly higher values were found in the French- and Italian-speaking regions than in the German-speaking region and in university hospitals than in non-university hospitals. Considering antibiotic stewardship policies, the presence of an antibiotic-stewardship group and the implementation of prescription restrictions were associated with a lower consumption of anti-MRSA antibiotics. Therefore, appointing an antibiotic stewardship group in addition to implementing restrictions in prescription for anti-MRSA antibiotics should be recommended.

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**Conflict of interest statement**
None declared.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.08.019.

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