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How to 'SAVE' antibiotics: effectiveness and sustainability of a new model of antibiotic stewardship intervention in the internal medicine area

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ABSTRACT

Background: Antibiotic stewardship (AS) is a cornerstone of the fight against antimicrobial resistance; however, evidence on the best practice to improve antibiotic prescription in various hospital settings is still scarce. This study aimed to measure the efficacy of a non-restrictive AS intervention in the internal medicine area of a tertiary-care hospital across a 3-year period.

Methods: The intervention comprised a 3-month 'intensive phase' based on education and guidelines provision, followed by 9 months of audits and feedback activities. The primary outcome was the overall antibiotic consumption measured as days of therapy (DOTs) and defined daily doses (DDDs). Secondary outcomes were carbapenem and fluoroquinolone consumption, all-cause in-hospital mortality, length of stay, incidence of *Clostridioides difficile* and carbapenem-resistant Enterobacterales bloodstream infections (CRE-BSIs). All outcomes were measured in the intervention wards comparing the pre-phase with the post-phase using an interrupted time-series model.

Results: A total of 145 337 patient days (PDs) and 14 159 admissions were included in the analysis. The intervention was associated with reduced DOTs*1000PDs (−162.2/$P = 0.005$) and DDDs*1000PDs (−183.6/$P \leq 0.001$). A sustained decrease in ward-related antibiotic consumption was also detected during the post-intervention phase and in the carbapenem/fluoroquinolone classes. The intervention was associated with an immediate reduction in length of stay (−1.72 days/$P < 0.001$) and all-cause mortality (−3.71 deaths*100 admissions/$P = 0.002$), with a decreasing trend over time. Rates of *Clostridioides difficile* infections and CRE-BSIs were not significantly impacted by the intervention.

Conclusions: The AS intervention was effective and safe in decreasing antibiotic consumption and length of stay in the internal medicine area. Enabling prescribers to judicious use of antimicrobials through active participation in AS initiatives is key to reach sustained results over time.

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BACKGROUND

Antibiotic exposure is considered one of the most critical antimicrobial resistance (AMR) drivers, and antibiotic stewardship (AS) initiatives are considered one of the cornerstones of the fight against AMR. There is strong evidence that AS is effective and safe in improving appropriateness of antibiotic prescriptions; however, no clear consensus has been reached on which interventions are associated with the best clinical and microbiological outcomes and which are the most sustainable over time [1].

In recent years, several examples of non-restrictive AS models have shown that periodic discussion of antibiotic prescriptions in the presence of the infectious diseases (ID) specialist can improve appropriateness of prescriptions in diverse settings [2,3]. Also, prolonged positive effects of those approaches were detected up to 8 years after the intervention cessation, suggesting higher sustainability compared with more restrictive approaches [4]. Additionally, even though strong evidence on the topic is lacking, restrictive approaches have been linked with a higher risk of unintended consequences, such as possible delays in treatment and negative professional culture [1].

According to recent publications from the European Centre for Disease Control and Prevention (ECDC), Italy is considered the European country with the highest burden of disease related to AMR [5]. A lack of institutional support and coordination at several levels has been identified as the main contributing factors towards the AMR issue in the country [6]. In the context of an increasing awareness of the significance of AMR as a major public health threat, a national plan for contrasting AMR was approved in Italy in 2017 to strengthen surveillance, infection control and rational antibiotic use [7].

In compliance with the provisions of this plan, an AS program (SAVE: Stewardship Antibiotica VErona) was started at the Verona University hospital in May 2018. The intervention was conceived as a non-restrictive intervention involving a multidisciplinary AS team (infectious diseases, microbiology, pharmacy, infection prevention and control, hospital epidemiology, and psychology) with the main aim of reducing overall antimicrobial consumption and AMR infections in the internal medicine area.

METHODS

Setting

The Verona University hospital is a 1350-bed tertiary care hospital located in two different sites in northern Italy. According to 2017 data from the yearly point prevalence survey (PPS), the local percentage of patients receiving at least one antibiotic agent reflects the national average (45.7% vs. 44.5%), with peaks in the geriatric (63%) and the intensive care (77.8%) areas. Four medical wards (two internal medicine and two geriatric) were enrolled in the AS program. According to the 2018 PPS, the included wards had very high rates of antibiotic prescriptions (all between 60% and 70%) in the pre-intervention period.

Intervention

The AS intervention was based on the continuative presence of a member of the AS team for a relatively short time period in the intervention ward and included several enabling elements from the behaviour changing framework, namely: education, guideline provision, audit and feedback, and incentives [8]. No restrictive elements were introduced in any phase of the intervention. Before starting the intervention, the official endorsement of the ward director was required, hospital budget points were allocated to the participating wards, and two 'champion physicians' per ward were nominated as reference contacts for the AS activities. Each ward underwent two intervention phases: an initial 3-month 'intensive phase' followed by a 9-month 'maintenance phase'. During the first phase, a dedicated ID specialist took part in the daily activities of the ward to observe common practices, discuss antibiotic prescriptions, and increase awareness and knowledge regarding AMR and hospital-acquired infections. At the end of the initial phase, quality improvement-certified guidelines for empirical antibiotic therapy were jointly drafted by the AS team and ward physicians. The guidelines targeted the most common infectious syndromes treated in the participating wards, with indications on potential treatment duration and 'switch to oral' strategies. Additionally, a 2-day CME-accredited training event on AS topics was offered to the whole medical staff.

During the 9-month maintenance phase, prospective audit and feedback activities were carried out. Revision of antibiotic prescriptions was conducted remotely by the ID physician every 7–14 days in the first 3 months and monthly in the last 6 months. Appropriateness of prescription was systematically evaluated in terms of the following parameters: written documentation of antibiotic start/change, choice of molecule, dosage, duration, and use of combinations. Empirical prescriptions were evaluated based on the local guidelines for empirical treatment, *in vitro* activity, and de-escalation of targeted treatment.

Written feedback was then provided to the AS reference physicians and the ward director within 48 hours from the auditing day. The written report contained a list of non-compliant prescriptions and some suggestions for revision. An ID specialist was available throughout the audit and feedback period to discuss clinical cases and provide written consultation upon request.

Outcomes and process indicators

Indicators relative to antibiotic consumption, clinical and microbiological outcomes were used to assess the efficacy and safety of the SAVE program. All indicators were extracted in an aggregate manner across the four included wards. Data collection was carried out retrospectively for the 12 months before the intervention and prospectively for the 24 months after the intervention start (12 months of intervention and 12 months follow-up).

Data on monthly antibiotic consumption were collected through electronic pharmacy records using single wards as the unit of analysis. Defined daily doses (DDDs), days of therapy (DOTs) and length of therapy (LOTs) were computed from electronic prescriptions recorded via the pharmacy electronic prescription software. Single prescriptions were converted into DDDs according to the 2019 ATC/DDD index issued by the World Health Organization [9]. Antibiotic-free days (AFDs) were calculated as the inverse of LOTs.

Cases of *C. difficile* infections were computed from the Microbiology laboratory database and defined as positivity of glutamate dehydrogenase and toxin A or B detected via an enzyme immunoassay technique. Cases of carbapenem-resistant Enterobacterales bacteraemia were defined as any blood culture growing Enterobacterales with phenotypic resistance to at least one carbapenem. Following current recommendations on the topic, only the first isolates/positive tests per patient in a 28-day period were counted [10].

The number of monthly patient days (PDs), monthly in-hospital mortality (number of in-hospital deaths per 100 admissions) and average monthly length of stay (LOS, computed as monthly PDs/monthly admissions) were collected via the hospital administrative database.

Percentages of patients on treatment and appropriateness of antibiotic prescriptions were also computed per each ward during the auditing and feedback phase. However, due to the lack of pre-intervention data on appropriateness of prescriptions (no official

guidelines were available before the intervention), the purpose of this metrics was for feedback provision only, and not for the assessment of the intervention effect.

Statistical analysis

The efficacy of the AS intervention was tested comparing the pre-intervention and post-intervention phases through a single-group interrupted time-series (ITS) analysis. The model was fit using an ordinary least squares regression analysis (Newey-west), and autocorrelation in the error distribution was tested using the Cumby and Huizinga general test for autocorrelation. All the analyses were carried out using STATA Software (© 2015 StataCorp LLC, Texas) [11].

Ethical aspects

Given the purpose and the design, the SAVE program was considered a quality improvement initiative rather than an experimental study. In agreement with the Verona University Hospital's ethical regulation, the protocol for data analysis and collection was approved by the Institutional Review Board (Prog. 2024CESC Verona e Rovigo, 29/01/2019), but no informed consent from individual patients was required.

RESULTS

The 1-year AS intervention covered almost 15% of the hospital capacity (a total of 147 beds) and targeted 32 senior physicians and 72 residents from June 2018 to May 2019. A total of 1116 prescriptions were revised during the audit and feedback phase in the intervention wards.

The intervention required 0.5 full-time equivalent (FTE) ID physicians per ward in the 'intensive phase' and 0.2 FTE per ward for the 9-month prospective audit and feedback activities. Monitoring of antimicrobial consumptions required a 0.2 FTE pharmacist for the four wards for the whole duration of the intervention. Contributions from the microbiology, and the infection prevention and control departments were provided as part of the routine clinical work. No other additional resources were dedicated to the AS activities.

The final analysis included the 12 months before and the 21 months after the start of the intervention (June 2017 to February 2020), accounting for a total of 145 337 PDs and 14 159 admissions in four different wards. Follow-up after the intervention cessation was truncated at 9 months instead of 12 due to significant changes in the patient case mix and antimicrobial consumption related to the start of the SARS-CoV2 pandemic.

Antimicrobial consumption

A significant reduction in overall antibiotic consumption was measured both in terms of DDDs and DOTs, with a remarkable decrease in the level of consumption and a significant declining trend in the post-intervention slope (Figure 1). The decrease in overall consumption in the intervention wards was also reflected by the AFD trend, which significantly increased at a rate of 3.87 AFDs*1000PDs per month ($P = 0.01$). As for consumption of target antibiotics, both fluoroquinolones and carbapenems showed a significant change in the level of consumption (−23.1 carbapenem DOTs*1000 PDs; $P = 0.03$ and −35.48 fluoroquinolones DOTs*1000 PDs; $P = 0.003$). However, only consumption of fluoroquinolones maintained a decisive declining trend during the post-intervention phase (−2.7 DOTs*1000PDs per month; $P = 0.0001$), while the carbapenem consumption slope was rather stable (−0.04 DOTs*1000PDs; $P > 0.05$) (Figures 2 and 3). Full results of the ITS analysis relative to antibiotic consumption are summarised in Table 1.

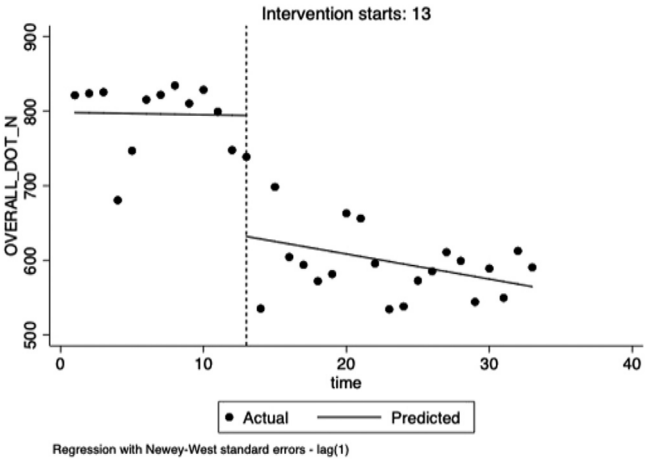

Figure 1. Interrupted time-series analysis of overall antibiotic consumption measured in DOTs*1000 PDs.

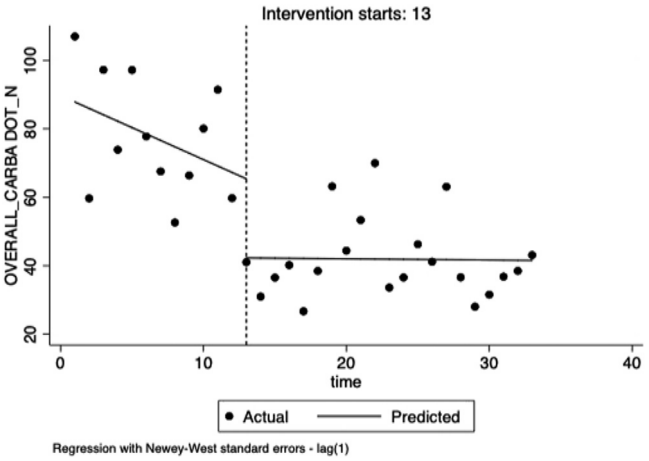

Figure 2. Interrupted time-series analysis of carbapenem consumption measured in DOTs*1000 PDs.

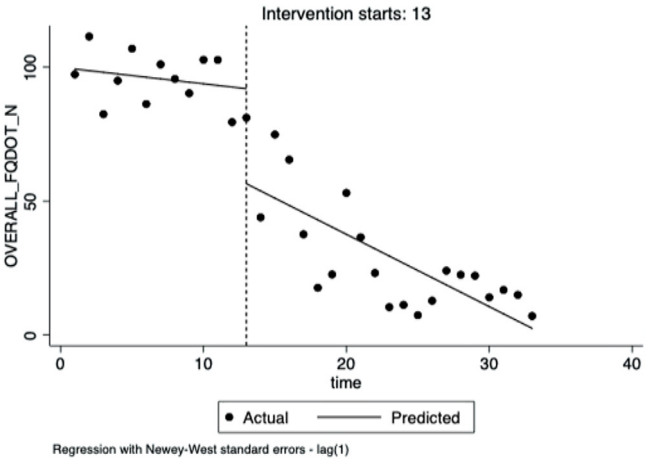

Figure 3. Interrupted time-series analysis of fluoroquinolone consumption measured in DOTs*1000 PDs.

Table 1
Defining parameters of the interrupted time series analysis of antibiotic consumption data.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-intervention slope
DDDs*1000PDs	628.72	11.89	−183.62	−15.52	−3.64
95% CI	536.12, 721.32	−2.70, 26.48	−307.75, −59.49	−30.24, −0.80	−7.20, −0.07
P-value	NA	0.107	0.005	0.039	0.0459
DOTs*1000PDs	798.03	−0.31	−162.23	−3.04	−3.36
95% CI	737.96, 858.10	−7.77, 7.14	−236.22, −88.23	−10.38, 4.29	−6.53, −0.19
P-value	NA	0.932	0.000	0.403	0.0387
AFDs*1000PDs	401.96	5.62	30.77	−1.74	3.87
95% CI	352.14, 451.78	−.37, 11.61	−32.44, 93.97	−8.37, 4.88	0.7281 7.0174
P-value	NA	0.065	0.328	0.595	0.0175
Carbapenems DDDs*1000PDs	64.68	−1.36	−16.75	1.36	0.0011
95% CI	53.47, 75.90	−3.38, 0.66	−36.48, 2.96	−0.78, 3.50	−0.66, 0.66
P-value	NA	0.179	0.093	0.203	0.9974
Carbapenems DOTs*1000PDs	87.82	−1.87	−23.10	1.83	−0.04
95% CI	75.27, 100.37	−4.15, 0.41	−44.67, −1.53	−0.57, 4.23	−0.79, 0.71
P-value	NA	0.104	0.037	0.130	0.9198
Fluoroquinolones DDDs*1000PDs	115.00	−2.41	−29.96	−0.23	−2.64
95% CI	97.52, 132.48	−4.90, 0.07	−55.05 −4.87	−2.82, 2.36	−3.83, −1.46
P-value	NA	0.057	0.021	0.857	0.0001
Fluoroquinolones DOTs*1000PDs	99.30	−0.61	−35.48	−2.09	−2.70
95% CI	90.92, 107.68	−2.07, 0.85	−57.61, −13.35	−3.75, −0.43	−3.88, −1.52
P-value	NA	0.398	0.003	0.016	0.0001

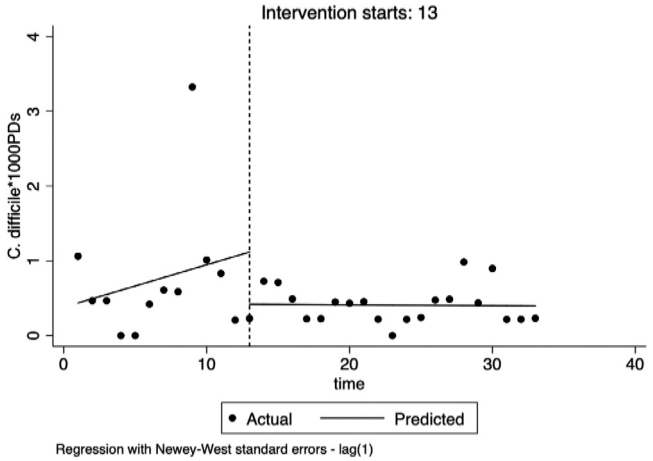

Figure 4. Interrupted time-series analysis of the monthly incidence of *Clostridioides difficile* infections.

Clinical and microbiological outcomes

No significant changes were detected relative to the incidence CRE bloodstream infections (CRE-BSIs) and *C. difficile* infections in the intervention wards (Figure 4). All-cause in-hospital mortality showed a significant change in level (−3.71*100 admissions; $P = 0.002$) and a significant decrease in the post-intervention slope (relative to the pre-intervention trend) of 0.26 deaths per 100 admissions in the intervention wards. Before the intervention, the mean monthly LOS showed a slight (but statistically significant) increase. A decrease in monthly mean LOS was detected after the intervention (−1.72 days; $P < 0.001$), followed by a decrease (relative to the preintervention trend) of −0.17 days per month ($P = 0.001$). The estimate produced by the post-trend analysis showed that monthly mean LOS remained fairly stable during the whole post-intervention period (+0.01 days; $P = 0.5$). Results of the ITS analysis relative to the clinical and microbiological data are summarised in Table 2.

Appropriateness of antibiotic prescription

The cross-sectional evaluation of antibiotic prescriptions enabled the AS team to analyse antibiotic prescriptions both quantitatively (point prevalence of patients receiving any antibiotic prescriptions) and qualitatively (prevalence of patients receiving inappropriate antibiotic treatment). A total of 1116 prescriptions were revised over the whole auditing phase. An average of 17 audits per intervention ward were performed during the 36-week maintenance phase. Overall, data collected during the audit and feedback phase showed a decreasing trend in both prevalence of patients on antibiotics and frequency of inappropriate treatments. In general, the lack of written documentation for starting/modifying antibiotics was the most frequent cause of error observed in the geriatric wards, while the choice of an antibiotic molecule not complying with the indications was the leading cause of inappropriateness in the internal medicine wards. The excessive duration of antibiotic therapy was another reason for frequent errors in all the wards (data not shown).

DISCUSSION

The SAVE program was conceived as an educational, quality improvement intervention aimed at reaching a sustained reduction in antibiotic consumption through a non-restrictive AS intervention conducted by a multidisciplinary team. The program started in May 2018 and involved four wards in the internal medicine area for 1 year. Medium-term follow-up (1 year after the intervention cessation) demonstrated a significant and sustained association with reduced antibiotic consumption, mortality and length of hospital stay.

To ensure intervention efficacy, the SAVE program was conceived as an enabling AS intervention, aimed at reaching a sustained change in physicians' prescribing behaviours. Several of the intervention elements were modelled in consultation with behavioural sciences experts before the start of the intervention and then tailored to the intervention wards during the implementation phase. The core elements of the intervention were the educational activities carried out by the AS team during the initial 'intensive phase'. Beside those core educational components, other elements were also deemed as necessary to ensure successful implementation, such as the endorsement by the hospital leadership, official recognition of the guidelines by the Quality Improvement Department, and use of incentives to participating wards (i.e. CME-accredited certifications, hospital budget points to the participating wards).

Table 2
Defining parameters of the interrupted time series analysis of clinical and microbiological outcomes.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-intervention slope
Clostridioides difficile *1000PDs	0.44	0.06	−0.70	−0.06	−0.001
95% CI	−0.20, 1.07	−0.08, 0.19	−1.95, 0.55	−0.19, 0.08	−0.02, 0.02
P-value	NA	0.400	0.263	0.402	0.9240
CRE BSI *1000PDs	0.27	0.02	−0.10	−0.02	−0.002
95% CI	0.03, 0.51	−0.01, 0.06	−0.45, 0.24	−0.07, 0.02	−0.02, 0.02
P-value	NA	0.225	0.552	0.248	0.7764
Deaths*100 admissions	11.07	0.33	−3.71	−0.26	0.06
95% CI	10.45, 11.69	0.19, 0.46	−5.96, −1.47	−0.46, −0.06	−0.09, 0.22
P-value	NA	0.000	0.002	0.012	0.4108
Mean LOS	9.46	0.19	−1.72	−0.17	0.01
95% CI	8.81, 10.09	0.10, 0.27	−2.37, −1.08	−0.27, −0.08	−0.0273, 0.0538
P-value	NA	0.000	0.000	0.001	0.5093

Compared with what is referred to in the literature as the more typical 'round-based' interventions or 'handshake stewardship', where the ID physician is periodically present to discuss antibiotic prescriptions [2,3], the SAVE program applied quite an innovative approach, where the AS team expertise was directly embedded in the ward routine during a short-term 'intensive phase'. This approach required daily presence of the ID physician on the ward, with the main aim of facilitating discussion on antimicrobial prescriptions without interfering with routine activities and creating a positive professional environment. In this context, awareness on the topic of AMR and hospital-acquired infections dramatically improved in all the included wards, and core elements such as antibiotic re-evaluation, culture collection before starting antibiotics, shortening treatment duration and 'switch to oral' strategies gradually became part of the clinical routine. The purpose of the audit and feedback phase was to maintain the effects of the intervention without having to rely on the daily presence of the AS team on the ward. The significant number of prescriptions that were reviewed by the AS team enabled the most relevant causes of error and protocol deviation to be reliably identified (i.e. lack of documentation, excessive duration and choice of an inappropriate molecule). Timely feedback provision was also a key factor contributing to optimising antibiotic use.

Although improving prescribing behaviours is the main target of every AS intervention, other process measures had to be selected as main outcomes because they are easier to measure and verify. Antibiotic consumption before and after the AS intervention was measured according to the main guidance on the topic [12] and overall consumption remarkably and consistently decreased across all the selected metrics (DOTs, DDDs and AFDs).

Ward-based data on antimicrobial consumption remain difficult to benchmark, since they are strongly influenced by local epidemiology and patient case mix. Data from a 2016 systematic review on antibiotic consumption in acute-care hospitals worldwide reported a mean value of 677 DDDs*1000 PDs (95% CI 634–720) across the internal medicine wards, with a very high between-study variance (I2 99%) [13]. This value was mainly computed from studies conducted in the first decade of 2000 in Western Europe and Mediterranean countries and is in line with the pre-intervention values of the Verona University hospital. After the AS intervention, the mean monthly consumption decreased from ca. 700 DDDs*1000 to 500 DDDs*1000PDs.

Although the amount of overall antibiotic consumption reduction was clinically and statistically significant, it is difficult to conclude whether the final values are satisfactory. So far, no databases or literature data have set the 'ideal consumption' for an internal medicine ward, and more data need to be systematically collected and shared among similar hospitals to set appropriate targets for AS in different settings [12]. For carbapenems, the average monthly consumption fell from 50 DDDs*1000 PD to ca. 35 DDDs*1000 PDs after the intervention. However, the post-intervention phase showed a stable/slightly increasing trend in consumption, probably related to the slightly increasing clinical burden of ESBL infection in patients hospitalised in those wards. Conversely, fluoroquinolone consumption showed a decisive and sustained decrease over the whole period.

The association of the AS intervention with improved clinical outcomes (i.e. LOS and mortality reduction) is in line with the most recent evidence from the literature [1,14]. Although it should be noted that a positive effect on mortality has less frequently been demonstrated by available studies on the topic [1]. Consistent with literature data, the effect on microbiological outcomes remains more challenging to demonstrate. Several reviews on the topic have shown how inadequate outcome measures or inappropriate study design are often biased towards detecting unrealistic positive effects on microbiological outcomes [15,16].

The ITS analysis was adopted to measure the intervention effect following several expert recommendations, mainly thanks to its ability to control for seasonality and pre-existing temporal trends. According to those recommendations, at least 10 points over 1 year for each intervention phase are needed to control for seasonality (a relevant parameter when considering antibiotic consumption). Additionally, at least 100 observations per data point should be available to ensure model stability [17,18]. According to those requirements, data recorded during the SAVE program were probably adequate to fit the model for antibiotic consumption, but they might have been less adequate when it came to relatively rare events, such as targeted MDR infections.

With the limit of those observations, the SAVE program was associated with a non-significant impact on *C. difficile* and CRE-BSIs. In some recently published studies, the inclusion of a greater number of observations, clustered over wider areas (i.e. the whole hospital) or more extended periods (i.e. quarters), has enabled adequately fit time-series models to be built and for the positive effects of AS to also be captured with rare microbiological outcomes such as CRE-BSIs [19,20].

The SAVE program was conceived as a multifaceted intervention. From the outset of the project the infection control team's active participation was foreseen with a view to maximising its educational impact. Thus, several activities targeted both AS and IPC aspects at the same time. As often happens during real-life AS interventions, the potential contribution of improved IPC adherence to reducing *C. difficile* infection and CRE-BSIs cannot be disentangled from the potential impact of improved antibiotic use.

One additional limitation of this study was the lack of a control group. Although the AS intervention was very likely the cause of such a remarkable reduction in antibiotic consumption, the inclusion of a control group would have been beneficial in ruling out potential confounders (other educational initiatives, historical trends, change of patient mix, or national policies) and in strength-

ening the association with improved clinical outcomes. The reason for not including a control group were mostly organisational and, since the SAVE program was implemented as a quality improvement intervention, all the wards with high antibiotic consumptions and similar characteristics were prioritised for receiving the intervention earlier. This organisational structure was chosen to increase the intervention efficacy in the first phase and maximise team efforts while preparing guidelines and educational activities. In this context, selecting a similar ward to be 'spared' from the intervention to work as a control group was unfeasible.

In conclusion, the SAVE program was associated with a significant reduction in antibiotic consumption, all-cause mortality and length of hospital stay in the internal medicine area. Dedicating full-time, short-term AS resources to intense enabling interventions could represent an effective model for AS intervention in this specific area. A more extended follow-up and the inclusion of different ward types is necessary to extend the generalisability of those results to other medical areas and to verify sustained efficacy over a prolonged period of time.

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Competing Interests

All authors have no conflict of interest to declare.

Ethical Approval

The protocol for data analysis and collection was approved by the Institutional Review Board (Prog. 2024CESC Verona e Rovigo, 29/01/2019), but no informed consent from individual patients was required

Sequence Information

Not applicable.

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