Antimicrobial stewardship experiences in acute-care hospitals of Northern Italy: Assessment of structure, process and outcome indicators, 2017-2019

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Highlights

- We assessed AMS programs of acute-care trusts of the region of Piedmont, Italy.

- All trusts implemented AMS, with varying levels of organization and delivery.

- Higher scores were found for process vs. structure indicators.

- Outcome indicator results suggest improvements in quality of care.

- A significant correlation between AMS structure and improved outcomes was found.

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Abstract

Background. Antimicrobial stewardship (AMS) programs are effective strategies for optimizing antimicrobial use. We aimed to assess AMS programs implemented in acute-care trusts of the region of Piedmont, Northern Italy.

Methods. AMS programs were investigated via a survey addressing structure, process and outcome indicators. For outcome indicators, annual means for the years 2017-2019 were considered, as well as the percentage change between 2017 and 2019. Outcome indicators were investigated in relation to structure and process scores using Spearman correlation.

Results. In total, 25 AMS programs were surveyed. Higher scores were achieved for process over structure indicators. Improvements in alcohol-based handrub usage (+30%), total antimicrobial usage (-4%), and percentages of MRSA and carbapenem-resistant Enterobacteriaceae (CRE) over invasive isolates (respectively -16 and -23%) were found between 2017 and 2019. Significant correlations were found between structure score and percentage change in total antimicrobial usage and CRE over invasive isolates (Spearman's ρ -0.603, p 0.006 and ρ -0.433, p 0.044 respectively).

Discussion. This study identified areas for improvement: accountability, microbiological laboratory quality management and feedback to clinicians. Improving the organization of AMS programs in particular should be prioritized.

Conclusion. Repeated measurements of structure and process indicators will be important to guide continuing quality improvement efforts.

Keywords: antimicrobial stewardship; quality indicators; antimicrobial usage; antimicrobial resistance; quality improvement; Italy

Background

The increasing spread of antimicrobial resistance (AMR) represents a global public health threat, and a significant challenge for healthcare delivery.[1,2] Inappropriate or excessive antibiotic use are important drivers of AMR, due to the ecological impact of these agents. Further, exposure to antibiotics increases the risk of adverse events, drug interactions, and developing *Clostridiodes difficile* infections.[3,4] Therefore, developing strategies to promote the appropriate use of antibiotics is of critical importance to reduce the selective pressure for the emergence of AMR and to increase patient safety. Appropriate antibiotic use involves a methodologic approach, which requires taking into account epidemiological, microbiological, clinical and pharmacological data. Antimicrobial stewardship (AMS) programs have proven to be effective and cost-effective strategies for optimizing antimicrobial use.[5] By definition, AMS interventions are a coherent set of actions

aiming to promote responsible antibiotic use, in order to achieve effective treatment or reduce the

probability of infection, while minimizing adverse consequences including AMR.[6]

Italy ranks among the highest consumers of antibiotics and broad-spectrum antibiotics in Europe.[7] A

national survey conducted in 2016 estimated a prevalence of antimicrobial use of 44.5% in Italian

acute-care hospitals, significantly higher than the European prevalence for the same year (30.5%).[7,8]

Italian AMR rates are also among the highest in Europe, with several AMR pathogens having

reached hyper-endemic levels.[9,10] The first Italian national action plan to contrast AMR (PNCAR),

issued in 2017, identified reducing the selective pressure for AMR and preserving the effectiveness

of antibiotics as urgent priorities. The national plan placed promoting appropriate antibiotic use

high among its objectives, underlining the importance of AMS programs. In particular, the plan

listed developing setting-specific and sustainable AMS programs among its short-term aims, and

commissioned regional health departments to report on the organization of AMS programs in each

region.[9]

The provision of healthcare in Italy is guaranteed through the National Health Service, with a

regionalized structure of healthcare management and delivery. Regional governments, through their

respective health departments, are responsible for planning, organizing, managing and ensuring the

delivery of health services. The implementation of policies such as those outlined in the national

action plan is formally devolved to the regional health departments.[11] Despite being recommended

by the National Prevention Plan, AMS programs are currently not mandatory in Italy. While at the

local level most Italian acute-care trusts have enacted some form of AMS intervention, few data are

available on the organization and effectiveness of these programs, particularly at the health system

level.[12,13]

In the region of Piedmont, in Northern Italy, AMS programs have been formally monitored since

2011. Following the recommendations of the national action plan, surrogate outcome measures

relevant to AMS programs have also been recorded since 2017. Ahead of the publication of the

updated national action plan, we aimed to assess key aspects of AMS programs implemented in acute-care trusts of the region of Piedmont, in order to compare progress across the region and to identify ongoing challenges and areas for improvement. A second objective of this study was to evaluate changes in three outcome measures against a score we attributed to structural and functional elements of AMS programs, to investigate whether these could represent appropriate metrics to evaluate the effectiveness of AMS programs.

Methods

Study design and data collection

AMS programs operating in acute-care trusts in the region of Piedmont were investigated via a survey conducted between May and June 2021. The survey was part of a wider healthcare-associated infections (HAI) and AMR prevention and control program, which is promoted annually by the regional health department and requires all public trusts to report data on indicators of HAI and AMR prevention and control activities. The 2021 edition of the HAI and AMR program collected data for the year 2019, with a lag due to the COVID-19 pandemic. Private and not-for-profit hospitals are also allowed to participate, on a voluntary basis. All 18 public health trusts of the region of Piedmont, consisting of a total of 49 hospitals, and 6 private and not-for-profit institutions regularly participating in the wider regional program were invited to complete the survey. If several hospitals in a trust implemented the same AMS program, only one response was required. The survey was sent to the Medical Direction of each hospital or trust, and completed by infection control personnel involved in the implementation of the AMS programs: infection control nurses, consultants in infectious diseases and hygiene, hospital management staff, and hospital pharmacists.

The survey addressed characteristics of AMS programs, divided into structure and process quality indicators, through a series of open and closed questions. The indicators were selected based on core elements identified by international guidelines and were reviewed by a multi-disciplinary panel including hospital pharmacists and consultants in infectious diseases, microbiology and hygiene.[14-16] In total, 5 structure indicators and 6 process indicators were identified, with a score ranging from 0 points (lowest score) to 10 points (highest score) for each category of indicators, based on existing scoring systems.[17-19] Table 1 reports the considered indicators and the score assigned to each element.

Table 1. Quality indicators and scoring system used for the evaluation of antimicrobial stewardship (AMS) programs in Northern Italy (n=25).

AMS program component	Score	Survey results, N (%)
Structure indicators		
AMS team		
• Dedicated AMS team	1	3 (12)
• Multidisciplinary team, including: infection control specialist, infectious disease consultant (or expert on antimicrobial therapy), microbiologist, and pharmacist	2	20 (80)
Accountability		
• Identification of an AMS program lead	1	9 (36)
• Lead clinician/infectious disease consultant	2	10 (40)
Mission statement		
• Definition of the objective of the intervention	1	10 (40)
• Formal mission statement	2	12 (48)
AMS policies		
• Availability of guidelines for common clinical conditions or participation in the development of regional guidelines based on local epidemiology	1	16 (64)
• Both	2	9 (36)
Microbiological laboratory quality management		
• <3% of blood cultures contaminated by peripheral blood or <5% of blood cultures from single draws in adult patients	1	9 (36)
• both	2	0 (0)

Process indicators		

AMS strategies
 	
  • Design, implementation and assessment of at least one strategy to improve antimicrobial use
 	
  • Two or more improvement strategies
	1
	
	2
		15 (60)
		
		9 (36)

Monitoring of adherence to antimicrobial policy/treatment guidelines	1	23 (92)

Monitoring of antimicrobial usage
 	
  • One to three antimicrobial agents or classes, in DDD per 1000 patient-days
 	
  • Over four antimicrobial agents or classes, in DDD per 1000 patient-days
	1
	
	2
		5 (20)
		
		16 (64)

Surveillance of antimicrobial resistance (AMR)
 	
  • percentage of methicillin-resistant *Staphylococcus aureus* or carbapenem-resistant Enterobacteriaceae over invasive isolates
 	
  • both
	1
	
	2
		1 (4)
		
		22 (88)

Regular feedback to clinicians
 	
  • at least annual reporting of antimicrobial consumption or AMR
 	
  • both
	1
	
	2
		8 (32)
		
		13 (52)

Education on AMS	1	25 (100)

The following trust characteristics were also collected through the survey: number of beds and number of full time equivalent (FTE) dedicated infection control nurses per 100 beds. Trusts were assigned to the following categories based on ownership: public, private and not-for-profit, and on the level of care provided: secondary, tertiary, teaching and specialized (i.e. delivering specialty-specific care). For trusts including multiple hospitals, the highest level of care was considered.

Outcome indicators

The following outcome indicators were considered: (1) alcohol-based handrub usage, (2) antimicrobial usage, and (3) AMR: percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacteriaceae (CRE) over invasive isolates. For all three indicators, the annual means for the years 2017-2019 were considered, as well as the percentage change between 2017 and 2019. The year 2017 was chosen as baseline as this was the first year hospital pharmacies were required to provide standardized antimicrobial usage data measured in defined daily doses (DDD) per 1000 patient-days for the regional HAI and AMR prevention and control program. No data was collected for 2020 due to concerns of the disruption caused by the COVID-19 pandemic on IPC and AMS activities.

For the current study, outcome indicators (1) and (2) were collected retrospectively via the AMS program survey. Alcohol-based handrub consumption was expressed in ml per patient-days, by calculating the total volume of alcohol-based handrub acquired by each hospital/trust in the considered year, divided by the total number of patient-days (pd), i.e. the total length of hospital stay in days of all patients admitted during considered year. Antimicrobial usage was expressed in DDD per 1000 pds. Trusts were asked to report antimicrobial usage data on a minimum of four antimicrobial classes up to all antimicrobial classes, as long as the same classes were monitored consecutively from 2017 to 2019. This approach was chosen to reflect individual AMS strategies, as monitoring antimicrobial usage is in itself an AMS intervention. Data were grouped in total

antimicrobial usage and usage of "Reserve" antimicrobials according to the WHO AWaRe classification.[20]

Data on MRSA and CRE were obtained from the regional surveillance system for AMR. The regional surveillance system, based on the ECDC European Antimicrobial Resistance Surveillance Network (EARS-net) protocol and definitions, annually collects data from participating laboratories on isolates from bloodstream and cerebrospinal fluid infections, and results of susceptibility testing.[21,22] For the current study, data on the annual mean percentage of MRSA and CRE over invasive isolates were considered, defined as the proportion of oxacillin and cefoxitin-resistant *S. aureus* isolates over all *S. aureus* invasive isolates and of carbapenem-resistant Acinetobacter spp., *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolates over all Acinetobacter spp., *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* invasive isolates respectively.

Statistical analysis

Trust characteristics (hospital category, ownership, number of beds, and number of FTE infection control nurses per 100 beds) and outcome measures were summarized using frequencies for qualitative variables, and means and standard deviation (SD) or medians and interquartile ranges (IQRs) for quantitative variables, based on results of normality testing (Shapiro-Wilk test). Trusts were grouped by percentiles (P) according to their structure and process scores: <25th P, 25th-75th P, and >75th P. Differences in characteristics and outcome indicators among the three groups were investigated using One-way ANOVA or Kruskal-Wallis tests respectively for normally and non-normally distributed variables. Variables were investigated in relation to structure and process scores using Spearman correlation and linear regression. Analyses were performed using SPSS v. 27.0 (SPSS Inc., Armonk, NY), and two-tailed statistical significance was set at <0.05.

Ethics

Considering this study was descriptive, non-interventional and part of a quality improvement initiative coordinated by a public entity (Region of Piedmont), and that no patient-level data were collected, no ethical approval was considered necessary.

Results

Survey results

In total, 17 out of 18 public health trusts of the region of Piedmont and all 6 private and not-for-profit institutions (respectively 5 and 1 hospitals) completed the survey, and all reported they had an AMS program in place. One trust, which includes three hospitals, provided three separate responses as different AMS programs were implemented in each hospital. Therefore, the total number of surveyed AMS programs was 25: 9 trusts providing secondary-level care, 9 trusts providing tertiary-level care, 3 teaching hospitals and 4 specialized hospitals. The mean number of beds was 417.4 (standard deviation, SD 244) and the mean number of FTE infection control nurses per 100 beds was 0.51 (SD 0.25).

Concerning outcome indicator data, 24 trusts provided alcohol-based handrub usage data, 19 trusts reported total antimicrobial usage data, and 14 trusts reported Reserve antimicrobial usage data. Monitored antimicrobial classes and agents are reported in Table 2.

Table 2. Antimicrobial agents and classes monitored as part of antimicrobial stewardship (AMS) interventions in 25 trusts in Northern Italy.

| Antimicrobial agent or class	N (%)
Aminoglycosides	11 (44)
Beta-lactam/beta-lactamase-inhibitor	14 (56)
Carbapenems	21 (84)
5th gen. Cephalosporins	17 (68)
4th gen. Cephalosporins	9 (36)
3rd gen. Cephalosporins	11 (44)
2nd gen. Cephalosporins	9 (36)
Colistin	13 (52)
Daptomycin	16 (64)
Fluoroquinolones	16 (64)
Fosfomycin	11 (44)
Glycopeptides	17 (68)
Linezolid	20 (80)
Macrolides	9 (36)
Tigecycline	16 (64)
All antimicrobials	8 (32)
No monitoring of antimicrobial usage	3 (12)

The most frequently monitored antimicrobials were carbapenems, linezolid, 5th generation cephalosporins, and glycopeptides. Eight trusts measured all antimicrobial usage, whereas 3 did not monitor antimicrobial usage at all. Antimicrobial resistance data were available from 23 trusts.

AMS scores

Participating trusts achieved a median AMS score of 14 (inter-quartile range, IQR 12-16). Higher scores were achieved for process rather than structure indicators: median 6 (IQR 4.5-7.5) and median 8 (IQR 7.5-9), respectively for AMS structure and process scores. No significant correlation was found between structure and process scores (Spearman's ρ 0.281, p 0.174).

Figure 1 shows structure and process scores according to hospital type. Tertiary-level care trusts achieved the highest structure scores, whereas teaching hospitals achieved the highest process scores. Specialized hospitals achieved the lowest scores for both structure and process indicators. Process scores were significantly differently distributed according to hospital type, contrary to structure scores (p 0.013 and p 0.615 at Kruskal-Wallis test, respectively).

Figure 1. Box plots of structure and process scores of 25 trusts in Northern Italy participating in the antimicrobial stewardship (AMS) program survey, according to hospital type.
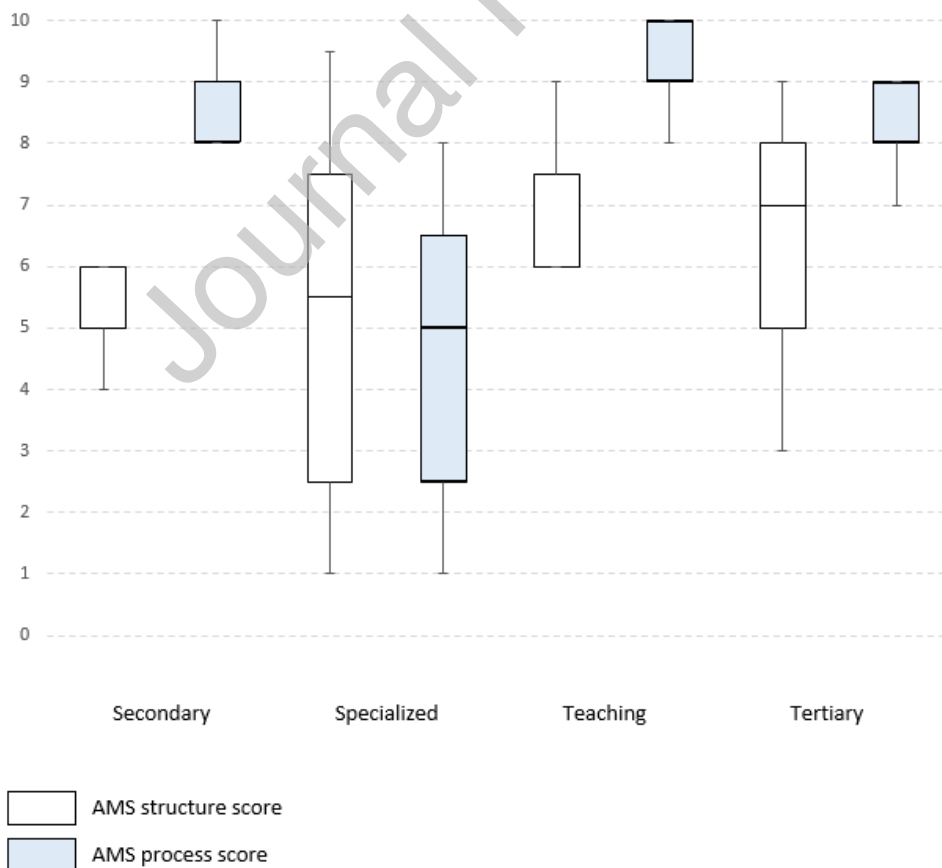
A significantly different distribution of process scores was also found according to ownership type, with significantly higher scores among public trusts (p 0.026 at Kruskal-Wallis test). No significant difference was found in structure or process scores according to the number of dedicated FTE nurses per 100 beds, whereas a higher number of beds was associated with higher process scores (p 0.013 at one-way ANOVA).

Scores assigned to each individual indicator are reported in Table 1. Concerning AMS program structure, the majority of trusts had a multidisciplinary AMS team in place and a definite mission statement. High scores were also achieved for AMS policies. The lowest scores were achieved for accountability and microbiological laboratory quality management, with over half of trusts failing to meet the chosen quality indicators.

High scores were achieved for almost all process items. Fifteen trusts designed, implemented and assessed at least one AMS strategy, and 9 trusts implemented two or more strategies. The most frequently implemented AMS strategies were audits (13 trusts), requiring approval for specific antimicrobials (7 trusts) and reviews of courses of therapy by infectious disease specialists (5 trusts). The most comprehensive AMS intervention, implemented in intensive care units of one trust, was a multi-faceted intervention which involved diagnostic stewardship interventions, improving infectious disease referrals and limiting the duration of empiric therapy. Interestingly, even though over 80% of trusts achieved high scores for AMR surveillance and monitoring of antimicrobial use, just over 50% regularly provided feedback to clinicians on both outcomes.

Detailed results for the considered outcome indicators, overall and stratified by structure, process and total AMS score percentile groups, are presented as Supplementary Table 1.

Antimicrobial usage

Overall, there was an increase in Reserve antimicrobial usage over the three considered years, with a median percentage change between 2017 and 2019 of 8.88% (IQR -9.72 – 40.97). However,

among trusts in the highest AMS structure, process and total score percentile groups a negative median percentage change was observed. Concerning total antimicrobial usage, a slight decrease was observed over the three considered years, with an overall median percentage change between 2017 and 2019 of -3.95% (IQR -13.68 – -2.08). A significant difference in total antimicrobial usage percentage change was found among trusts stratified according to structure score percentiles. As shown in Figure 2, a moderate correlation was found between structure score and percentage change in total antimicrobial usage (Spearman's ρ -0.603, p 0.006). No correlation was identified analyzing process score against percentage change in total antimicrobial usage.

Figure 2. Scatter plot of structure scores vs. percentage change in total antimicrobial usage of 19 trusts in Northern Italy participating in the antimicrobial stewardship (AMS) program survey.
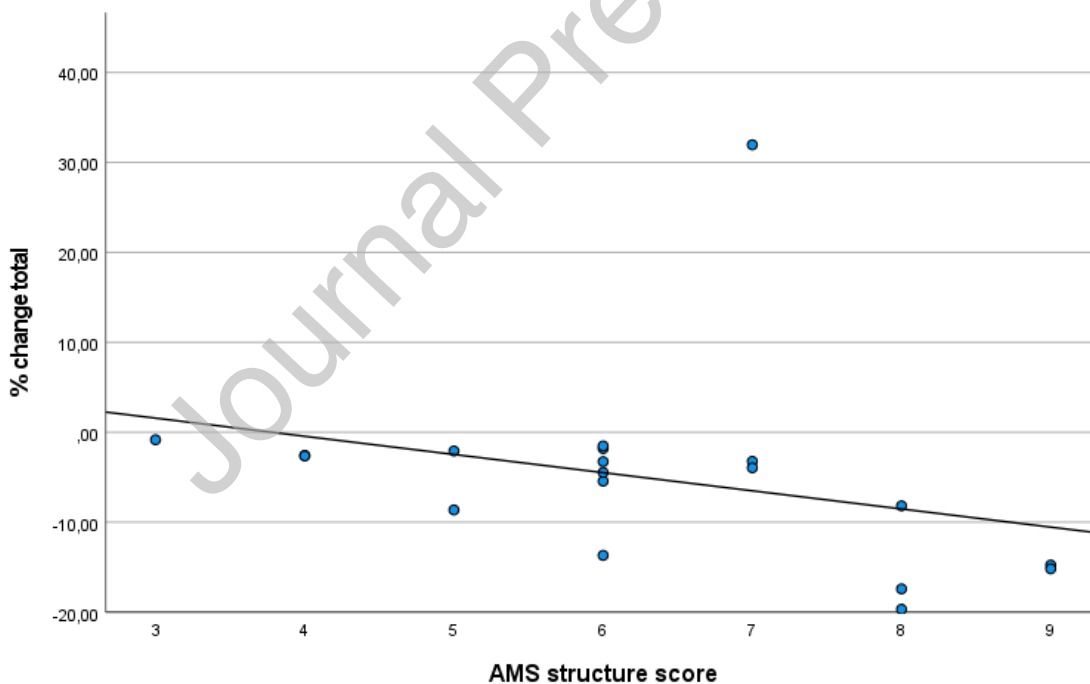
Black line: fitted linear regression (R^2 0.097).

AMR

Overall, there was a progressive decrease in percentage of MRSA over invasive isolates during the three considered years, from a median of 43.15% (IQR 33.15 – 49.73) in 2017 to 36.5% (IQR 29.16 – 44.08) in 2019, and with an overall median percentage change between 2017 and 2019 of -15.84% (IQR -25.99 – 18.99). Median MRSA percentages were generally higher among trusts in the highest AMS structure, process and total score percentile groups compared to trusts in the lower AMS structure, process and total score percentile groups. Median percentage changes were also greater among trusts in the highest AMS structure, process and total score percentile groups compared to trusts in the lower AMS structure, process and total score percentile groups. Concerning the percentage of CRE over invasive isolates among all trusts, a decrease was observed between 2017 and 2019, with a median of 16.57% (IQR 8.3 – 31.2) and 10% (IQR 6.54 – 23.3) in 2017 and 2019 respectively, resulting in an overall median percentage change of -23.17% (IQR -50.26 – 9.87). A progressive increase was found in median percentage change according to structure score percentile groups, with the greatest difference achieved among highest scoring trusts. However, differences in MRSA and CRE percentages or percentage changes in MRSA and CRE among groups did not reach statistical significance. A weak correlation was identified analyzing structure score against percentage change in CRE (Spearman's ρ -0.433, p 0.044). No significant correlation was found between structure and process scores vs. percentage change in MRSA, nor between process scores and percentage change in CRE.

Overall, there was a progressive increase in alcohol-based handrub usage over the three considered years, from a mean usage of 12.28 ml/pd (SD 6.2) in 2017 to 15.66 ml/pd (SD 6.83) in 2019, and with an overall median percentage change between 2017 and 2019 of 29.46% (IQR 15.12 – 46.39). No significant correlation was identified between structure or process scores against percentage change in alcohol-based handrub usage, nor between percentage change in MRSA and percentage change in alcohol-based handrub usage. However, a moderate correlation was identified analyzing

percentage change in alcohol-based handrub usage against percentage change in CRE (Spearman's ρ 0.481, p 0.027).

Considering antimicrobial usage, a moderate correlation was identified analyzing percentage change in total antimicrobial usage against percentage change in CRE (Spearman's ρ 0.515, p 0.035). No significant correlation was found percentage change in total antimicrobial usage vs. percentage change in MRSA.

Discussion

This study reports health system level data and results from AMS programs implemented in the region of Piedmont. The scoring system we developed allowed to compare regional programs according to key structure and process elements. Our study found all trusts implemented some form of AMS program, with varying levels of organization and delivery. Similar inter-facility differences were found in a previous survey of AMS programs of another Northern Italian region, Emilia-Romagna.[12] In our region, higher scores were achieved concerning process rather than structure indicators, with trusts implementing more frequently post-prescription or 'back-end' strategies compared to restrictive or 'front-end' strategies.[23] According to a review by Viale *et al.*, back-end strategies have been associated with slower and less impactful results in terms of reducing antimicrobial consumption, however they appear to be more acceptable by clinicians and could be more effective in improving prescription appropriateness.[23]

Process scores significantly differed according to hospital type and ownership type, with higher scores among teaching hospitals and public trusts, respectively. Tertiary-level care trusts achieved the highest structure scores, whereas teaching hospitals achieved the highest process scores.

Concerning outcome indicators, results of this study suggest improvements in alcohol-based handrub usage (+30% between 2017 and 2019), total antimicrobial usage (-4%), and percentages of

MRSA and CRE over invasive isolates (respectively -16 and -23%). On the other hand, an increase in Reserve antimicrobial usage of almost 9% was identified, which could be in part due to the introduction of novel agents, such as anti-pseudomonal cephalosporins. However, the underlying issue could also be the chosen categorization: most AMS interventions in this study focused on sparing carbapenems, when according to the WHO AWaRe classification the majority of carbapenems are classified as Watch antimicrobials. In fact, to evaluate the effectiveness of AMS programs in English NHS hospitals, Scobie *et al* used an England-modified version of the classification, which classified carbapenems as Reserve agents.[19] Further analyses are required to investigate the impact of AMS programs in general and of carbapenem-sparing strategies in particular on the usage of specific antimicrobials, to investigate potential shifts to other classes of agents.[7] Our study found a greater reduction in CRE rates compared to MRSA rates, which is in line with national AMR trends.[21] This could represent a further indication of the greater focus placed on CRE compared to MRSA. However, MRSA rates are considerably high in our region: 36.5% in 2019, compared to population-weighted EU/EEA mean of 15.5% for the same year.[22] MRSA has a significant burden, and was recently estimated to be the global leading pathogen–drug combination for attributable deaths due to bacterial AMR in 2019. Therefore, an increase in awareness to the importance of this pathogen and novel strategies to contrast MRSA are required.[1]

Assessing the effectiveness of AMS programs is a recognized challenge, and currently there is a lack of consensus concerning the most appropriate outcome indicators.[16] To this end, this study aimed to evaluate three potential outcome metrics in practice: alcohol-based handrub usage, antimicrobial usage and AMR. Significant correlations were found between structure score and percentage change in total antimicrobial usage, structure score and percentage change in CRE, percentage change in alcohol-based handrub usage and percentage change in CRE, and percentage change in total antimicrobial usage and percentage change in CRE.

The first metric, alcohol-based handrub usage, was chosen as a proxy of infection prevention and control (IPC) activities. IPC practices support AMS efforts as they aim to reduce the rate of healthcare-associated infections, the spread of AMR bacteria and the use of additional antibiotics.[23] Our study found significant differences in alcohol-based handrub usage among trusts according to process scores. Previous reports also suggest more comprehensive AMS programs could be associated with higher compliance with IPC strategies.[24]

The second indicator we investigated, antimicrobial usage, is a frequently used metric to evaluate the effectiveness of AMS programs.[16] The moderate correlation found in this study between structure score and percentage change in total antimicrobial usage supports the validity of the indicator, in line with results of the study by Scobie *et al*, which found a small but significant association between lower AMS program scores and increase in total antimicrobial prescribing between 2016 and 2017.[19]

Less evidence exists on the relationship between AMS programs and the third indicator we investigated, AMR.[23] This study found a weak correlation between structure score and percentage change in the proportion of CRE over invasive isolates. Interestingly, a stronger correlation was found between AMS structure score and percentage change in total antimicrobial use vs. proportion of CRE among invasive isolates, which could indicate that a longer follow-up is necessary to ascertain the impact of AMS programs on AMR. Further, our study found a significant moderate correlation between percentage change in total antimicrobial usage and percentage change in CRE.

This study had several limitations that should be considered when interpreting results. First, there were limitations due to the study design. Selection and self-reporting biases cannot be excluded. Responders of the survey were infection control practitioners involved in the AMS programs, which could affect study validity. Despite almost all public trusts of the region participating in the survey, due to the relatively limited number of observations it was not possible to evaluate the impact of individual program elements on outcome indicators. The heterogeneity in scores we identified

reflects a lack of standard requirements for AMS programs, which allows trusts to implement the program that is more suitable to their needs and capabilities. Nonetheless, further investigations are required to determine which are the most effective interventions, in order to prioritize their implementation. Second, there were several possible biases associated with the chosen outcome indicators. Measuring antibiotic usage in DDDs has inherent limitations,[25] and in this study we only considered antimicrobials monitored as part of AMS interventions. Three trusts (scoring among the lowest for all indicators) did not provide any antimicrobial usage data, and therefore were excluded from most analyses. Nonetheless, we analyzed changes in usage of the same monitored classes of agents for each trust during the considered time frame. Several confounding factors could have affected the impact of AMS programs on outcome indicators, such as fidelity with AMS strategies, IPC practices, healthcare activity, patient complexity, and AMR rates. We make no claim of a causal relationship between AMS programs and outcome trends, however results of this study are encouraging and suggest improvements in quality of care.

In conclusion, this survey assessed key aspects of AMS programs implemented in acute-care trusts of the region of Piedmont, and reported outcome data at the healthcare system-level. This study identified important areas for improvement, as well as settings where these interventions should be primarily focused. The ECDC previously highlighted the importance of accountability among factors contributing negatively on AMR issues in Italy.[10] Results of this study reinforce the need to address accountability issues in our region, and call attention to other areas for improvement, such as increasing microbiological laboratory quality management and providing regular feedback on outcomes to clinicians. A solution could be increasing the involvement of hospital pharmacists, including in the role of AMS program lead. Improving the organization of AMS programs in particular should be prioritized, as this study found a significant correlation between structure indicators and improved outcomes. Repeated measurements of structure and process indicators will be important to guide continuing quality improvement efforts, particularly considering these indicators are by and of themselves sensitive to changes in the quality of care.[16] As stated in the

national action plan to contrast AMR, regular monitoring of outcome measures is an essential component of AMS strategies, both to provide a regional benchmark and to contribute evidence in support of the objectives and actions outlined by the plan.[9] Finally, further longer-term studies are necessary to assess the relationship with clinical outcomes, in an integrated approach to AMS, IPC and patient safety.

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Conflict of interest statement

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References

[1]   Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in
2019: a systematic analysis. Lancet 2022;399(10325):629-655. doi:10.1016/S0140-
6736(21)02724-0

[2]   O'Neil J. Tackling drug-resistant infections globally: final report and recommendations. Ro
A, ed. Resistance. London, United Kingdom: 2016; 1, 84

[3]   Alshammari TM, Larrat EP, Morrill HJ, Caffrey AR, Quilliam BJ, LaPlante KL. Risk of
hepatotoxicity associated with fluoroquinolones: a national case-control safety study. Am J
Health Syst Pharm 2014 Jan 1;71(1):37-43. doi: 10.2146/ajhp130165

[4]   Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for
Clostridium difficile infection after exposure to antibiotics. J Antimicrob Chemother 2012
Mar;67(3):742-8. doi: 10.1093/jac/dkr508

[5]   Wagner B, Filice GA, Drekonja D, et al. Antimicrobial Stewardship Programs in Inpatient
Hospital Settings: A Systematic Review. Infect Control Hosp Epidemiol 2014;35(10):1209-
1228. doi:10.1086/678057

[6]   Dyar OJ, Huttner B, Schouten J, Pulcini C. What is antimicrobial stewardship? Clin
Microbiol Infect 2017;23(11):793-798. doi:10.1016/j.cmi.2017.08.026

[7]   Vicentini C, Quattrocolo F, D'Ambrosio A, et al. Point prevalence data on antimicrobial
usage in Italian acute-care hospitals: Evaluation and comparison of results from two national
surveys (2011-2016). Infect Control Hosp Epidemiol 2020;41(5):579-584.
doi:10.1017/ice.2020.18

[8]   Plachouras D, Kärki T, Hansen S, et al. Antimicrobial use in European acute care hospitals:
results from the second point prevalence survey (PPS) of healthcare-associated infections and
antimicrobial use, 2016 to 2017. Euro Surveill 2018;23(46): pii:1800393.

[9]   Ministero della Salute. Piano Nazionale di contrasto dell'antimicrobico-resistenza (PNCAR) 2017-2020. Roma: Ministero della Salute; 2017.

[10]   European Centre for Disease Prevention and Control. ECDC Country Visit to Italy to Discuss Antimicrobial Resistance Issues. Stockholm: ECDC; 2017.

[11]   Rechel B, Jakubowski E, McKee M, Nolte E, editors. Organization and financing of public health services in Europe. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2018.

[12]   Pan A, Gagliotti C, Resi D, Moro ML. Antimicrobial stewardship programmes in Emilia-Romagna, Italy. J Glob Antimicrob Resist 2013;1(3):175-179. doi:10.1016/j.jgar.2013.05.004

[13]   Kallen MC, Binda F, ten Oever J, et al. Comparison of antimicrobial stewardship programmes in acute-care hospitals in four European countries: A cross-sectional survey. Int J Antimicrob Agents 2019;54(3):338-345. doi:10.1016/j.ijantimicag.2019.06.005

[14]   Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007 Jan 15;44(2):159-77. doi: 10.1086/510393.

[15]   Buyle FM, Metz-Gercek S, Mechtler R, et al. Development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals. Eur J Clin Microbiol Infect Dis 2013;32(9):1161-1170. doi:10.1007/s10096-013-1862-4

[16]   O'Riordan F, Shiely F, Byrne S, Fleming A. Quality indicators for hospital antimicrobial

stewardship programmes: A systematic review. J Antimicrob Chemother 2021;76(6):1406-

1419. doi:10.1093/jac/dkab034

[17]   Cooke J, Alexander K, Charani E, et al. Antimicrobial stewardship: An evidence-based,

antimicrobial self-assessment toolkit (ASAT) for acute hospitals. J Antimicrob Chemother

2010;65(12):2669-2673. doi:10.1093/jac/dkq367

[18]   Pakyz AL, Moczygemba LR, Wang H, Stevens MP, Edmond MB. An evaluation of the

association between an antimicrobial stewardship score and antimicrobial usage. J

Antimicrob Chemother 2014;70(5):1588-1591. doi:10.1093/jac/dku555

[19]   Scobie A, Budd EL, Harris RJ, Hopkins S, Shetty N. Antimicrobial stewardship: An

evaluation of structure and process and their association with antimicrobial prescribing in

NHS hospitals in England. J Antimicrob Chemother 2019;74(4):1143-1152.

doi:10.1093/jac/dky538

[20]   World Health Organization. 2021 WHO access, watch, reserve, classification of antibiotics

for evaluation and monitoring of use. Geneva (Switzerland): WHO; 2021.

[21]   Bellino S, Iacchini S, Monaco M, Del Grosso M, Camilli R, Errico G, D'Ancona F, Pantosti

A, Pezzotti P, Maraglino F, Iannazzo S. AR-ISS: sorveglianza nazionale dell'Antibiotico-

Resistenza. Dati 2019. Roma: Istituto Superiore di Sanità; 2020.

[22]   European Centre for Disease Prevention and Control. Antimicrobial resistance in the

EU/EEA (EARS-Net) - Annual Epidemiological Report 2019. Stockholm: ECDC; 2020.

[23]   Viale P, Giannella M, Bartoletti M, Tedeschi S, Lewis R. Considerations About

Antimicrobial Stewardship in Settings with Epidemic Extended-Spectrum β-Lactamase-

Producing or Carbapenem-Resistant Enterobacteriaceae. Infect Dis Ther 2015;4(1):65-83.

doi:10.1007/s40121-015-0081-y

[24]   Quirós RE, Bardossy AC, Angeleri P, et al. Antimicrobial stewardship programs in adult

intensive care units in Latin America: Implementation, assessments, and impact on outcomes. Infect Control Hosp Epidemiol 2021:1-10. doi:10.1017/ice.2021.80

[25]   Akpan MR, Ahmad R, Shebl NA, Ashiru-Oredope D. A review of quality measures for assessing the impact of antimicrobial stewardship programs in hospitals. Antibiotics 2016;5(1). doi:10.3390/antibiotics5010005