Surgical antimicrobial prophylaxis prescribing practices and impact on infection risk: Results from a multicenter surveillance study in Italy (2012-2017)

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Methods. A prospective study was conducted in 42 hospitals participating in the national surveillance system for SSIs. SAP compliance was evaluated considering: antibiotic choice, duration of administration and timing of first dose. Trends in the consumption of five BSAs were also evaluated.
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Conclusions. These findings suggest appropriate narrow-spectrum agents could be more effective than BSAs in preventing SSIs. Interventions to improve SAP compliance with guidelines could significantly contribute to contrasting AMR by reducing SSIs and promoting a more prudent use of antimicrobials.

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Abstract

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Background

Surgical Site Infections (SSIs) significantly increase morbidity, mortality and healthcare costs and are considered to be among the most preventable healthcare-associated infections (HCAIs).[1] Appropriate preventive strategies, such as surgical antimicrobial prophylaxis (SAP), have proven to substantially reduce their risk[2]: up to 50% of SSIs may be preventable administering SAP according to evidence-based guidelines.[3] In Italy, national SAP guidelines have been available since 2003 and were updated in 2011.[4]

However, the inappropriate over-administration of SAP and the indiscriminate use of broad-spectrum agents (BSAs) increases the risk of adverse reactions and promotes the emergence of resistant bacteria.[2] Italy is one of the European countries with the highest rates of antimicrobial-resistant (AMR) pathogens such as meticillin-resistant S. Aureus (MRSA) and carbapenem-resistant K. Pneumoniae, Enterobacteriaceae and A. Baumannii; the last two having reached hyper-endemic levels.[5] A recent review[6] estimated that in 2015 around a third of deaths attributable to AMR infections in Europe were in Italy. To address this major public health threat, the Italian Ministry of Health issued the 2017-2020 National Action Plan to fight Antimicrobial Resistance[7] and defined targets for the reduction of HCAIs and antimicrobial consumption.

SAP contributes significantly to antibiotic consumption: according to the most recent European Centre for Disease Prevention and Control (ECDC) Point Prevalence Survey performed in Italy,[8] SAP accounts for 17.4% of all antibiotics prescribed in acute care hospitals. The optimization of prophylactic prescribing practices has long been considered crucial in the global attempt to prevent AMR.[9] Previous studies have estimated compliance with SAP guidelines in Italy ranges from 20%

to 84.5%.[10,11] It has been suggested that Italian surgeons do not routinely follow recommendations and excessively and inappropriately administer antibiotics for the prevention of SSIs,[10] often choosing for prophylaxis antibiotics the national guidelines reserve for the treatment of multi-resistant infections, such as third- and fourth-generation cephalosporins, carbapenems and combinations of penicillin and beta-lactamase inhibitors.[11] Italy is one of the largest consumers of BSAs in Europe, ranking second for the proportion of BSAs among all antibiotics for systemic use in acute-care hospitals[12] and first for the overall consumption of penicillin–beta-lactamase inhibitor combinations.[5]

For the current study, SAP data collected through the Italian surveillance system for SSIs (Sistema Nazionale Sorveglianza Infezioni del Sito Chirurgico, SNICh) between 2012 and 2017 was evaluated to assess (1) prescribing practices and SAP compliance with the Italian national guidelines and (2) the association between SAP compliance and SSI risk.

Materials and methods

A prospective study was conducted in 42 hospitals in the north-west of Italy participating in SNICh. Participation in the network is voluntary, surveillance is conducted for a minimum of three months each year and continuous surveillance is encouraged. The national protocol[13] is based on the ECDC HAI-SSI network protocol[14] and applies the same definitions for SSIs. Patients undergoing included procedures are identified at admission. Infection control staff collect demographic and clinical data, including the following information regarding SAP: SAP administration, chosen antibiotic agent(s), beginning and end dates, timing of first dose within 120 minutes prior to the surgical incision. Patients are monitored for 30 days after the operation, or one year for surgeries involving the implant of prosthetic material. Post-discharge surveillance is performed through post-operative visits in the same hospital or through a standardized telephone interview.

Compliance with Ethical Standards

As stated in the SNICh protocol,[13] considering the programme's aims are the surveillance of diseases and the improvement of healthcare quality, and that the programme is coordinated by public entities (Italian Centre for Disease Control, CCM, Ministry of Health, Regions of Emilia-Romagna and Piedmont), the written consent of patients involved in surveillance or any other authorization from the Ethics Committee and/or the Protection Commissioner is not requested. All involved patients are provided with an information sheet to notify them of their participation in the surveillance programme and all collected data is anonymised.

Included procedures

For the current study, SAP and SSI data from elective procedures performed between January 1st, 2012, and December 31st, 2017 were analysed. According to the national guidelines, SAP is recommended for clean and clean-contaminated procedures. Contaminated or dirty/infected procedures were excluded from the analysis since it could not be excluded that antibiotics were administrated as therapy rather than prophylaxis. Although procedures monitored through SNICh are classified into NSHN operative procedure categories according to ICD-9-CM codes,[15] for the current study procedures involving a common anatomic site or surgical discipline were combined when the national guidelines' indications for SAP were aligned. The included procedures were: hip and knee arthroplasty, colorectal surgery, cranial and spinal surgery (excluding procedures with endo-nasal, paranasal and oropharyngeal access), cardio-vascular and thoracic surgery (excluding pace-maker and defibrillator insertion), laparoscopic cholecystectomy, prostate surgery.

Compliance assessment

SAP compliance with the national guidelines was evaluated considering the following key components of SAP: antibiotic choice, duration of administration and timing of first dose.[16] For each procedure, all three parameters were evaluated separately and SAP was considered entirely adherent to the guidelines if all three were concordant and no information was missing. If data on one or more of the parameters was missing, the procedure could not be evaluated for overall SAP compliance.

The choice of antibiotic was considered adequate if concordant with the national guidelines[4] or narrow-spectrum and active against the most likely pathogens. BSAs were considered inadequate if they were not specifically recommended by the guidelines. An infectious disease specialist was consulted to determine whether agents should be considered adequate or inadequate for each procedure category. The criteria for evaluation of agent adherence are summarized in the Appendix. Timing was considered compliant if the first dose was administered within 120 minutes prior to incision. If SAP was discontinued within 24 hours (or 48 hours for cardio-vascular and thoracic surgery), duration was considered compliant.

Furthermore, the use of five BSAs inserted in the 'Watch' and 'Reserve' groups of antimicrobial agents of the WHO Model List of Essential Medicines[17] (third- and fourth-generation cephalosporins, glycopeptides, carbapenems, quinolones and piperacillin/tazobactam), was evaluated for each surgical category.

Statistical analysis

Data analysis was performed resorting to a custom computational pipeline designed on top of R framework.[18] The association between SAP compliance and SSI risk was expressed as Risk Ratio (RR) with 95% Confidence Interval (CI) and P value.

To evaluate the impact of confounding factors on SSI risk, a multi-group analysis was performed. The following independent risk factors for SSI[19] were included: age, sex, Infection Risk Index (IRI), pre-operative hospital stay. IRI was calculated following NHSN methodology, according to: procedure duration, American Society of Anaesthesiology (ASA) physical status score and wound contamination class.[15] SSI risk was evaluated stratifying patients in different risk groups for each factor: age (<65 years, 65-80, >80), sex (female, male), IRI (0-1, 2-3), pre-operative stay (<2 days, 2-4 days, >4 days). The same independent variables were included in a multivariable logistic regression model, and results were expressed as Odds Ratio (OR).

The risk analysis was performed with epiR[20] and meta[21] packages to compute OR and RR, incidental risks, and 95% CIs. The pipeline also computed Fisher's Exact Test for Count Data for each confusion matrix and returned its P value, to better assess the overall robustness of further computations. Fisher test enforcement guarantees stricter constraints and more reliable results.

For the trend analysis, the pipeline automatically computed two timelines that contained the absolute and relative (yearly averaged) counts of observed occurrences for each observed variable or stratification of interest. A linear regression model was then fitted against both timelines and the resulted linear models were tested against Mann-Kendall test to eventually detect monotonic trends.

Results

Between 2012 and 2017, 24 861 surgical procedures were monitored. The characteristics of the study population and adherence to SAP guidelines are summarized in Table 1. Over 95% of patients (23 925) received a prophylactic antibiotic regimen and in 72.43% of procedures (18 008), data on all three considered parameters was available, allowing overall compliance to be assessed. Full compliance with national guidelines was achieved in 46.4% of cases (11 536), ranging from 30.43% for colon surgery to 86.71% for cholecystectomy.

Table 1. Characteristics of monitored procedures and adherence to surgical antibiotic prophylaxis (SAP) national guidelines,[4] 2012 to 2017

Characteristic	
Monitored procedures, N(%)	
Hip and knee arthroplasty	14 530 (58.44)
Colorectal surgery	6029 (24.25)
Cranial and spinal surgery	733 (2.95)
Cardio-vascular and thoracic surgery	1890 (7.6)
Laparoscopic cholecystectomy	587 (2.36)
Prostate surgery	1091 (4.39)
Total	*24 861*
Patient age, years	
Median	72
25th percentile	64
75th percentile	79
Male sex, N (%)	11 661 (46.9)
Infection Risk Index, N (%)	
0	11 790 (47.42)
1	10 050 (40.42)
2	1909 (7.68)
3	116 (0.47)
Not applicable	996 (4.01)
Endoscopic or laparoscopic procedure, N (%)	2909 (11.7)
Mean pre-operative hospital stay, days	2.42
Mean hospital stay, days	
Infection	21.67
No infection	11.60
Antimicrobial prophylaxis, N (%)	23 925 (96.24)
Compliance with SAP guidelines, N (%)	
Antibiotic choice	19 427 (78.14)
Duration	15 189 (61.1)
Timing	18 070 (72.68)
Overall compliance	11 536 (46.4)

The annual RR associated with receiving SAP in compliance with national guidelines are shown in Table 2. For all categories except prostate surgery, an improvement in overall compliance over time was observed, most notably for cardio-vascular and thoracic surgery (RR 1.69). When analysing the parameters separately, a significant decrease in compliance over time was found for SAP duration for hip and knee (of 2% each year) and prostate surgery (of 13% each year), and timing for cranial and spinal surgery (of 9% each year). Considering all procedures, a significant annual improvement in compliance was observed for all three parameters (of 15% for antibiotic choice, 3% for duration, 6% for timing and 22% overall) and significant increasing trends over time were found for overall compliance (Absolute Mann-Kendall test for trends, p 0.024) and for all parameters except antibiotic choice (p 0.26).

Table 2. Annual Risk Ratio (RR) and 95% Confidence Interval (CI) associated with receiving surgical antibiotic prophylaxis (SAP) in compliance with national guidelines[4] by procedure category, 2012 to 2017

	Antibiotic choice		**Duration**		**Timing**		**Overall compliance**	
Procedure category	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
Hip and knee arthroplasty	1.09 (1.08-1.10)	0.17	0.98 (0.98-0.99)	<0.01	1.07 (1.06-1.08)	<0.01	1.20 (1.18-1.23)	<0.01
Colorectal surgery	1.29 (1.24-1.34)	0.28	1.09 (1.05-1.13)	<0.01	1.04 (1.03-1.05)	0.02	1.21 (1.15-1.28)	0.02
Cranial and spinal surgery	1.02 (0.99-1.06)	0.23	1.31 (1.22-1.41)	0.22	0.91 (0.88-0.94)	<0.01	1.1 (1.02-1.19)	<0.01
Cardio-vascular and thoracic surgery	1.08 (1.05-1.11)	0.09	1.73 (1.63-1.83)	0.02	1.13 (1.11-1.15)	0.61	1.69 (1.59-1.81)	0.03
Laparoscopic cholecystectomy*	1.03 (1-1.07)	0.97	-		-		1.03 (1-1.07)	0.97
Prostate surgery*	1.21 (0.85-1.73)	0.95	0.87 (0.83-0.92)	<0.01	-		-	
All	1.15 (1.14-1.16)	<0.01	1.03 (1.02-1.04)	<0.01	1.06 (1.05-1.06)	<0.01	1.22 (1.20-1.25)	<0.01

*Due to surveillance not having been performed continuously every year for these categories or to the small number of procedures in some subgroups, compliance could not be assessed for all parameters.

The use of BSAs and the results of the Absolute Mann-Kendall test for trends are summarized in Table 3. Considering all BSAs together, no apparent trend over the considered time period was observed. There were non-significant decreases in the six-year trends for third- and fourth-generation cephalosporins and piperacillin/tazobactam considering all procedures, third- and fourth-generation cephalosporins in hip and knee arthroplasty (p 0.06) and quinolones in colorectal surgery (p 0.06). Non-significant increasing trends were found for piperacillin/tazobactam in colorectal and prostate surgery (p 0.26 and p 0.051 respectively) and glycopeptides in cranial and spinal surgery (p 0.18).

Table 3. Frequency of procedures in which broad-spectrum antibiotics (BSA) were used by year and results of the Absolute Mann-Kendall test for trends

	2012 N (%)	**2013 N (%)**	**2014 N (%)**	**2015 N (%)**	**2016 N (%)**	**2017 N (%)**	**p**
BSA (all procedures)							
Third- and fourth-generation cephalosporins	261 (7.72)	144 (3.79)	50 (1.10)	93 (2.19)	66 (1.62)	55 (1.14)	0.13
Glycopeptides	1029 (30.42)	1414 (37.25)	1545 (33.93)	1493 (35.21)	1208 (29.16)	1125 (23.29)	1
Carbapenems	7 (0.21)	10 (0.26)	3 (0.07)	20 (0.47)	9 (0.22)	7 (0.15)	1
Quinolones	54 (1.6)	75 (1.98)	53 (1.16)	88 (2.08)	73 (1.79)	60 (1.25)	1
Piperacillin/tazobactam	65 (1.92)	115 (3.03)	56 (1.23)	112 (2.64)	150 (3.68)	129 (2.68)	0.26
Procedure category (all BSAs)							
Hip and knee arthroplasty	1174 (56.06)	1498 (63.02)	1553 (53.08)	1445 (64.68)	1171 (52.46)	1117(41.88)	0.71
Colorectal surgery	207 (19.11)	234 (21.16)	110 (12.05)	206 (20.98)	225(22.21)	187 (20.06)	0.71
Cranial and spinal surgery	34 (27.87)	1 (4.55)	0	11 (5.21)	22 (24.44)	14 (5.98)	1
Cardio-vascular and thoracic surgery*	-	17 (11.97)	37 (8.28)	73 (21.28)	51 (14.53)	30 (4.94)	0.81
Laparoscopic cholecystectomy	0	5 (5.88)	3 (3.16)	1 (0.83)	8 (5.8)	4 (3.92)	0.45
Prostate surgery	1 (2.7)	3 (4.69)	4 (3.39)	70 (20)	29 (11.42)	24 (8.96)	0.13
All	1416 (41.86)	1758 (46.31)	1707 (37.49)	1806 (42.59)	1506 (36.93)	1376 (28.61)	1

*No procedures of this category were monitored in 2012.

Table 4 shows the association between SAP compliance and SSI risk. Complete compliance was associated with a reduced risk in all procedure groups except colon surgery (where no significant trend was found); the strongest and most significant protective effect was observed for cranial and spinal surgery (RR 0.37) and cardio-vascular and thoracic surgery (RR 0.46). Analysis by parameter showed that adequate antibiotic choice and duration of administration significantly reduced SSI risk by approximately 40% and 50%, and overall compliance was associated with a RR of 0.65. Conversely, appropriate timing was associated with a slightly increased risk (RR 1.05), although this result was non-significant.

Table 4. Association between surgical antibiotic prophylaxis (SAP) compliance with national guidelines[4] and surgical site infection (SSI) risk by procedure category, 2012 to 2017

	Antibiotic choice		**Duration**		**Timing**		**Overall compliance**	
Procedure category	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
Hip and knee arthroplasty	0.6 (0.42-0.86)	<0.01	0.63 (0.37-1.06)	0.09	1.1 (0.6-2)	0.76	0.75 (0.56-1)	0.06
Colorectal surgery	1.28 (1.09-1.5)	<0.01	0.88 (0.79-1)	0.052	0.95 (0.62-1.45)	0.81	1.07 (0.95-1.2)	0.27
Cranial and spinal surgery	0.48 (0.07-3.21)	0.45	0.79 (0.23-2.77)	0.72	0.37 (0.1-1.31)	0.14	0.37 (0.18-0.76)	0.02
Cardio-vascular and thoracic surgery	0.19 (0.14-0.25)	<0.01	0.54 (0.37-0.78)	<0.01	1.16 (0.38-3.56)	0.799	0.46 (0.37-0.58)	<0.01
Laparoscopic cholecystectomy	0.43 (0.03-7.08)	0.66	0.46 (0.03-7.31)	0.65	0.15 (0.01-2.78)	0.8	0.43 (0.03-7.08)	0.66
Prostate surgery	0.64 (0.35-1.16)	0.18	0.8 (0.44-1.46)	0.48	0.1 (0.01-0.88)	0.01	0.69 (0.43-1.11)	0.17
All	0.57 (0.5-0.65)	<0.01	0.51 (0.45-0.57)	<0.01	1.05 (0.77-1.44)	0.75	0.65 (0.59-0.72)	<0.01

The results of the multi-group risk analysis are shown in Figure 1. Of the considered confounding factors, the strongest predictor of SSI risk was pre-surgery hospital stay (p 0.02).

Figure 1. SSI risk ratio (RR) and 95% Confidence Interval (CI) associated with inadequate surgical antibiotic prophylaxis (according to national guidelines)[4] in multiple risk groups

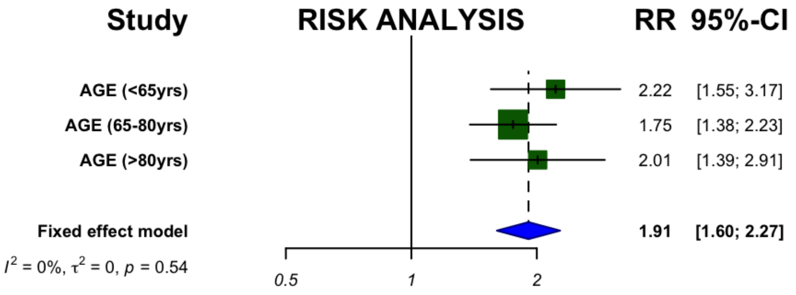

Fig. 1a Risk analysis according to age

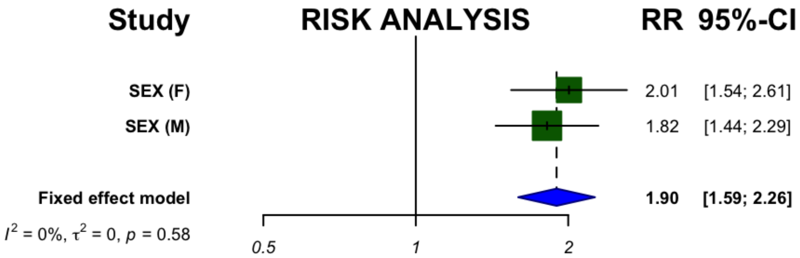

Fig. 1b Risk analysis according to sex (F, female, M, male)

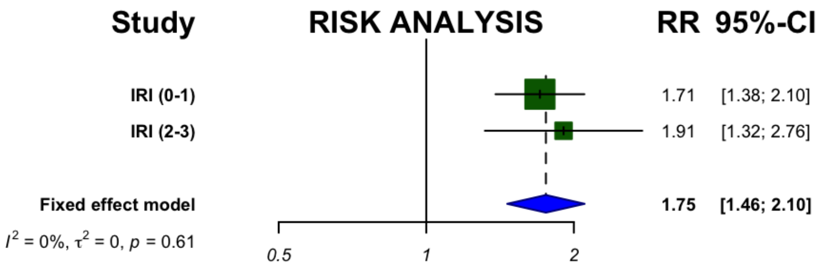

Fig. 1c Risk analysis according to Infection Risk Index (IRI)

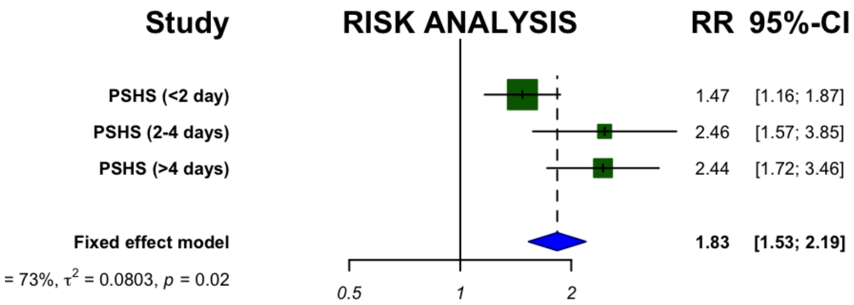

Fig. 1d Risk analysis according to pre-surgery hospital stay (PSHS)

Logistic regression analysis confirmed adequate antibiotic choice and duration significantly decrease SSI risk, compared to receiving inadequate SAP according to these parameters: an OR of 0.65 (95% CI 0.52-0.81, p<0.01) was found for adequate antibiotic choice and of 0.6 (95% CI 0.48-0.75, p<0.01) for adequate duration of administration, considering all procedure categories. The logistic model also identified Infection Risk Index and pre-operative hospital stay as the other most significant factors associated with SSI risk: having an Infection Risk Index score of 2-3 compared to 0-1 was associated with an OR of 2.67 (95% CI 2.12-3.36, p<0.01) and a pre-operative hospital stay above four days compared to less than four days was associated with an OR of 1.67 (95% CI 1.34-2.09, p<0.01).

Discussion

The main findings of this study were: (1) a sustained increase in compliance with SAP national guidelines over the considered six years and (2) a statistically significant SSI risk reduction with overall SAP compliance, adequate antibiotic choice and duration of administration.

In the current study, SAP was found to be completely compliant with national guidelines in 46.4% of cases, varying by procedure category. An improvement in overall compliance of 22% each year was observed and significant increasing trends over the considered six years were found for overall compliance, timing and duration. It is possible that participation in a surveillance network contributed to the amelioration in prescribing practices due to the "surveillance effect", i.e. an improvement of clinical practices and guideline adherence for the simple fact of being aware of being observed.[22]

Some target areas for the improvement of BSA prescribing practices were identified. First of all, albeit in a small number of procedures, carbapenems were used for SAP when this class of antibiotics should be reserved for the treatment of multi-drug resistant infections.[23] Secondly, increasing trends were found for piperacillin/tazobactam consumption in colorectal and prostate surgery and glycopeptides in cranial and spinal surgery. These trends probably reflect an increase in the incidence of extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacteria and MRSA, and should be addressed through targeted stewardship programmes.

On the other hand, a decrease was observed in the six-year trends for the use of third- and fourth-generation cephalosporins and piperacillin/tazobactam in all procedures, third- and fourth-generation cephalosporins in hip and knee arthroplasty and quinolones in colorectal surgery. These results are encouraging and should be further investigated to determine whether underlying epidemiological changes occurred or if specific strategies were implemented to promote improvements in prescribing practices.

The criteria used for the assessment of agent appropriateness in this study, following the national guidelines' recommendations, led BSAs to be classified as inadequate, except in few specific cases. In this study, antibiotic agent compliance was found to independently decrease SSI risk by more than 40%. Previous studies comparing agents with a narrower versus broader spectrum of activity have provided little evidence suggesting BSAs are more effective in preventing SSIs, although small sample sizes limited the ability to detect a statistically significant difference.[24] The findings of the current study suggest appropriate narrow-spectrum agents could be in fact more effective than BSAs in reducing infection rates and therefore the use of BSAs for SAP is not only potentially harmful, but also not justified.

This study had limitations that should be considered when interpreting the results. First of all, surveillance in Italy is voluntary and it is possible that the hospitals willing to participate in the programme are those with better infection prevention and control practices and guideline adherence. Secondly, the use of data routinely collected through a standardized surveillance system had some disadvantages. An assessment of specific patients' characteristics which could have explained some prescribing choices (such as the presence of antibiotic allergies) was not possible. In accordance with the SNICh protocol, timing was considered adequate if SAP administration began within 120 minutes prior to the surgical incision, whereas a more stringent indicator (30 to 60 minutes) is considered more effective.[25] This may have led to an overestimation of timing appropriateness and have hindered the results of the risk analysis, indeed the independent effect of timing on SSI risk was found to be non-significant. Moreover, to increase the generalizability of the results of this study, local guidelines were not considered; although local protocols should generally be aligned with national recommendations, they may differ due to the specific epidemiological context. Finally, even though several known risk factors for SSI[19] were included in the logistic regression model, other confounding factors not taken into account, such as body mass index, the presence of comorbidities or immunodeficiency, could have influenced the results.

The most recent ECDC Annual Epidemiological Report for Antimicrobial consumption[23] highlighted the importance of national consumption data to understand the epidemiology of AMR. As antibiotic consumption and AMR trends are country-specific, reliable national data is required for tailored stewardship interventions. Considering HCAIs are responsible for a large proportion of the burden of AMR,[6] enhanced prevention and control measures for SSIs are needed. Interventions to improve SAP compliance with national guidelines could significantly contribute to contrasting AMR, both by reducing the burden of HCAIs and by promoting a more prudent use of antimicrobials. This study has identified target areas for future interventions and could be useful to guide quality improvement programs and to promote patient safety through enhanced systematic surveillance of surgical interventions and monitoring of SAP prescribing practices.

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Competing interests

None declared.

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Appendix. Criteria for evaluation of surgical antibiotic prophylaxis adherence, by procedure category

Procedure category	Recommended [5] and adequate agents
Hip and knee arthroplasty	• First- or second-generation cephalosporin • Aminoglycoside ± clindamycin If indicated*†: • Vancomycin
Colorectal surgery	• Cefoxitin • Cefazolin + metronidazole • Aminoglycoside + either clindamycin or metronidazole • Amoxicillin + clavulanic acid If indicated*: • Ertapenem
Cranial and spinal surgery (excluding procedures with endo-nasal, paranasal and oropharyngeal access)	• First- or second-generation cephalosporin • Amoxicillin + clavulanic acid If indicated*: • Vancomycin
Cardio-vascular and thoracic surgery (excluding pace-maker and defibrillator insertion)	• First- or second-generation cephalosporin • Amoxicillin + clavulanic acid If indicated: • Clindamycin ± aminoglycoside[a] • Vancomycin in case of implant of prosthetic material
Laparoscopic cholecystectomy	No prophylaxis if ASA‡ score <3 and no implant of prosthetic material; If ASA score ≥3 or implant of prosthetic material: • First- or second-generation cephalosporin • Amoxicillin + clavulanic acid If indicated*: • Clindamycin ± gentamicin • Trimethoprim/sulfamethoxazole
Prostate surgery	• First- or second-generation cephalosporin • Clindamycin + either aminoglycoside or metronidazole • Aminoglycoside ± metronidazole If indicated*: • Clindamycin ± either gentamicin or quinolone

*If the patient is allergic to β-lactam antibiotics.
†If the patient is colonized, infected or at risk of being colonized with methicillin-resistant Staphylococcus aureus.
‡American Society of Anaesthesiology physical status score.

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