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SAVE 'STEWARDSHIP ANTIBIOTICA VERONA': RESULTS OF AN ENABLING AND MULTIDIMENSIONAL ANTIMICROBIAL STEWARDSHIP INTERVENTION PROMOTING PRESCRIBING APPROPRIATENESS ACROSS THE ENTIRE SURGICAL PATH OF CARE

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SAVE 'stewardship antibiotica Verona':
results of an enabling and multidimensional antimicrobial stewardship intervention promoting prescribing appropriateness across the entire surgical path of care
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SOMMARIO

Introduzione: Nell'ambito del Progetto SAVE di Stewardship Antibiotica dell'Azienda Ospedaliera Universitaria Integrata di Verona), è stato condotto un intervento di Miglioramento della Qualità diretto all'area chirurgica dell'ospedale, che vanta un elevato volume di procedure. L'intervento, invece di concentrarsi su un aspetto o una specifica abilità (per esempio la profilassi antibiotica preoperatoria), si è posto come obiettivo quello di migliorare globalmente la pratica prescrittiva lungo tutto il corso dell'attività chirurgica. L'approccio impiegato è stato organico e di tipo persuasivo, con l'inclusione di tecniche di *behavior change.* al fine di favorire il coinvolgimento dei chirurghi come attori primari nell'ottimizzazione dell'impiego degli antibiotici all'interno dei loro reparti.

Metodi: L'intervento di Stewardship ha previsto un periodo prolugato di addestramento sul campo con la partecipazione quotidiana dello specialista di Malattie Infettive al giro visite per 4-8 settimane, seguito da 9 mesi di monitoraggio tramite un processo di *Audit* e *Feedback;* tra i due periodi è stato organizzato un evento educativo formale. La prima fase ha offerto l'opportunità per lo sviluppo di linee guida specifiche per ciascun reparto e per l'identificazione dei determinanti psico-sociali che influenzano la pratica prescrittiva così come le barriere che ostacolano i cambiamenti auspicabili in essa. L'*outcome* primario è stato rappresentato dalla variazione nei consumi complessivi di antimicrobici espresso come *Days of Therapy* (DOTs), *Daily Defined Doses* (DDDs) e *Length of Therapy* (LOTs) per 1000 giorni-paziente (PDs). Come *outcomes* secondari sono stati considerati:

- la variazione nei consumi straificati secondo le classi AWaRe proposte dall'OMS ed in base alle categorie di maggior interesse, considerando il contesto epidemiologico locale ed i requisiti nazionali (fluorochinoloni, carbapenemi, antibiotici con attività anti-MRSA).
- La mortalità intraospedaliera, la lunghezza media delle degenze (LOS), l'incidenza di infezioni da *Clostridium difficile* (CDI), e di batteriemie causate da *Enterobacteriaceae* resistenti ai carbapenemi (CRE-BSI).

L'efficacia dell'intervento è stata valutata mediante l'impiego dell'*interrupted-time-series analysis* (ITSA), confrontando i 12 mesi precedenti a quelli successive all'avvio dell'intervento.

Risultati: Cento undici chirurghi e 18 anestesisti (di cui 76 medici in formazione specialistica) sono stati coinvolti in cinque reparti chirurgici e in una terapia intensiva post-chirurgica (urologia, chirurgia generale, traumatologia, cardiochirurgia e terapia-intentiva cardiotoracica). Complessivamente durante gli *audits* sono state valutate 710 prescrizioni di antimicrobici rilevando una prevalenza media di pazienti in antibioticoterapia tra il 22% (in cardiochirurgia) e il 74% (in terapia intensiva cardiotoracica) del totale. L'appropriatezza prescrittiva generale nel periodo post-intervento è stata superior al 70% in tutti I reparti coinvolti con livelli di appropriatezza della profilassi antibiotica pre-procedura tra il 61 e il 73%; solo il 40% delle profilassi osservate è stata prolungata oltre le 24 ore. L'analisi ITS ha rilevato un riduzione significative nel consumo complessivo di antimicrobici in 3 su 5 reparti, con una variazione verso il basso della pendenza dei trend in urologia (-65 DOTs*1000PDs/month, P=0.038) e un cambio di livello immediato in traumatologia e cardiochirurgia (-111.6 DOTs*1000PDs P=0.032, -167 DOTs*1000PDs P=0.027). Nonostante i dati grezzi di consumo abbiano mostrato livelli ridotti di consumo degli antimicrobici inclusi nella classe WATCH in tutti I reparti inclusi nel post-intervento (tra -27% E -43%), l'analisi ITS ha confermato un effetto positivo dell'intervento unicamente nei reparti di area cardiotoracica (trend post-intervento: cardiochirurgia -10.9 DOT*1000PDs/month, P<0.001; terapia intensiva cardiotoracica -83 DDDs*1000PDs/month, P< 0.001) dove si è osservata una riduzione significatica del livello post-intervento anche per gli antibiotici della classe RESERVE (-142 DOTs*1000PDs, P<0.01; -251 DDDs*1000PDs, P=0.007), dei carbapenemi e degli anti-MRSA L'analisi ITS dei consumi degli antimicrobici ITS ha mostrato risultati meno costanti per gli antimicrobici della classe ACCESS. Ridurre il consumo di fluorochinoloni non è risultato impegnativo, come dimostra la riduzione del consume grezzo superiore al 60% in tutti i reparti; tuttavia, l'analisi dei trend temporali con l'analisi ITS ha fatto emergere dei trend significativamente in

riduzione solo in ruologia e in chirurgia generale (dove si registravano i consumi più cospicui pre-intervento) in contrasto ai reparti di traumatologia e chirurgia generale dove si è notata una variazione in positivo come esito della stabilizzazione dei consumi in seguito al rapido trend in discesa nel pre-intervento. L'assenza di variazioni clinicamente significative nei dati di mortalità intra-ospedaliera e nella lunghezza media della degenza, conferma la sostanziale sicurezza dell'intervento. La bassa incidenza di infezioni da *C.difficile* e di batterimie causate da CRE non si è associata ad alcuna variazione significativa tra i due periodi.

Conclusioni: Un intervento persuasivo di stewardship anitmicrobica volto a migliorare la qualità delle cure offerte durante l'intero percorso di cura in ambito chirurgico può condurre ad un miglioramento della appropriatezza prescrittiva e produrre variazioni desiderabili nel consumo di antibiotici, senza che emergano effetti avversi. Data la grande variabilità esistente tra le diverse specialità chirurgiche, l'adozione di un approccio personalizzato nell'attuazione dell'intervento e nella definizione a priori delle variazioni di consumo di antibiotici che si desidera ottenere, rappresentano elementi chiavi per il successo di tali iniziative. I risultati di questo studio forniscono preziosi spunti anche per un'eventuale riorganizzazione del servizio di consulenze infettivologiche rivolto all'area chirurgica, in grado di meglio rispondere alle esigenze peculiari che essa presenta.

ABSTRACT

Background: As a part of the hospital-wide Antimicrobial Stewardship (AS) SAVE project, a Quality Improvement (QI) intervention was implemented in the surgical area of the Verona University Hospital. Rather than focusing on specific elements (i.e. Surgical Antibiotic Prophylaxis, SAP), the intervention was aimed at globally improving the antimicrobial prescribing practice across the entire surgical pathway. An enabling approach was adopted to foster surgeons to play a leading role in the optimizations of antimicrobial use in their wards.

Methods: The QI intervention encompass a prolonged on the field training with an Infectious Disease (ID) specialist attending the clinical rounds daily for 4-8 weeks, followed by a 9-months auditing and feedback; an educational workshop, CME-accredited, was held between the two. The first phase was also capitalized for the development of ward-dedicated guidelines. The primary outcome was the variation in antibiotic consumption measured by Days of Therapy (DOTs) and Daily Defined Doses (DDDs) per 1000 patient-days (PDs). Variation in consumption, stratified according to the WHO AWaRe and the main classes of interest considering the epidemiological context (fluoroquinolones, carbapenems, and anti-MRSA agents), in-hospital mortality, length of hospital stay (LOS), incidence of *Clostridium difficile* infections (CDI), and carbapenem-resistant *Enterobacteriaceae* bloodstream infections (CRE-BSI) were the secondary outcomes. The interrupted-time-series analysis (ITSA) was used to evaluate the AS intervention effectiveness, comparing the 12-month pre- and post-intervention periods.

Results: Eighty-six surgeons and 18 anesthesiologists were involved in 5 surgical and one surgical-dedicated Intensive Care Unit (ICU). Overall, 710 prescriptions were reviewed and the mean prevalence of patients receiving antibiotics ranged from 22% in the cardiac surgery to 74% in the ICU. Post-intervention global prescribing appropriateness exceeded 70% in all the wards, SAP appropriateness levels ranging 61-73 and not exceeding the 24-hours duration in more than 60%. The ITSA identified significant reduction in overall antimicrobial consumption in 3/5 wards, with downward slope in

urology (-65 DOTs*1000PDs/month, P=0.038) and abruptly level change in traumatology and cardiac surgery (-111.6 DOTs*1000PDs P=0.032, -167 DOTs*1000PDs P=0.027). Although raw data showed lower WATCH usage in all the wards (from -27% to -43%), the ITSA confirmed significant desirable effects of the intervention only in the Cardiothoracic area (post-intervention: Cardiac surgery -10.9 DOT*1000PDs/month, P<0.001; ICU -83 DDDs*1000PDs/month, P< 0.001) where a significant reduction in the level of RESERVE (-142 DOTs*1000PDs, P<0.01; -251 DDDs*1000PDs, P=0.007), carbapenems, and anti-MRSA agents was also observed. Fluoroquinolones raw consumption decreased more than 60% everywhere; however, when assessed by ITSA, significant downward trends emerged only in Urology and General surgery (starting from higher baseline levels) as opposed to Traumatology and General Surgery, showing positive change in slope, presenting a sharp decrease in the pre-intervention year then stabilizing. The absence of significant variation in the in-hospital mortality and LOS confirmed the safety of the intervention. The incidence of *C.difficile* and CRE-BSI was low, with no significant trends emerging.

Conclusion A QI intervention targeting the entire surgical pathways can enhance prescribing appropriateness and safely achieve valuable variation in antibiotic consumption. As great variability exists across different surgical specialities, a tailored approach in the intervention implementation and pre-definition of the desirable variation of targeted antimicrobial class consumption represent key elements for success. The study also provides useful insights prompting a reorganization of the ID consultation service to adequately address the peculiarity of the surgical area.

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INTRODUCTION

Antimicrobial Stewardship and the Antimicrobial resistance burden

The threat represented by antimicrobial resistance (AMR) in the current time is dramatically portrayed by a recent work published by the European Center for Disease Control and Prevention (ECDC). Starting from 2015 European AMR Surveillance data, the Authors estimates that approximately 670,000 infections and 33,000 deaths attributable to AMR occur every year in Europe. In this context, the Italian situation is uttermost critical, as it individually contributes to almost one-third of those figures, holding the highest burden of disease related to AMR in Europe. (1)

The excess mortality and morbidity carried by infections caused by antibiotic-resistant bacteria as well as the dramatic impact they elicit on the health systems (in terms of cost of hospitalization and resource consumption) and society, urged the World Health Organization (WHO) to enlist AMR as one of the most critical health challenges in the coming decades and to claim strategic plans to contrast it (2).

As well-established evidence identified antibiotic exposure as one of the most critical antimicrobial resistance drivers (3), several international health authorities have proposed strategies and plan to prioritize responsible use of antibiotics to guarantee the best treatment for today's patients at the same time preserving adequate resources for next generations (4, 5).
In Italy, where AMR pathogens categorized as of critical priority by the WHO have all reached hyperendemic levels, the first national policy document to contrast the AMR phenomenon (Piano Nazionale di Contrasto all'Antibiotico Resistenza) has been approved in November 2017. A dedicated section of the plan address the correct use of antibiotics in humans, drawing the reference framework for local initiatives: general goals settled by the plan are the reduction in the overall consumption of systemic antibiotics (> 10% in 2020 compared to 2016) and in the consumption of fluoroquinolones (> 10% in the territory and > 5% in the hospital) associated with the reduction in the prevalence of MRSA and carbapenem-resistant *Enterobacteriaceae* (CRE) isolated from blood (> 10%). Systematical microbiological surveillance of

AMR and consumption of alcohol-hand-rub solution at a regional level are also required by 2020 (6).

One of the most concise while comprehensive definition states: 'Antimicrobial Stewardship is a coherent set of actions which promote using antimicrobials in ways that ensure sustainable access to effective therapy for all who need them'. This description encompasses both the need for rationale (i.e. according to evidence-based medicine) and responsible prescribing habits, which means being able to ponder the immediate and the future consequences of that practice within a complex environment. The need for a consistent strategy, aimed at maximizing efficacy and the one of leadership able to nudge rather than force systems and players towards an improvement is also enlightened (7).

The Infectious Disease Society of America (IDSA) guidelines detailed essential components of an AMS program, that should encompass a set of coordinated interventions designed to improve and measure the appropriate use of antibiotics by promoting the selection of the optimal therapeutic regimen in terms of dosage, duration, and route of administration'. Optimal therapy is described as the one clinically effective while carrying the minimum risk of toxicity and selection of resistances (8, 9).

Antibiotic Stewardship: planning and organizational structure

Antimicrobial Stewardship requires a multidisciplinary effort with several experts from all the disciplines related to antimicrobial prescription called to work coordinately within an AMS team. In the European landscape, core members come usually from the infectious diseases and clinical microbiology area; essential supports should be provided by a pharmacist with professional expertise on antimicrobials. Additional members could include infection prevention and control (IPC) practitioners, nurses, and contributors from the information technology (IT) department or program managers.

The engagement of medical doctors from more specialized departments is valuable for AS programs targeting specific areas, to strengthen the collaboration between the AMS team and the prescribers: the appointment of

a ‘program champion’, a health professional trusted by colleagues and provided with a deep understanding of antibiotic prescribing processes, has proven effective in some medical areas. Additionally, ensuring a formal and factual endorsement and support from the hospital administration is a key requirement for successful AMS intervention. (10)

A careful assessment of the local context where the intervention is going to be implemented should precede it starts. This usually covers epidemiological elements (such as the prevalence of antimicrobial consumptions and hospital-acquired infections) as well as psychosocial determinants of prescribing patterns in place; already evident barriers and facilitators to improving prescribing practice should be taken into account when designing the intervention, to maximize its impact.

Increasingly literature targeting standardized or semi-structured tools to assess those areas is available (questionnaires, face-to-face interviews, direct observations, or focus groups). (11-14)

Behaviour-change techniques could be incorporated in the intervention design using a theory- and context-driven approach, to increase its acceptability and sustainability. (19) The ‘behaviour change wheel’ approach, suggested by Michie et al. in 2011, is considered by several scientists an acceptable framework for the implementation of effective AS interventions. (15)

The last Cochrane systematic review on AMS interventions, used the terms ‘persuasive’ or ‘restrictive’ derived from the ‘behaviour change framework’, to categorize different intervention types. The adoption of persuasive and enabling approaches (mainly including periodic audits and feedback) was associated with improved efficacy (16, 17) and the inclusion of more structured behaviour change interventions would be beneficial (18).

A practical example of fruitful social science contribution to AMS is represented by The Dutch Unique Method for Antimicrobial Stewardship (DUMAS) in acute healthcare facilities. In this study, the AMS team foster an active engagement of every stakeholder involved in antibiotic prescribing. Through a ‘planning-acting-reflecting’ process, the periodic and structured discussions between the AMS team were used to shape the present and future actions also enlightening the complexity of the human prescribing decision-

making process. The DUMAS experience resulted in a sustained improvement of prescribing habits over 12 months, allowing prescribers to maintain their autonomy, encouraging their collaboration and empowerment while reducing their resistance to behaviour change. (19, 20)

During the audit and feedback process, communication competencies can reinforce prescribers' achievements, underlining effort and strengths, and acknowledging the complexity of behaviour change. A motivational communication approach with prescribers could help increasing acceptance of AMS recommendations and build trustful relationships between the AMS provider and the ward staff. (21, 22)

Better communication strategies can also improve prescribers' competencies in other areas, such as decision-making and communication skills (e.g., doctor-to-patient communication skills and teamwork relationship dynamics).

Follow up after the intervention completion is a crucial phase to assess the AMS intervention sustainability. Monitoring and benchmarking prescribing patterns and appropriateness employing audit and feedback fosters clinicians to reflect on their practices. Positive feedback, rewarding desirable change in practice, results in sustained engagement in the new behaviour. (23)

Additionally, the re-assessment of the prescribing drivers allows to explore possible risk factors of relapse and optimize the intervention's sustainability. (24) A structured setting for allowing analysis and discussion of the results achieved needs to be planned; this will also offer an opportunity for further goals setting, facilitated by peer support and team engagement.

Antimicrobial Stewardship and Surgical Practice

The rise in AMR, if not appropriately contrasted, will progressively hamper the success of complex medical procedures such as major surgeries, implantation of prosthetic materials, organ transplants, and immunosuppressive therapies (25). This scenario is already evident in some geographical settings, like the Italian one, where hyperendemicity of carbapenem-resistant and third-generation-cephalosporins resistant *Enterobacteriaceae* represents a daily challenge for the health professionals.

In this epidemiological context, hospital-acquired infections (HAIs) occurring in patients undergoing surgery, are regarded as one of the most fearsome complications, hampering the recovery from, and the intrinsic efficacy of the surgical procedures. The overuse of antibiotics often is driven by this fear and by the misconception that "the more antibiotics the better" in preventing infections and undesirable prolongation of the hospital stay. At the same time, treating infections that could be caused by multi-drug-resistant (MDR) pathogens may appear too complex for the surgeons facing them, preventing them from autonomously prescribing antibiotics and leading to systematic outsourcing that task to the ID or the internal medicine consultant. Other times, antimicrobials are used as a cover for known or possible breakdowns in other elements of surgical site infection prevention.

Many incorrect prescribing behaviours such as prolongation of the Surgical Antibiotic prophylaxis (SAP) beyond the Operatory Room (OR) or of the empirical therapy, redundant antimicrobial coverage, and prescription of oral antimicrobials at the time of discharge from hospital arise from that fears.

The increasing awareness of the need for AMS activities specifically targeting the surgical context recently led to the development of Surgeons driven Initiatives focusing on infectious issues frequently encountered in the surgical practice. (26)

A panel of experts from the Surgical Infection Society (SIS) and the Word Society for Emergency Surgery (WSES) enlisted the opportunities for AMS in the surgical areas and the profitable role the surgeons could play in it: Surgical Antibiotic prophylaxis (SAP) is currently considered a key component of the perioperative infection prevention bundles. Approximately 5% of antimicrobials prescribed in the whole hospital are employed for SAP. Adherence to evidence-based medicine protocols for SAP, especially in terms of timing of appropriate timing and spectrum, although increasing results are still problematically low. Many AMS efforts in the surgical setting focused specifically on this prescribing dimension, reporting variable success. (27)

Although representing a daily task for the surgeons, prescribing antibiotics to treat infections in surgical patients bring some peculiar challenges: sometimes antibiotics should be initiated before a clear diagnosis of infection is evident or definite while in other cases the therapy start should be safely postponed

after adequate sample collections; Infection could present without systemic sign and symptoms, and adequate microbiological sample collection could require invasive procedure rather than rely only upon blood culture; source control is often paramount to eradicate infections, with the need for further antibiotic therapy reduced a few days when the foster is adequately and timely achieved; on the contrary, the optimal duration of treatment in the more complex case, especially if deep SSI is suspected, is ill-defined and needs to be tailored to the individual patient's characteristics and clinical evolution. Team dynamics and local culture tends to play a stronger influence on prescribing patterns and habits, compared to the medical environment. Finally, considering the breadth of the spectrum of the surgical specialitiesties (ranging from the one performing quite exclusively clean procedures, to the intra-abdominal surgery, where clean procedures are virtually absent) a great variability in the affecting infectious issues exist. All these elements required multidisciplinary and multifaceted AMS approaches able to actively engage surgeons as pivotal actors in the prescribing process and to customize activities according to the actual needs of each specific surgical unit.

Antibiotic Stewardship: outcomes and process indicators

Measuring variation in prescribing volumes and appropriateness is an intrinsic and essential activity in AMS efforts, as outlined by the IDSA definition. This notwithstanding, adequate and reliable measurement of AMS intervention's efficacy is still challenging for research in the AMS field. Being the. improvement in the 'appropriateness of prescription' the actual and primary goal of every AMS activities, shared and objective definition and metrics to evaluate appropriateness are still lacking. Considerable research efforts have been made to identify relevant quality indicators that might help define the concept of 'appropriate use'. (28) Some of the most reported quality indicators are 'adherence to guidelines', 'optimized dosing or route of administration', 'de-escalation according to *in vitro* susceptibility. Considering their close association with the quality of antibiotic use, diagnostic behaviours could also be evaluated at the same time as treatment's appropriateness (e.g., timing of culture collection).

These quality indicators, although encompassing the aspects of prescriptions, always require a revision of individual prescriptions, and they remain subjective and hard to standardize and quantitatively count. To overcome this challenge, most studies adopt indirect process indicators to demonstrate the intervention's effectiveness. Antibiotic consumption represents the most used for this purpose.

Measuring antibiotic consumption for AMS purposes usually targets the overall consumption for systemic antibiotics (ATC J01 class) and, when possible, additional stratification by antibiotic classes or single targeted agents. (29) Monitoring individual agents or at least broad-spectrum antibiotics, high-volume or top-ranking antimicrobials have been proposed in addition, to capture their variation and a possible shift in use. The AWaRE index, introduced by the World Health Organization, is a valuable tool for data stratification and performance evaluation; antibiotics are categorized into three classes: Access (antibiotic of choice for the most common infections, should be available at all times, affordable and quality assured); Watch (highest-priority critically important antibiotics to be recommended only for limited indications); Reserve (to be used as a last resort, when all other antibiotics have failed). (30, 31)

Different standardized metrics for the computation of antibiotic use in the hospital setting have been proposed. Defined Daily Doses (DDDs), i.e., the assumed average maintenance dose per day used for its main indication in adults represents the most widely employed metric worldwide.

The Days of Therapy (DOTs), i.e., the administration of a single agent on a given day regardless of the number of doses administered or dosage strength, has been proposed more recently and represents the metric of choice in the United States, as more informative on actual patients' exposure to antimicrobials. When data on individual prescriptions could be retrieved, the Length of Therapy (LOT) could also provide useful information for directing AMS efforts, as they are not influenced by combination treatment. Antibiotic costs should be documented in addition to antibiotic consumption, but they do not provide a suitable basis for the evaluation of AS intervention efficacy. The WHO recommends using at least two metrics since each measurement has some drawbacks. DDDs, for example, are easily obtained from the

pharmacy databases but are scarcely reliable in populations with significant dosing issues (renal impairment or paediatrics). DOTs offer a more reliable measure of consumption in special populations, but they require the collection of single prescriptions (ideally via a computerized system). (32)

Normalization of absolute antibiotic consumption for at-risk days is necessary to allow for comparison and process monitoring. Patients Days, Days Present, or Occupied Bed Days are usually employed according to how the hospital handles administrative data. Since different denominators can produce relevant variations in measurements, it is always relevant to state how denominators are computed (e.g., state whether PDs are calculated on calendar days, passages of midnight).

In settings suffering from resource constraints, Point Prevalence Surveys (PPSs) on antibiotic use can provide some basic information on antibiotic consumption, through a cross-sectional record of every antibiotic prescription with specific indications, administration routes, and standardized patient risk factors. The employ of standardized, international, protocol for PPS allows for benchmarking between healthcare facilities. In addition, periodical PPSs in the same setting could provide useful data to inform AMS program design and priorities. (10)

The main hypothesis grounding ASPs' rationale is that antibiotic usage exerts a selective pressure driving the rise of AMR. Therefore, a decrease in antibiotic use should minimize the selective pressure on bacterial flora thus contributing to the reversal of the AMR phenomenon.

Despite this sound rationale, the effect of AMS programs curbing AMR infections has been poorly demonstrated, especially when focusing on specific multi-drug-resistant phenotypes (16). Few systematic reviews have been published on this subject. Some evidence of ASPs efficacy in reducing AMR rates has been suggested regarding methicillin-resistant *Staphylococcus aureus*, imipenem-resistant *Pseudomonas aeruginosa,* and Extended-spectrum-beta-lactamase (ESBL) producing Enterobacteriaceae. (33-36) More consistent evidence supporting AMS role in reducing the incidence of *Clostridium difficile* infections exists. Conversely, more conflicting results have been obtained when addressing other AMR phenotypes, such as carbapenem-resistant Gram-negative bacteria. (33, 36, 37). These contrasting

results are at least partially due to our partial understanding of the complex relationship between antibiotic exposure and resistance development. Additionally, studies exploring ASPs' effect on microbiological outcomes often suffer from relevant methodological limitations that can significantly impair the results' strength. (16) Relevant variation in microbiological outcomes requires a prolonged period of follow-up, often exceeding the feasibility of the AMS intervention. Moreover, the relationship between those two variables could escape the linear relationship assumed by many statistical models, thus not emerging while already present. (38)

The safety of AMS intervention has been established by many studies, with some achieving a significant reduction in the Length of Hospital Stay (LOS). (16, 37) According to the Cochrane review, some 'unintended consequences of AS' such as 'treatment delay' or 'negative professional culture' could be potentially associated with restrictive interventions and need to be explored whenever possible. (16)

The Verona University Hospital, health performance and epidemiology

The 'Azienda Ospedaliera Universitaria Integrata di Verona' hospital (AOVR) is a 1350-bed tertiary care health service in Verona, Veneto region, Italy. Two hospitals, located in two different 8-km far sites, operate under the same administration. Different medical and surgical departments are located in each site: the "Ospedale Civile Maggiore, Borgo Trento" host 70% of the bed capacity while the "Policlinico G. B. Rossi, Borgo Roma" the 30% left. In 2017 the AOVR average daily census was approximately 1100 patients, with 49500 admissions and 39753 surgical procedures per year, with increasing trends in the last 5 years; The Average Length of Hospital Stay (LOS) was of 7.8 days in 2017.

Around 5000 healthcare workers are employed by the hospital, with about 700 senior physicians and close to 1000 junior doctors (specialist trainees, medical fellows, or university researchers). Many excellence and referral centres for medical and surgical disease are present in the hospital that

Represents the regional hub for several procedures (oncological surgery, neonatal emergency, burn-unit, solid organ transplantation). Infectious Diseases consultation service is available in both facilities 24/7 through

dedicated specialists during working days and on-call consult during non-working hours (remote consult for one site and in-person consult for the other site).

A Point of Prevalence Survey (PPS) is performed annually following the ECDC protocol; it provides estimated figures regarding hospital-acquired infections and antimicrobial usage.

The most recent PPS data (2018) shows that 52.5% of the admitted patient is aged 65 or above with 71.6% of the patients suffering from a non-fatal condition according to McCabe score (10.9% from a rapidly fatal one). At least one invasive device is carried by 78.3% of the included patients, with 21.4% patients having a central-line catheter inserted and 34.3% a urinary catheter (39.7% in the surgical area, more than 55% in the geriatric area). Patients undergoing a surgical procedure represents on average 34.7% of the total admitted patients. Patients admitted in the medical, surgical, intensive areas account for 43% (8% in the geriatric ward), 35%, and 5% of the total admitted patients, respectively.

Before March 2018, the hospital hadn't a formal AMS program in place.

Local guidelines addressing antibiotic treatment and Surgical Antibiotic Prophylaxis (SAP) although existing, were not updated in the previous 5 years and suffered for lack of adherence and knowledge among the prescribers. A post-authorization policy regarding a few antibiotic classes (carbapenems, anti-MRSA drugs other than glycopeptides, new beta-lactams/beta-lactamase inhibitors) required an Infectious Disease (ID) written consult within 48 hours from the initial prescription to be confirmed.

Estimates regarding antibiotic consumption and antibiotic-resistance rate in the surgical area before the starting of the SAVE program can be retrieved from the 2018 PPS and annual microbiology report. (Table 1)

In December 2018, 35% of the total admitted patients were hospitalized in the surgical area; 45.8% of all the included patients were receiving at least one systemic antibiotic agent, with 18% receiving combination therapy. Prevalence was higher in the intensive care (70.4%) followed by the surgical areas (53.9%).

On average, 45% of antibiotics targeted hospital-acquired infections. Pneumonia, abdominal sepsis, and bacteremia were the three most common treatment indications, accounting for more than 45% of the total prescriptions. In the surgical area, the reason for prescribing antibiotics was to treat an infection in 35.6% of patients and as prophylaxis in 59.4%; 21% of the prescriptions for surgical prophylaxis had a duration longer than 24 hours. Twenty-one precents of the surgical patients had a central vascular access in place the day of observation and 39% had a bladder catheter. Prevalence of Hospital Acquired Infections (HAI) was especially concerning, as doubling the European rate (6% in the 2011-2012 PPS) (39); the prevalence was higher in the surgical area of the hospital with Surgical Site Infections (SSI) accounting for the 12% of the total HAIs.

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Considering the whole hospital beta-lactam/beta-lactamase inhibitors (BL/BLIs) alone represented 42.3% of the agents prescribed as treatment, followed by carbapenems and third or fourth-generation cephalosporin, both accounting for 10% of prescriptions. A considerable reduction in fluoroquinolones prescriptions was recorded compared to 2015 data, with a drop from 11.2% to 5.6 % of the total. As for surgical prophylaxis, first-generation cephalosporins were the most prescribed agent, followed by BL/BLIs (39.3% and 27%, respectively). In this context, the Alcohol Hand Rub (AHR) consumption in the AOVR showed unacceptably low levels, considerably below the national average of 22.5 liters*1000PDs for large hospitals (i.e. more than 500 beds). (40)

Table 1: Benchmarking AOVR data with national and EU PPS

	AOVR 2018	**ITA PPS 2016-17**	**EU PPS 2016-17**
Patients receiving systemic antimicrobials	45.8%	44.5%	30.5%
Systemic antimicrobial consumption (ATC J01) DDDs/100PDs	77.84	64.6	46
HAI prevalence *Surgical Area*	11.4% *12.5%*	9.3% *hospitals* *> 500 beds*	6% (2012 PPS)
Alcohol hand rub consumption	15 l/1000PDS	22.5 l/1000PDs *hospitals* *> 500 beds*	23.9 l/1000PDs

The percentage of patients receiving at least one antibiotic agent in 2017 PPS appears similar to the national average (45.7% versus 44.5%), but it is considerably higher than the European one (30.5%), with Italy representing the fifth EU country with the highest rate of hospitalized patients receiving antibiotics during the survey period.
In 2017, local consumption of systemic antimicrobials (J01 ATC class) resulted higher than the national average from 2016-2017 PPS (73.36 versus 64.6 DDDs*100PDs).

According to the 2018 report published by the local Committee for Infection Prevention and Control (IPC), blood cultures collected in the surgical areas, both general and specialized surgery, grew gram-positive bacteria in more than 60% of cases. Considering all the microbiological samples analyzed, the prevalence of Methicillin-resistant *S.aureus* (MRSA)on total *S.aureus* isolates was approximately 30%, whit higher values in the General Surgery area (35.2%); Third-Generation cephalosporins resistant Enterobacteriaceae represents more than 30% of the overall Enterobacteriaceae *isolates*. Resistance to carbapenems in *K.pneumoniae* isolates showed more variability with the highest prevalence observed in the specialized surgery (43.3%) compared to general surgery and specialized ICU.

Table 2. selected data from the annual microbiological report (AOVR Surgical Area)

2018	Positive Blood Colture (BC) (/total)	Gram Negative BC	Gram positive BC	MRSA (Prevalence on total *S.aureus* isolates, *all sample*s, **BC**))	3CR-*Enterobacteriacea* (Prevalence on total Enterobacteriacea, *all sample*s, **BC**)	CR-KP (Prevalence on total *K.pneunmoniae all sample*s, **BC**))
General Surgery	716(/4202)	219 (30.6%)	435 (60.8%)	*35.2%*	*31%*	*29.2%*
Specialized Surgery	252(/2814)	70 (27.8%)	160 (63.5%)	*29.9%*	*38.5%*	*43.3%*
Specialized ICU	355(/3294)	139 (39.1%)	209 (58.9%)	*32.9%*	*34.3%*	*35%*

Comparing these data with the European Surveillance one provided by the European AMR Surveillance report (41), the prevalence of third-generation-cephalosporins resistant *Enterobacteriaceae* appears higher than the European average (15.1% for *E.coli*, 31.7% for K.pneumoniae) while the rate of carbapenem-resistant *K.pneumoniae* is extremely concerning, approaching 4-folds the European prevalence (7.5%) and being also higher than the reported Italian average (26.8%). The MRSA prevalence in AOVR, although slightly inferior to the Italian one (34%) appears still double the European average (16.4%). Even if these comparisons should take into account the different samples included (European Surveillance being limited to invasive isolates), a dramatic landscape emerges, with multi-drug-resistant (MDR) Enterobacteriaceae representing a serious threat, in line with many Italian hospital situations (1). Antimicrobial resistance in gram-positive bacteria, especially *S.aureus* and vancomycin-resistant *Enterococcus faecium* (VRE), also needs to be efficacely contrasted.

The SAVE program

The first multidisciplinary AMS committee of the AOVR was formally appointed in March 2018 by the hospital administration, on the initiative and proposal of the Infectious and Tropical Disease Unit Director. It was entrusted with the designing and implementation of an AMS program addressing the whole hospital and named 'SAVE (Stewardship Antibiotica Verona)'; The Infectious and Tropical Disease Unit coordinate the activities of the multidisciplinary group whose members were selected among the hospital professionals of key discipline implicated in the antimicrobial prescribing process and management (Infectious Disease, Microbiology, Pharmacy, Infection Prevention and Control, Hospital Hygiene and Epidemiology, and Psychology). The several disciplines involved were assigned specific tasks and goals within the program:

- Microbiology: in addition to the routinely expertise supporting the ID consultant during the intervention, the appropriateness of the diagnostic procedures and sample management in the pre-analytic phase was monitored. Contribution in the surveillance of AMR and

support the accuracy of the data-flow ensuring the AMS microbiology outcome measurement.

- Pharmacy: monitoring the antimicrobial consumption, providing antimicrobial usage data and their computation into the selected indicators; Tracking prescriptions of antimicrobials requiring post-authorization by the ID specialist.
- Infection Prevention and Control (IPC) Department: implementation of the existing IPC policies and Standard Operative Procedures (SOP) with direct observation of the involved wards adherence during daily clinical practice. Ensuring the integration of the AMS activities.
- Clinical Psychology: contributing to the intervention design according to the 'Behavior Change framework theory'
- Infectious Disease: coordination of the AMS team and activities; responsible for the daily implementation of the intervention in the hospital departments and data analysis.
- Hospital Hygiene and Epidemiology: collecting data on the selected process and outcome indicators.

The SAVE team met periodically to design, schedule and verified the AS intervention implementation, discussing and addressing the specific issues affecting antimicrobial prescribing practice in the individual involved department as well as in the hospital as a whole.

The SAVE program was designed as a Quality Improvement project, applied in the real hospital work setting and continuously influenced by the ongoing learning process. For its intrinsic nature, a careful plan should be developed, encompassing the established aims, the predefined metrics, and the time frame for conclusive and interim analysis of the efficacy as well as of the emerging barriers and facilitators to implementation.

The model of the Plan-Do-Study-Act (42) cycle provides a useful approach for action-oriented learning within the quality improvement interventions; it requires firstly to plan the change then to observe the results and finally to act on what has been learnt during the process, allowing a continuous redefinition of the initial transition and proposed goal, for improvement. This kind of project led to output that can be applied to further quality improvement

initiatives and provide valuable insights on the most successful strategies to achieve measurable progress.

Based on the hospital Point of Prevalence Survey (PPS), carried out in 2017, and the available antimicrobial consumption data (from the pharmacy annual report) the AMS team developed a calendar for a stepped-wedge implementation of the SAVE intervention in the whole hospital, including blocks of new wards every three months and to cover the medical and surgical areas over three years; the Intensive Care Units, Hematology, Obstetrics-Gynecology, and Pediatrics areas were not included, as the particular aspect of the patients' case-mix and antimicrobial prescribing patterns in that settings was thought to require a dedicated intervention to be carried out later. The units with more than 60% prevalence of patients receiving antibiotic treatment were granted a 'high priority, wards with a prevalence ranging between 30 and 60% were prioritized as 'medium', and wards with less than 30% of prevalence of antibiotic prescription were prioritized as 'low' (Table 3 summarizes the prioritization of the AS intervention in the hospital wards).

Table 3. Pre-intervention antimicrobial consumption estimates by ward and intervention prioritization

Ward name	**DDD*100 PDs 2017** (pharmacy database)	**Prevalence of patients receiving antimicrobials (%)** (2017 PPS)	**Priority**
Internal Medicine B	86	63	High priority
Internal Medicine C	62	62	
Geriatrics A	70	61	
Geriatrics B	80	61	
Maxillo-facial surgery	129	82	
Endocrinology and Gastroenterology	74	69	
Pneumology	45	61	
Urology	99	68	
General Surgery BT	78	71	
Internal Medicine D	76	45	Medium priority
General Surgery A	65	48	
Internal Medicine BT	59	42	
Traumatology	35	52	
ENT	43	40	
General Surgery B	76	37	
Heart Surgery	51	19	Low priority
Neurosurgery	29	16	
Nephrology	67	27	

Neurology B	32	20	
Neurology A	31	5	
Cardiology	45	22	
Gastroenterology B and Rheumatology	42	14	
Psychiatry	14	0	
Oftalmology	13	0	

According to the literature, adequate indicators for antimicrobial consumption and clinical outcomes were selected to ensure the intervention's measurability in terms of safety and efficacy. The Interrupted Time Serie (ITS) Analysis was chosen as statistical method, considering the quality improvement the quasi-experimental nature of the project (43). Periodic analysis of hospital antimicrobial consumption data and annual PPS results was performed highlighting the emergence of issues and needs (e.g. MDR outbreak) that should prompt variation in the schedule of intervention implementation in the individual departments.

The first block of wards involved from June 2018 to March 2020 was 4 general medicine wards, equally distributed in the two Borgo Roma and Borgo Trento Hospital. In those departments the AMS intervention achieved an immediate reduction in the level of overall antibiotic consumption, both in terms of DOTs*1000 PDs (-162.2; P=0.005) and DDDs*1000 PDs (-183.6; P=<0.001) and consumption kept decreasing during the whole post-intervention phase, with a monthly rate of 3.6 DDD*100PDs (P= 0.04) and 3.36 DOTs*1000PDs (P=0.03). Reduction in consumption was consistent also in the two target antibiotic classes of fluoroquinolones and carbapenems (-35.5 DOTs*1000PDs and - 23.1 DOTs*1000PDs, P=0.03 and 0.003 respectively) with only fluoroquinolones keeping a long-term significant reduction (-2.1 DOTs*1000PDs, P=0.016). Reduction in the mean length of hospital stay and all-cause mortality rates occurred in the post-intervention period; rates of *Clostridium difficile* and carbapenem-resistant Enterobacteriaceae bloodstream infections tended to reduce, although non-significantly, in both the early and the long-term phase after the intervention. (44).

As planned, the intervention was then extended to surgical departments in the hospital. Despite results in the medical areas appear promising, a separate analysis should be conducted to confirm the effectiveness of the intervention

in the surgical area; indeed, the unique dimensions of the surgical antibiotic prophylaxis and the post-surgical infection along with the different relational dynamics and areas of expertise of the prescribers represents peculiarity of the surgical pathway of care strongly influencing the prescribing patterns and habits.

This work aims to describe the results of the SAVE project in the first block of surgical wards that have completed the one-year intervention implementation.

METHODS

Study setting

The SAVE project scheduled a stepped implementation of the AMS intervention in all the medical and surgical units of the hospital over 3 years, starting from the ones ranked in the top positions for patients' exposure to antibiotics, based on the 2017 hospital Point of Prevalence Survey (PPS) of antimicrobial use. Four internal medicine departments were involved first (May- September 2018) then the project start focusing on the surgical areas. Five surgical units were involved in the save project in the period October 2018-February 2020; one surgical-specialized Intensive Care Unit (ICU) was also included due to its shared path of care and high rate of co-managed patients with one of the surgical units. The original plan was to keep involving 2 units every 4-6 months in 2020 but the covid-19 pandemic claimed reallocation of the hospital resources with ID specialists, microbiologists and IPC practitioners called to focus on covid-19 related issues and surgical activities limited to urgent procedures for prolonged periods.

The main characteristics of each surgical unit are provided below:

Urology. A 32 beds-units (10 reserved for short-stay hospitalization, i.e. week-surgery) with surgical expertise focusing on oncologic pathologies, prostatic disease and post-traumatic bladder and renal damage. Laparoscopic and robotic techniques are employed frequently. The staff is made up of senior doctors co-adjuvate by junior physicians, as the residency training, especially the first 3 years, took place prevalently in the Operatory Room (OR) and in the ward. The ward and the related ambulatorial. Activities and Day-Hospital are all located in the principal building of the Borgo Trento Hospital, along with all the ORs and the ICUs.

General Surgery. A 40 beds-unit performing pancreatic and hepatobiliary as well as oncological colorectal surgery with expertise on laparoscopic and robotic approaches. Vascular surgery is also performed. It represents the main unit for urgent surgical hospitalization from the Emergency Room (ER) in the Borgo Roma hospital, so urgent and elective surgical patients are equally present. The senior medical staff is supported by junior surgeons during their residency rotation.

Traumatology. The ward capacity was 30 beds when the intervention started but increased to 40 beds in the first-year post-intervention. Hospitalized patients were affected by a traumatic injury (with a high rate of hip and femoral fracture in the elderly) with a minority undergoing elective surgery for prosthetic joint replacement and infections, and correction of congenital malformation in children.

Cardiac Surgery. A 34-bedded unit highly specialized in cardiac surgery ward with a transplant unit. More than 200 coronary artery bypass graft surgeries and 400 valvular procedures are performed annually. Correction of congenital cardiac malformation is also performed. A considerable amount of the surgical patients, especially the ones undergoing complex procedures, are co-managed with the Cardiothoracic ICU, where patients are transferred for post-surgical recovery or in case of critical illness or complication. This 12-beds unit also hospitalized complex patients needing critical care from the Thoracic surgery unit and children with cardiac malformation. In both units, the senior medical staff is supported by junior doctors during their residency rotation.

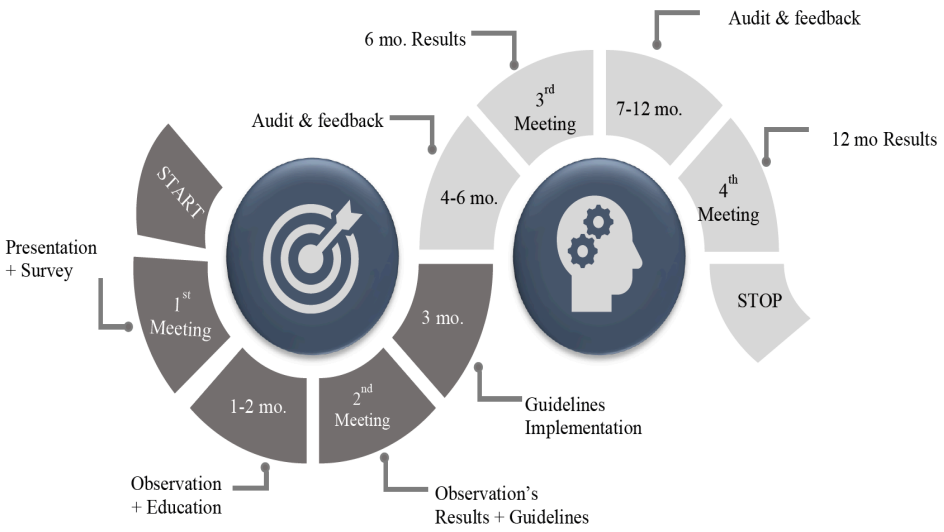
The SAVE intervention

The AMS intervention implementation took place in October 2018 in General Surgery and started the next month (November 2018) in the traumatology and Urology Units; Cardiac surgery and the Cardiothoracic ICU were involved starting from March 2019.

The intervention was articulated in 2 subsequent phases, with an overall one-year duration. A 3-month 'intensive phase' was followed by a 'maintenance phase' for an additionally 9-months. A preliminary assessment took place before the implementation phase: during a dedicated meeting with the Responsible for the SAVE project and the ID physician responsible for the actual implementation in the specific surgical unit, the Unit's Director granted his endorsement and appointed two medical staff members (at least one senior surgeon) as the local Champion for AMS; they were entrusted for intervention coordination and support. Then, a presentation meeting attended by the whole

medical staff and the nurse coordinator was held to explain the project's rationale, structure, and objectives.

The SAVE intervention timeline is represented in Figure 1.



1. Intensive phase (1st-3rd month)

This intervention phase included two main components.

The first period focused on observation of the current surgical and clinical daily practice as well as on education and training on the field. A dedicated ID specialist with expertise in AMS attended the surgical unit daily with special emphasis on:

- revision and discussion of every antibiotic prescription with the surgeon in charge in terms of indication, antimicrobial agent, posology, and duration of treatment. The general approach and existing protocols for SAP were also discussed.
- clinical rounds and department meetings to foster multidisciplinary management of patients with infectious issues.
- provision of written ID consultations upon request of the surgeon in charge;
- identification of the most encountered infectious issues and surgical procedures requiring SAP. Along with antimicrobial therapeutical management, diagnostic procedures and surgical management of infectious complications to be addressed by the local guidance protocol were discussed;

- auditing infection control practices performed by the IPC department.

The ID physician also seized this phase to carefully evaluate determinants of prescribing habits within the specific surgical unit context using 3 predefined, qualitative checklists: 1)
quality indicators of antibiotic prescription; 2) individual and contextual determinants of antibiotic prescribing; 3) adherence to infection prevention and control practices.

These tools helped in identifying areas to be prioritized during the intervention

An implementation phase followed, introduced by a second plenary meeting to present, and discuss results of the observation phase. Tailored strategies to address the most challenging aspects of antimicrobials prescriptions and corrective actions to improve behaviours in the emerged highly critical elements were proposed by the AMS team. Finally, a draft proposal for guidelines for SAP and empirical antibiotic therapy was presented in detail. In the next 4-6 weeks the guideline proposal was applied and tested in the daily clinical practice with close ID specialist support, to appraise its actual feasibility and make the requisite correction if any. Then formal approval was signed by the AMS team, the surgical unit's Director and Champions, and the Hospital Committee for Quality Improvement.

2. Maintenance phase (4th-12th month)

Periodic Audit and feedback activities started soon after the guidelines official approval. Audits were performed weekly in the first 2-3 months period, then every month by the Infectious Disease specialist responsible for intervention implementation in that specific surgical unit, supported by ID junior doctors in their last year of residency. The prescribing appropriateness evaluation was performed periodically by revision of every prescription of systemic antibiotics (ATC class J01) on a random day of the week, Monday to Saturday. A pre-defined 'Audit record form' was employed to standardize audits practice and prescribing dimensions to be analyzed. A first stratification classified prescriptions into empirical treatment, targeted treatment, and surgical/perioperative prophylaxis. Secondly, prescriptions

were compared to guidelines and microbiological data when available in terms of 7 dimensions: written indication, antibiotic molecule choice, posology, duration, combination therapy, other reasons for inappropriateness (i.e., not complying with the ID written consultation).
Allergies and recommendations provided by the ID consultant were also collected.
Periodic feedback modality was agreed with the local Champions and the Unit's Director to allow customization based on individual ward needs and clinical routine organization. The ID specialist was available during the whole audit and feedback period to discuss clinical cases and provide written consult upon request. Periodical reports to present the audit and feedback activity results and provide further improvement recommendations were sent to the ward's Champions and Director and face-to-face meetings to discuss them were held upon the ward's request.

A formal Educational workshop was offered to the whole surgical staff through a CME accredited 8-hours course. The educational sessions focused on the rational and correct management of SAP, the most frequent infectious issues occurring in the surgical patient and IPC practice to prevent HAI with specific emphasis on SSI. Course attendance was compulsory for the two AMS Champions appointed for each ward but also open to all the surgeons willing to participate and junior surgeons' attendance was especially incentivized. The learning objectives were verified via a final multiple-choice test. Participants scoring at least 75% in the final test were accredited by the CME and obtained a two-year validity certificate for antibiotic prescribing competence. Periodic editions of the course were planned for the certificate refresh. The IPC department also held periodic meetings with the nursing staff to enforce adherence to IPC protocols.

Process indicators

Antimicrobial Stewardship primary goals are the improvement of antimicrobial prescribing appropriateness with the final aim of improving patients' care and curbing antimicrobial-resistance surge. Appropriateness evaluation is hard to standardize and to be quantitatively measured while

antimicrobial-resistant infections rate (measured by both incidence or prevalence metrics) required a long period for significant variation to occur, with many confounders playing a role in addition to antimicrobial prescribing patterns. For these reasons, intermediate indicators, whose variation is feasible and timely fashioned to be collected and analyzed, are usually selected as primary outcomes to evaluate AMS intervention effectiveness.
Antimicrobial usage metrics are the most encountered indirect process indicator adequate for this purpose. As overuse of antimicrobials is thought to cause individual patients adverse events (e.g. *C.difficile* infection) and foster antimicrobial resistance, reduction in antimicrobial consumption is often regarded as a desirable outcome. Some appropriateness evaluations, always qualitatively measured, are also often reported in the literature. Finally, clinical outcome indicators, aimed at guaranteeing the general safety of the intervention, are less frequently reported to complement consumption or appropriateness data.

Several indicators were selected to capture the efficacy and ensure the safety of the SAVE intervention. Aggregation at the level of the single department or per area of care (e.g., general medicine, surgery) was performed. Data were collected retrospectively for the 12 months before the intervention and prospectively after the intervention start then encompassing the whole intervention 12-months duration. Additional follow-up, beyond intervention completion, was planned.
The following table details the selected indicators and their units of measurement.

Table 4 selected antimicrobial usage, clinical and microbiological indicators

Indicators	**Unit of measure**
Defined Daily Doses of antibiotics for systemic use (ATC J01) **(overall consumption, carbapenems, fluoroquinolones, anti-MRSA antimicrobials*)**	DDD*1000 PDs (per ward or area of care)
Day of Therapy of antibiotics for systemic use (ATC J01) **(overall consumption, carbapenems, fluoroquinolones, anti-MRSA antimicrobials*)**	DOT*1000 PDs (per ward or area of care)
Length-of-treatment	LOT*1000 PDs

Incidence of blood stream infection (BSI) (Total BSI, gram-positive BSI, gram-negative BSI, thrid-generation cephalosporins-resistant gram-negative BSI, carabapenem-resistant gram-negative BSI)	No. of blood-stream-infection (BSI) *100 admitted patients
Incidence of Clostridium difficile infections	No. of C. difficile positive samples (GDH + / EIA toxin +) *100 admitted patients
Monthly in-hospital mortality	Patients who died during the hospital stay/total admitted patients in the same month
Average monthly length-of-stay (LOS)	PDs monthly/total patients admitted in the same month

Audit data

Percentages of patients administered with at least one dose of antimicrobials and prescribing appropriateness were assessed through periodic cross-sectional audits. Results were graphically displayed over time. The graphs were visually inspected every month, and a comprehensive report detailing the trend of appropriateness and more frequent cause for inappropriateness was provided to each surgical unit every three-six months.

Antimicrobial Usage data

Data on monthly antibiotic usage were collected retrospectively through the electronic prescribing software statistical suite (Bustermed®) using single wards as the unit of analysis; data based on the actual administration of drugs (as checked by a nurse during real-time dispensation to the patient) were employed in preference to the ones based on prescription (as checked by the doctor during prescribing practice). For the units not employing the electronic prescribing software (i.e. Intensive Care Units), DDDs were computed through the pharmacy records of antibiotic procurements by single wards.

The total amount of drug administered/procured was converted in DDDs according to the 2019 ATC/DDD index issued by the World Health Organization [ATC/DDD]. DOTs and LOTs were computed by the pharmacist of the SAVE team from single doses of administered antibiotics using a homemade database and worksheet based on Access® and Excel® software (45).

Hospital admissions, Patient-days (PDs), and length of hospital stay were provided by the hospital administrative data management service; PDs were

computed by dividing each patient's length of stay (expressed by hours) per 24 hours.

Microbiological and Clinical data

Cases of *C. difficile* infections were provided by the Microbiology Laboratory and defined as positivity of Glutamate Dehydrogenase (GDH) and toxin A or B detected via an enzyme immunoassay technique. Cases of bloodstream infection (BSI) were provided by the Microbiology Laboratory and defined as any blood culture growing any pathogen in at least one set (2 bottles). Third-generation-cephalosporins-resistance and Carbapenem-resistance were defined as phenotypic resistance to cefotaxime and ceftazidime (or both) and at least one carbapenem respectively. Following current recommendations on the topic, only the first isolates/positive tests per patient in a 28-days-period were counted. (46)

Statistical analysis

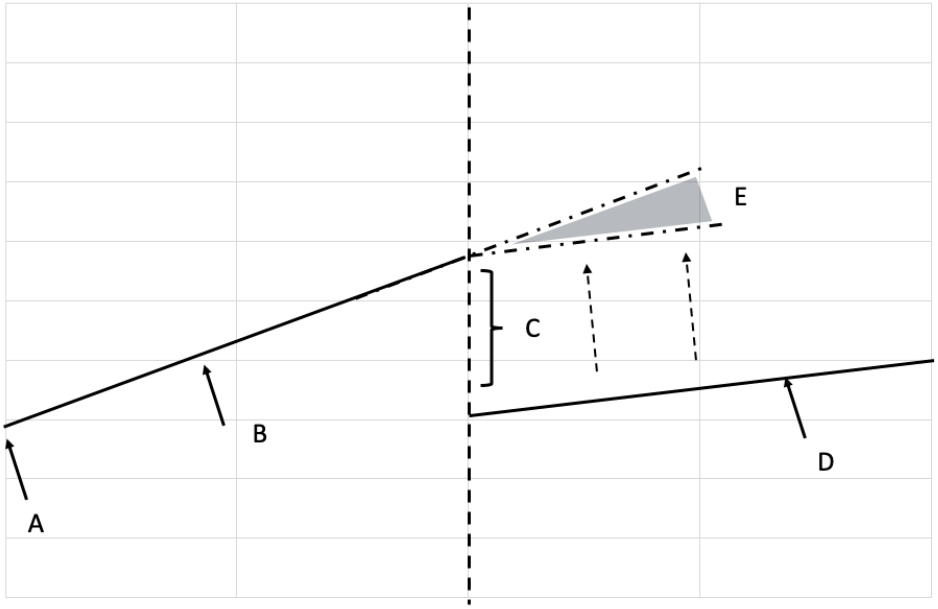
The hypothesis of any intervention effect on the selected outcomes was tested comparing the pre-intervention and the postintervention period for each surgical ward, carrying out a single-group interrupted time series (ITS) analysis.

The hypothetical effect of the AMS intervention in modifying the antibiotic consumption and the clinical and microbiological outcomes indicators was interpreted according to the 5 parameters defining the ITS analysis:

- Baseline (Fig. 2; A): intercept of the regression line with the y axis. It represents the starting level of the outcome in the pre-intervention period;
- Pre-intervention trend (Fig. 2; B): the regression line slope in the pre-intervention data time-series;
- Change in level (Fig. 2; C): the difference between the two regressions lines (pre-intervention and post-intervention) y-axis value at the time-point when the intervention starts. It provides an estimate of the immediate impact of the intervention under evaluation;
- Post-intervention trend (Fig. 2; D): post-intervention period regression line slope;
- Trend difference (Fig 2; E): graphically represented as the width of the

angle formed between the pre-intervention and postintervention
regression slope. It is a parameter that estimates the overall effect in the intervention, considering the total variation occurring between the two periods slope.

Figure 2: Main parameters defining the Interrupted Time Series (ITS) analysis



The model was fit using an ordinary least squares regression analysis (Neweywest); the Cumby and Huizinga general test for autocorrelation was employed to test the autocorrelation in the error distribution. All the analyses were performed using STATA Software (© 2015 StataCorp LLC, Texas). (47)

Data confidentiality and ethical aspects

No direct access to individual patient's clinical records was needed for the antimicrobial usage and microbiological data, as well as the other clinical indicators (i.e., ward-mortality and the average length of stay) as they were collected in an aggregate manner via the hospital administrative database, the electronic prescribing software and the pharmacy database, the microbiology databases.

For the auditing process, direct access to patient records was required, but collected data were anonymized before entering the database. Referral to

individual specific patients occurred only during the feedback provided by the ID specialist to the prescriber directly responsible for that patient and aimed at a real-time improvement of the patient care, as in the routinely specialist consultation.

AMS programs effectiveness in improving patients care through increased antimicrobial prescribing appropriateness is well documented in the literature and AMS programs are nowadays standard quality requirements for health care delivery in many settings (48). The Italian 2017 national plan for contrasting AMR included a dedicated section on the correct use of antibiotics in the human context providing a reference framework for AMS activities and antimicrobial consumption goals at a national and regional level.

Most of the selected indicators on antibiotic consumption and resistance included for the SAVE project evaluation were adopted in line with those national and international requirements (6, 49)

To incentivize and promote the active participation and adherence of individual medical and surgical units to the AMS activities, the hospital CEO included the SAVE project among the budget objectives proposed to each hospital department for the period 2018-2021. This notwithstanding, the actual decision to join the program was left to each clinical unit Director. As the program approach was persuasive and enabling, aimed at improving knowledge and implementation of the most recent scientific evidence, and no new restrictive procedures were implemented, the medical staff maintained complete autonomy in their clinical practice and the final decision-power about the diagnostic and therapeutic process. All these elements shaped the SAVE project as a Quality improvement initiative.

Institutional Review Board approval was obtained for data collection and results' publications (Prog. 2024CESC Verona e Rovigo, 29/01/2019) and the informed consent was not deemed necessary from individual patients admitted in the participating departments.

RESULTS

Urology

The SAVE intervention in the Urology ward started in November 2018 (pre-intervention period: November 2017-October 2018; post-intervention period: November 2018-October 2019). Fourteen senior and 27 junior surgeons prescribing antimicrobials to the hospitalized patients were involved.

Guidelines for SAP and empirical antimicrobial therapy were approved and disseminated in February 2019. Audits for evaluating antimicrobial prescription appropriateness were performed from May to August and feedback were provided directly to ward staff during routinely consulting activities.

Prescribing Appropriateness

Thirteen audits were performed weekly in the period May to August 2019; 238 antibiotic prescriptions in 221 patients were reviewed. The overall prevalence of patients prescribed with at least one antibiotic was 63.5% (221 on 348 patients hospitalized). Fifty-four percent of the total prescriptions addressed SAP, 30% represented empirical therapy and 15% was aimed at targeted antibiotic treatment.

Beta-lactams/beta-lactamase inhibitor associations represented 65% of the prescriptions with amoxicillin-clavulanate resulting in the individual most prescribed agent (50% of the total); Third generation-cephalosporins were prescribed in 15% of cases, followed by carbapenems (11%) and anti-gram-positive agents (11%). Considering only therapeutical prescriptions, the defined or presumptive source of the infectious process was represented by the urinary tract in 66% of cases, followed by the abdomen (13%). Primary bloodstream infection was indicated as the reason for prescription in 12% of cases, lung infection accounted only for 5% of total prescriptions; a clear source of infection couldn't be identified in the 4% of cases.

Overall prescribing appropriateness was 71%. For SAP appropriateness was 61% (72 out of 118 prescriptions); the main reason for inappropriateness was unnecessary prescription (17 out of 46 inappropriate prescriptions), excessive duration (16/46), and incorrect choice of antimicrobial agent (15/46).

Seventy-eight percent of antibiotics prescribed for SAP were administered for less than 24 hours.

Forty percent (27 out of 67) of the prescriptions for empirical therapy were inappropriate: 14 were judged as unnecessary antibiotic prescriptions and 7 as excessive duration of therapy. Two of the 34 prescriptions for targeted therapy resulted inappropriate, both for the excessive duration.

Figure 3. Prevalence of patients receiving antibiotics in the Urology unit

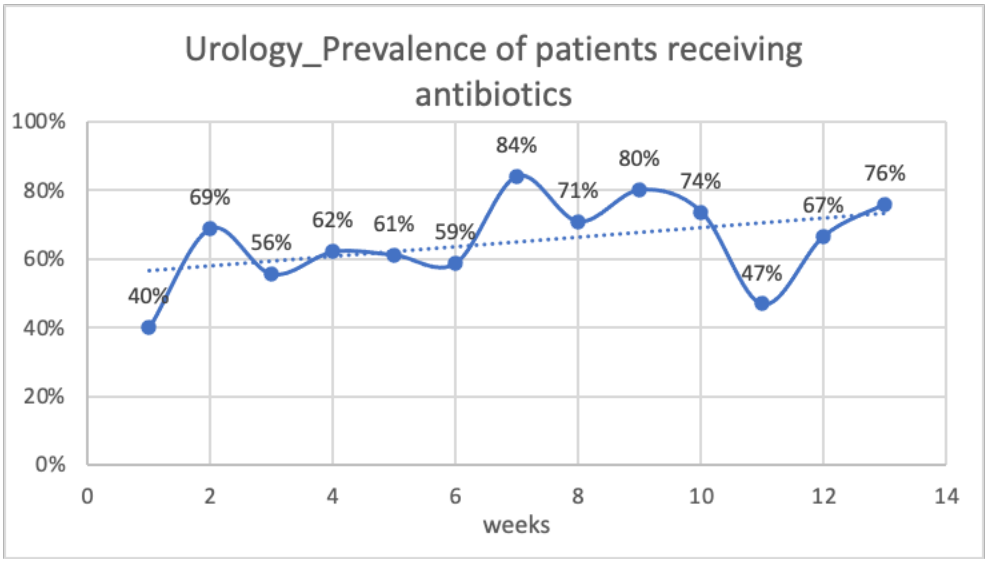
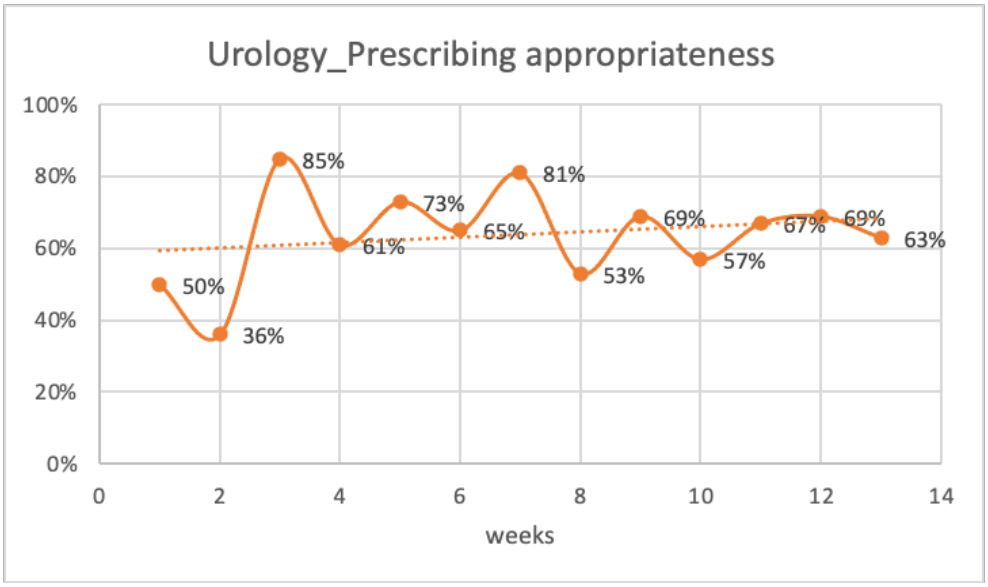


Figure 4. Prescribing appropriateness in the Urology unit



Antimicrobial Consumption

Overall normalized antimicrobial consumption (expressed as DOT per 1000 PDs) showed lower levels during the post-intervention period (874,2 vs 1018,1, -14,1%). The fluoroquinolones (14,6 vs 93,4, -84,3%), carbapenems (59,3 vs 92,4; -35,8%) and anti-MRSA agents (42,9 vs 55,0, -22,0%) consumption was consistently lower in the post-intervention period. Exposure to antimicrobials included in the WHO Access class increased (516,7 vs 437,2, +18,2%) while reduction in the consumption of the Watch (330,3 vs 516,0, -36,0%) and the Reserve agents (20,3 vs 43,2, -53,2%) occurred. Additionally, considerable shift in relative composition of consumption was observed in the post-intervention period with Access agents overtaking the Watch (Access from 42,9% to 59,1%, Watch from 50,7% to 37,8% of the total) and proportion of Reserve agents almost halving (4.2% to 2.3% of the total). Fluroquinolones and carbapenems dropped from 9% of the total consumption to 1.7% and 6.8%, respectively; no variations occurred for anti-MRSA agents, representing approximately the 5% of the total consumption in both the periods. Considering individual J01 agents, amoxicillin/clavulanate (from 263,6 to 389,2, +47,6%) drove the increment in the Access class consumption, while cefazolin (from 115,8 to 82, -29,1%), principally employed for SAP, showed a substantial reduction in consumption. Decrease in the consumption of piperacillin-tazobactam (from 292,3 to 190,0, -35,0%), ciprofloxacin (from 90,4 to 12,0, -86,8%), and meropenem (from 80,0 to 48,3, -39,6%) accounted for shift in usage of the Watch agents, while overall third- and fourth generation-cephalosporins were stable across the two periods. Linezolid (from 17,6 to 6,7, -62,1%) and ceftazidime-avibactam (4,2 vs 0,4, -90,6%) significantly contributed to the reduction in the Reserve agents use. Complete data on consumption of ATC-J01 agents are provided in table 5.

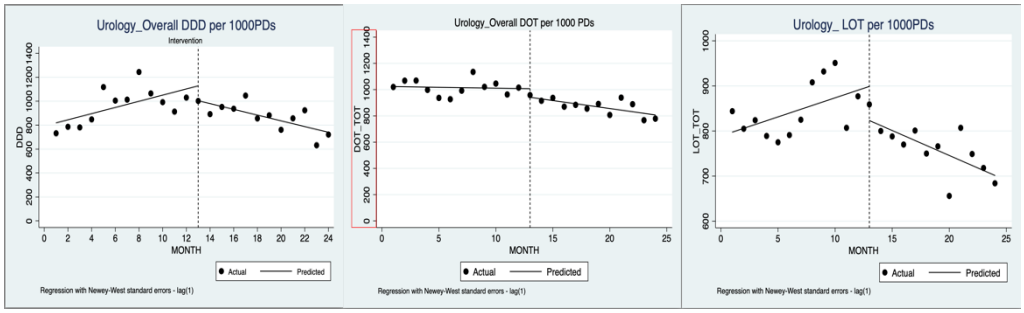
Table 5: Urology ward, antimicrobial consumption (DOTs per 1000PDs) of ATC-J01 antimicrobial agents

DOTs x1000PDs	Pre-Intervention (%)	Post-intervention (%)	Δ (%)
Daptomycin	17,9 (1,8%)	18,1 (2,1%)	0,3 (1,5%)
Fosfomycin	0,1 (0,0%)	1,7 (0,2%)	1,6 (1108,0%)
Linezolid	17,6 (1,7%)	6,7 (0,8%)	- 10,9 (-62,1%)
Amikacin	3,1 (0,3%)	0,1 (0,0%)	- 2,9 (-96,0%)
Gentamicin	25,4 (2,5%)	23,6 (2,7%)	- 1,8 (-7,0%)
Ertapenem	12,7 (1,2%)	10,6 (1,2%)	- 2,1 (-16,3%)
Imipenem + Cilastatin	3,7 (0,4%)	0,4 (0,0%)	- 3,3 (-88,9%)
Meropenem	80,0 (7,9%)	48,3 (5,5%)	- 31,6 (-39,6%)
Ceftaroline fosamil	-	0,6 (0,1%)	0,6 (-)
Ceftolozane + Tazobactam	0,7 (0,1%)	-	- 0,7 (-100,0%)
Cefazolin	115,8 (11,4%)	82,1 (9,4%)	- 33,6 (-29,1%)
Cefuroxime	0,5 (0,1%)	16,7 (1,9%)	16,2 (3116,3%)
Cefixime	-	0,3 (0,0%)	0,3 (-)
Cefotaxime	0,6 (0,1%)	9,5 (1,1%)	8,9 (1441,0%)
Ceftazidime	19,4 (1,9%)	9,1 (1,0%)	- 10,2 (-52,8%)
Ceftazidima + Avibactam	4,2 (0,4%)	0,4 (0,0%)	- 3,8 (-90,6%)
Ceftriaxone	6,6 (0,6%)	4,2 (0,5%)	- 2,4 (-35,8%)
Cefepime	-	0,7 (0,1%)	0,7 (NA)
Metronidazole	6,1 (0,6%)	5,6 (0,6%)	- 0,5 (-7,7%)
Ciprofloxacin	90,4 (8,9%)	12,0 (1,4%)	- 78,4 (-86,8%)
Levofloxacin	9,7 (1,0%)	2,7 (0,3%)	- 7,1 (-72,6%)
Teicoplanin	1,3 (0,1%)	3,3 (0,4%)	2,0 (148,8%)
Vancomycin	18,6 (1,8%)	17,4 (2,0%)	- 1,2 (-6,3%)
Clindamycina	7,1 (0,7%)	2,8 (0,3%)	- 4,3 (-60,3%)
Clarithromycin	0,9 (0,1%)	0,9 (0,1%)	- (0%)
Amoxicillin	0,4 (0,0%)	-	- 0,4 (-100,0%)
Ampicillin	-	0,1 (0,0%)	0,1 (NA)
Piperacillin	1,0 (0,1%)	2,3 (0,3%)	1,3 (129,4%)
Amoxicillin + clavulanate	263,6 (25,9%)	389,2 (44,5%)	125,6 (47,6%)
Ampicillin + Sulbactam	-	1,6 (0,2%)	1,6 (NA)
Piperacillin + Tazobactam	292,3 (28,7%)	190,0 (21,7%)	- 102,2 (-35,0%)
Oxacillin	0,5 (0,0%)	1,4 (0,2%)	0,9 (179,8%)
Colistin	7,4 (0,7%)	0,3 (0,0%)	- 7,1 (-95,9%)
Trimethoprim-sulphametoxazole	1,1 (0,1%)	10,2 (1,2%)	9,1 (847,5%)

Doxiciclin	0,1 (0,0%)	-	-0,1 (-100,0%)
Tigecyclina	7,2 (0,7%)	0,8 (0,1%)	- 6,4 (-89,4%)
TOTAL	**1.018,1**	**874,2**	**- 143,9 (-14,1%)**
Fluoroquinolones	93,4 (9,2%)	14,6 (1,7%)	- 78,8 (-84,3%)
Carbapenems	92,4 (9,1%)	59,3 (6,8%)	- 33,1 (-35,8%)
Anti_MRSA antimicrobials*	55,0 (5,4%)	42,9 (4,9%)	- 12,1 (-22,0%)
Access	437,2 (42,9%)	516,7 (59,1%)	79,5 (18,2%)
Watch	516,0 (50,7%)	330,3 (37,8%)	- 185,8 (-36,0%)
Reserve	43,2 (4,2%)	20,3 (2,3%)	-23,0 (-53,2%)
Overall JO1 Expenditures € x1000PDs	9.355 (0,7%)	7.041 (0,1%)	-2314,2 (-25%)
Fluoroquinolones Expenditures € x1000PDs	69 (0,7%)	9 (0,1%)	-58.3 (-85%)
Carbapenems Expenditures € x1000PDs	1.617 (17,3%)	800 (11,4%)	-817,4 (-51%)
New Cephalosporins Expenditures € x1000PDs	584 (6,2%)	90 (1,3%)	-493,3 (-85%)
* ***Vancomycin + teicoplanin + daptomycin + linezolid + ceftaroline + ceftobiprole***			

When the impact of the SAVE intervention was evaluated by ITS Analysis, significant variation in the overall antibiotic consumption emerged. For all the three consumption indicators (DDD, DOT, and LOT) emerged a significant and favorable (i.e. towards decreasing consumption) change in slope (-124.2 DDDs*1000PDs/month P=0.001; -65.8 DOTs*1000PDs/month P= 0.038; -19.5 LOT*1000PDs/month P= 0.001) and downward post-intervention trend (-24 DDDs*1000PDs/month P< 0.001; -12.2 DOTs*1000PDs/month P= 0.0025; -11.1 LOT*1000PDs/month P< 0.001). Normalized DOTs also showed a significant and considerable immediate change in level associated with the implementation of the AMS intervention (-65.8 DOTs*1000PDs/month, P=0.03). Figure 6 provides visual display of these results.

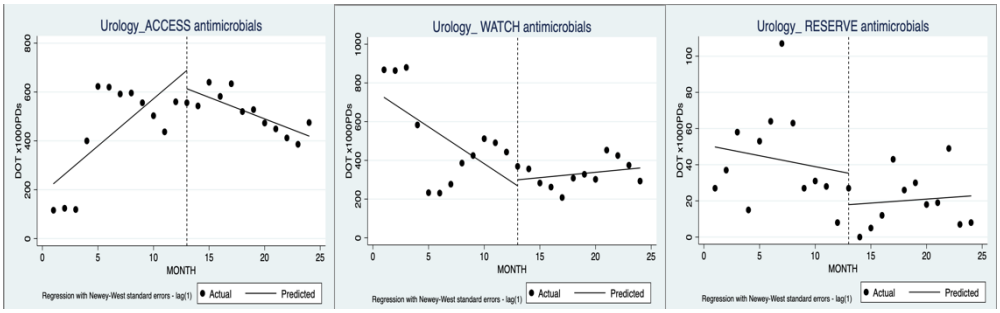
*Figure 6. ITSA of Overall consumption in Urology (DDDs, DOTs and LOTs *1000PDs).*



Significant inversion in slope and downward post-intervention trend occurred for the Access antibiotics (-56.3 DOTs*1000PDs/month P= 0.002; -17.6 DOTs*1000PDs/month, P= 0.0019) while opposite direction change in slope was observed for the Watch agents (+43.6 DOTs*1000PDs/month, P=0.037). No significant variation was observed for the Reserve agents.

Figure 7, provides a visual display of these results.

*Figure 7. ITSA of Access, Watch and Reserve antimicrobials consumption in Urology(DOTs *1000PDs).*



Fluoroquinolone consumption, expressed as both DDDs and DOTs, showed a significant decreasing trend (-8.5 DDDs*1000PDs/month, P=0.012; -15.1 DOTs*1000PDs/month, P=0.004) yet in the pre-intervention period, associated with a positive (towards increased consumption) change in DOTs slope (+12.2 DOTs*1000PDs/month, P=0.019) when intervention was introduced; Both the DDDs and DOTs slope kept significant downward direction in the post-intervention period (-2.1 DDDs*1000PDs/month, P<0.001 ; - 3 DOTs*1000PDs/month P<0.001). Carbapenems DDDs but not DOTs showed significant downward pre-intervention slope and upward change in slope (-5.9 DDDs*1000PDs/month, P=0.008, +9.1 DDDs*1000PDs/month, P= 0.005).

Overall expenditures for J01 antimicrobials didn't show any significant variation over time but a statistically significant and considerable upward change in level and slope was observed when considering carbapenems related expenditures. Results of the ITS analysis relative to antibiotic consumption in the Urology department are summarized in Table 6.

Table 6: Urology ward, Defining parameters of the interrupted time series analysis of antibiotic consumption.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
DDDs x1000PDs (95% CI) *P-value*	818.9 (684.3; 953.4)	25.8 (2.8; 48.8) ***P: 0.030***	-124.2 (-330.3; +81.9)	-49.8 (-76.1; -23.4) ***P: 0.001***	-24 (-36.8; -11.1)

	NA		*P:0.22*		***P: 0.0009***
DOTs x1000PDs (95% CI) *P-value*	1023.4 (961.5; 1085.2) *NA*	-1.4 (-8.3; 5.6) *P: 0.690*	-65.8 (-124.7; -6.9) ***P: 0.030***	-10.8 (--21.0; -0.67) ***P: 0.038***	-12.2 (-19.5; -4.8) ***P: 0.0025***
LOTs x1000PDs (95% CI) *P-value*	797.5 (749.0; 846) *NA*	8.5 (-0.4; 17.3) *P: 0.059*	-75.7 (-160.0; 8.8) *P: 0.076*	-19.5 (-29.5; -9.6) ***P: 0.001***	-11.1 (-16.1 -6.1) ***P: 0.0002***
Fluoroquinolone DOTs x1000PDs (95% CI) *P-value*	176.6 (108.1; 245.1) *NA*	-15.1 (-24.8; -5.5) ***P: 0.004***	+36.1 (-30.3; 102.5) ***P: 0.270***	+12.2 (2.2; 22.1) ***P: 0.019***	-3 (-4.1; -1.8) ***P: 0.0000***
Carbapenems DOTs x1000PDs (95% CI) *P-value*	107.5 (77.3; 137.7) *NA*	-2.8 CI: (-7.5; 1.9) *P: 0.232*	-30.9 (-67.7; 5.8) *P: 0.094*	5.7 (-0.4; 11.9) *P: 0.067*	2.9 (-1.0; 6.9) *P: 0.14*
Anti-MRSA DOTs x1000PDs (95% CI) *P-value*	52.03846 (13.6; 90.5) *NA*	0.5 (-5.3; 6.4) *P: 0.850*	-5.7 (-58.7; 47.3) *P: 0.825*	-2.4 (-8.4; 3.7) *P: 0.424*	-1.8 (-4.4; 0.7) *P: 0.15*
Fluoroquinolone DDDs x1000PDs (95% CI) *P-value*	110.6 (63.6; 157.7) *NA*	-8.5 (-15.0; -2.1) ***P: 0.012***	14.2 (-27.4; 55.7) *P: 0.486*	6.4 (-0.4; 13.2) *P: 0.062*	-2.1 (-3.1; -1.2) ***P: 0.0002***
Carbapenems DDDs x1000PDs (95% CI) *P-value*	118.7308 (91.6; 145.9) *NA*	-5.9 (-10.1; -1.7) P: **0.008**	-7.0 (-41.6; 27.5) *P: 0.675*	+9.1 (3.1; 15.0) ***P: 0.005***	3.2 (-1.1; 7.3) *P:0.13*
Anti-MRSA DDDs x1000PDs (95% CI) *P-value*	61.2 (11.9; 110.5) *NA*	1.3 (-6.8; 9.5) P: 0.741	-17.1 (-94.4; 60.2) P: 0.65	-1.8 (-11.8; 8.1) P: 0.704	-0.5 (-6.6; 5.6) P 0.86
ACCESS DOTs x1000PDs (95% CI) *P-value*	224.5 (-1; 450) *NA*	38.7 (8.3; 69.1) ***P: 0.015***	-75.1 (-291.1; 140.9) *P: 0.477*	-56.3 (-89; -23.6) ***P: 0.002***	-17.6 (-27.9; -7.3) ***P: 0.0019***
WATCH DOTs x1000PDs (95% CI) *P-value*	725.6 (429.3; 1021.8) *NA*	-38.1 (-75.6; -0.5) ***P: 0.047***	31.2 (-226; 288.3) *P: 0.803*	+43.6 (2.9; 84.4) ***P: 0.037***	5.5 (-7.8; 18.9) *P: 0.3967*
RESERVE DOTs x1000PDs (95% CI) *P-value*	49.8; (22.9; 76.8) *NA*	-1.2 (-5.3; 2.9) *P: 0.546*	-17.4 (-59.3; 24.6) *P: 0.397*	1.7 (-3.2; 6.5) *P: 0.483*	0.4 (2.4; 3.3) *P: 0.8*
Overall JO1 Expenditures € x1000PDs	10602.9 (9172.4; 12033.3) *NA*	-226.8 (-557.6; 104) *P: 0.168*	-932.1 (-4379.8; 2515.5) *P: 0.579*	243.6 (-250.5; 737.7) *P: 0.316*	16.7902 (-343.2; 376.8) *P: 0.9235*
Fluoroquinolones Expenditures € x1000PDs	124.2 (82.7; 165.7) *NA*	-10.1 (-15.7; -.0.5) ***P: 0.001***	21.7 (-16.0; 59.4) *P: 0.244*	7.4 (1.4; 13.4) ***P: 0.018***	-2.7 (-3.7; -1.6) ***P: 0.0000***
Carbapenems Expenditures € x1000PDs	2939.1 (2424.7; 3453.5) *NA*	-240.4 (-307.3; -173.4) ***P: 0.000***	+628.6 (27.2; 1230.0) ***P: 0.041***	+261.5 (180.3; 342.7) ***P: 0.000***	21.2 (-29.3; 71.6) *P: 0.3924*
New Cephalosporins Expenditures € x1000PDs	60.9 (-617.8; 739.5) *NA*	95.1 (-127.2; 317.5) *P: 0.383*	-1340.4 (-3477.4; 796.7) *P: 0.206*	-53.7 (-283.3; 176) *P: 0.631*	41.4 (-25.5; 108.3) *P: 0.2113*

Clinical and microbiological outcomes

During the whole observed period, 2781 patients were admitted to the urology ward (1379 in the pre-intervention and 1402 in the post-intervention period, monthly mean 116 patients/month); the mean length of hospital stay was stable at 5.1 days across the two periods as confirmed by the ITS analysis,

that couldn't identify any significant trend. Mortality was low in both periods (0.36% vs 0.5%, pre- and post-intervention, respectively) with a total of 12 death occurring in 24 months; due to the low number of events, running ITS analysis was not possible.

Only 2 C.*difficile* infections were diagnosed during 24 months, they were evenly distributed in the two periods. Bloodstream infections were 48 (incidence per 100 admitted patients= 3.48%) in the pre-intervention year and 73 (incidence per 100 admitted patients= 5.21%) in the post-intervention one, with the pre-intervention starting level estimated at 3.1 BSI/100 admitted patients, and no significant trend emerging at the ITS analysis. Gram-negative bacteria were responsible of 31 and 42 BSI (64% and 57% of the total BSI, incidence per 100 admitted patients= 2.25% and 3%) in the pre- and post-intervention periods, respectively; as for total BSI, ITS analysis didn't detect significant trends nor change in slope when considering individually BSI caused by gram-positive and gram-negative bacteria. BSI caused by third-generation-cephalosporins resistant and carbapenem-resistant bacteria occurred at a very low rate in both periods (less than 1 event per month) thus ITS analysis was not performed. Results of the ITS analysis relative to the clinical and microbiological data are summarized in Table 7.

Table 7: Urology, Clinical and microbiological indicators

	Pre-intervention	Post-intervention	Overall
Patient Days (PDs) (n=14099)	*7016*	*7083*	14099
Admission (n=2781)	*1379*	*1402*	2781
Length of Hospital Stay (mean)	*5.1*	*5.1*	*5.1*
In-hospital mortality (n=12)	*0.36% (5)*	*0.5% (7)*	*0.43%*
Bloodstream Infections, incidence (n=121)	*3.48% (48)*	*5.21% (73)*	*4,35%*
C.*difficile* Infections incidence (n=2)	*0.07% (1)*	*0.07% (1)*	*0.07%*
Gram-positive BSI incidence (n= 45)	1.16% (16)	*2.07% (29)*	*1.62%*
Gram-negative BSI incidence (n=73)	2.25% (31)	3% (42)	2.63%
Third-generation cephalosporin-resistant BSI incidence (n=9) [prevalence of gram-negative BSI]	*0.15% (2) [6.45%]*	0.5% (7) [16.7%]	0.32% [12%]
Carbapenem Resistant BSI incidence (n=6) [prevalence of gram-negative BSI]	*0.36% (5) [16%]*	*0.07% (1) [2%]*	*0.22% [8.22%]*

Table 8: Urology, defining parameters of the interrupted time series analysis of clinical outcomes.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
Length of Hospital stay (95% CI) *P-value*	5.1 (4.6; 5.6) *NA*	0.007 (-0.08; 0.09) *P: 0.868*	0.29 (-0.72; 1.30) *P: 0.560*	-0.05 (-0.15; 0.05) *P: 0.297*	-0.05 (-0.12; 0.03) *P: 0.23*
Admission (95% CI) *P-value*	116.2 (106.8; 125.7) *NA*	-0.2 (-1.5; 1.0) *P: 0.690*	-2.0 (-11.6; 7.6) *P: 0.667*	1.2 (-0.5; 3) *P: 0.166*	1 (-0.2; 2.2) *P: 0.1098*
Bloodstream Infections (/100 admission) (95% CI) *P-value*	3.1 (1.9; 4.3) *NA*	0.07 (-02; 0.33) *P: 0.589*	1.86; (-2.6; 6.2) *P: 0.391*	-0.19 (-0.7; 0.36) *P: 0.491*	-0.11 (-0.57; 0.34) *P: 0.6056*
Gram positive BSI (/100 admission) (95% CI) *P-value*	1.19 (0.19, 2.5)	-0.008 (0.18; 0.16) *P: 0.929*	1.4 (-0.32; 3.13) *P: 0.105*	-0.66 (-0.31; 0-18) *P: 0.582*	-0.07 (-0.24; 0.96) *P: 0.3771*
Gram negative BSI (/100 admission) (95% CI) *P-value*	0.17 (0.89; 2.58) *NA*	0.1 (-0.09; 0.3) *P: 0.301*	0.45 *(-2.6; 3.5)* *P: 0.762*	-0.16 (-0.56; 0.24) *P: 0.405*	-0.06 (-0.38; 0.25) *P: 0.6799*

General Surgery

General Surgery was involved in SAVE AMS intervention since October 2018 (pre-intervention period: October 2018-September 2018; post-intervention period: October2018-September 2019). Twelve senior and 9 junior surgeons prescribing antimicrobials to the hospitalized patients were involved. Guidelines for SAP and empirical antimicrobial therapy were approved and disseminated in March 2019. Audits for evaluating antimicrobial prescription appropriateness were performed from April to July 2019.

Prescribing Appropriateness

Twelve audits were performed weekly since April 2019. Prescriptions reviewed were 215, patients receiving at least one antibiotic were 185, 43% of the total 422 patients resulting hospitalized in the observed days. A slightly decreasing trend in the prevalence of patients receiving antibiotic therapy was observed across the four months of observation, the mean prevalence being 47.5% in the first, 44% in the second, and 40.8% in the third month.

Empirical therapy accounted for 50% of the prescriptions, SAP represented 32% while targeted therapy 17%.

Beta-lactams/beta-lactamase inhibitor associations represented 68% of the total with amoxicillin-clavulanate resulting the most prescribed individual agent (46% of the total); Carbapenems accounted for 13% of the prescriptions, followed by vancomycin (7%); third-generation cephalosporins were prescribed only in the 3% of the cases. Considering only therapeutical prescriptions, the defined or presumptive source of the infectious process was represented by the abdomen in 49% of cases. *C.difficile* infections were the cause of 11% of prescriptions observed. Nine percent of patients had primary bacteremia and 4% pneumonia as the cause of antibiotic prescription; a definite source of infection couldn't be identified in the 8%.

Overall prescribing appropriateness was 78%. For SAP appropriateness was 73% (44 out of 60 prescriptions); the main reasons for inappropriateness were excessive duration (13 of the 16 inappropriate prescriptions) and incorrect choice of antimicrobial agent (3 out of 16). Seventy-three percent of

antibiotics prescribed for SAP were administered for less than 24 hours; 36% (33 out of 92) of the empirical therapy prescriptions were inappropriate: 14 were judged as unnecessary antibiotic prescription, 7 as excessive duration of therapy, 4 as an incorrect choice of the antibiotic agent and 2 as unnecessary combined therapy.

Four out of 32 prescriptions (12.5%) for targeted therapy resulted inappropriate, 2 for excessive duration, 1 for the missed opportunity for de-escalation, and 1 for incorrect antibiotic choice. Overall appropriateness improved across the 12 time points as average appropriateness was 64.8% in the first month versus 72% and 84% in the second and third ones. Seventy-five percent of the prescriptions were registered on the clinical electronic records of the patient reporting the specific indication for starting antibiotics.

Figure 8. Prevalence of patients receiving antibiotics in the General Surgery unit

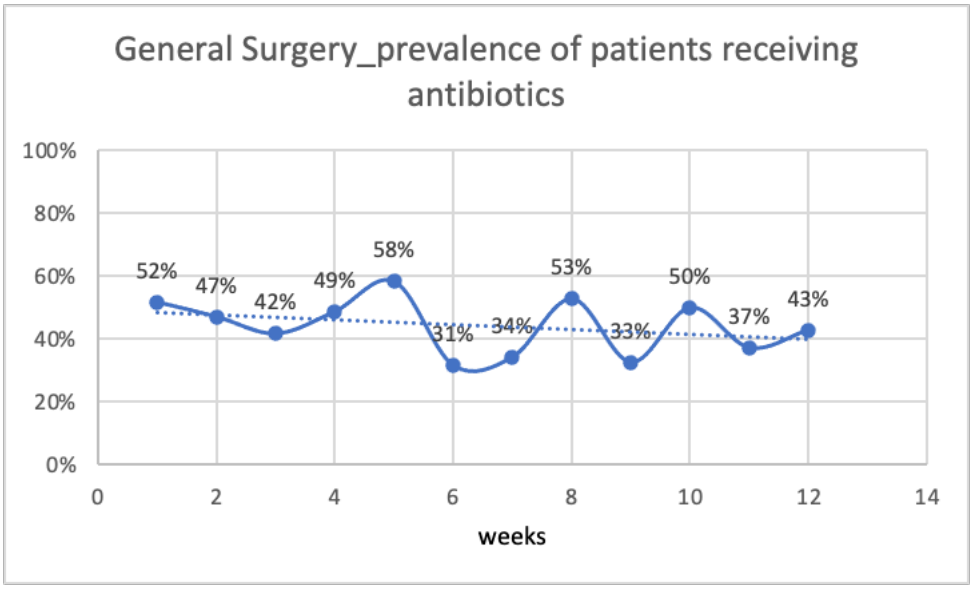
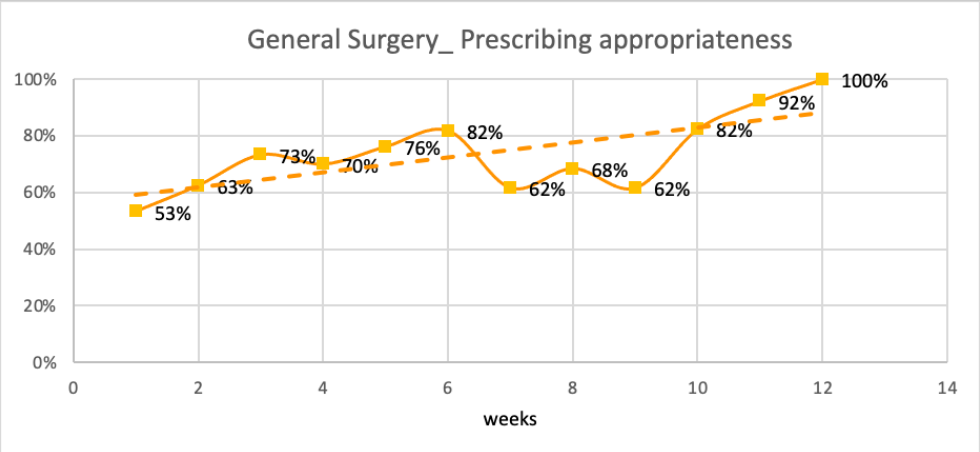


Figure 9. Prescribing appropriateness in the General Surgery unit



Antimicrobial Consumption

Overall consumption of ATC J01 antimicrobials, expressed by DOTs per 1000PDs was slightly lower in the post-intervention period compared to the pre-intervention one (727.5 vs 798.7, -71.2 DOTs, -9%) but the ITS analysis didn't identify statistically significant variation in consumption trends or levels for any indicators (DDDs, DOTs or LOTs).

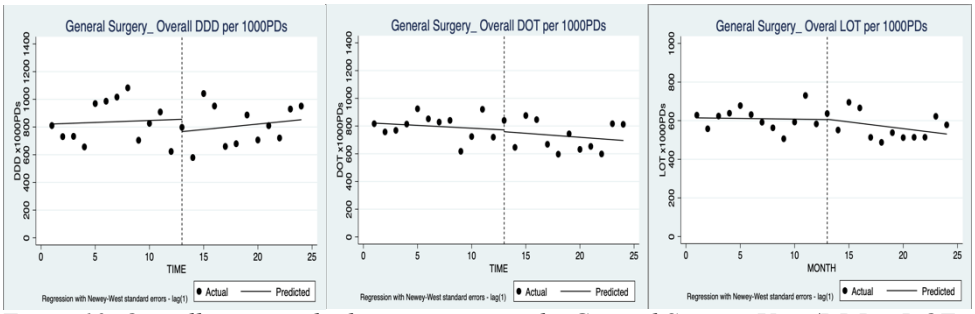


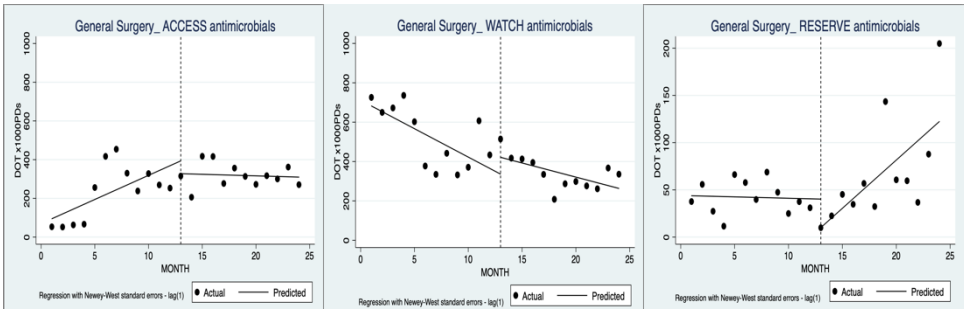
*Figure 10. Overall antimicrobial consumption in the General Surgery Unit (DDDs, DOTs, LOTs *1000PDs)*

The consumption of fluoroquinolones was substantially lower in the post-intervention period (17.7 DOTs vs 88.8, -71,1 DOTs, -80%) while usage of carbapenems (64.4 vs 49.1, +15.3 DOTs, + 31%) and anti-MRSA drugs moderately increased (318,7 vs 231.7, +87 DOTs, +38%). ITS analysis confirmed a statistically significant reduction in level and downward port-intervention trend for both fluoroquinolones DOTs (-47.3 DOTs*1000PDs P=0.013; -2.5 DOTs*1000PDs/month, P=0.009) and DDDs (-51.6 DDDs*1000PDs, P= 0.028; -3.0 DDDs*1000PDs/month, P= 0.025); post-intervention slope of anti-MRSA drugs DDDs but not of DOTs was also significantly upward (+12 DDDs*1000PDs/month, P=0.011). The higher consumption was observed for antimicrobials included in the WHO Watch class but usage decrease in the post intervention period (343.47 vs 524.36, -180.89 DOTs, -34,5%); Access and Reserve antimicrobials usage was higher in the post-intervention period (access: 316.55 vs 230.8, +86.75 DOTs, +37%; Reserve 67.48 vs 42.86, +24.7 DOTs, +58%). ITS analysis revealed: A significant change in Access consumption slope from an increasing trend across the time in the pre-intervention to stable consumption in the post-intervention year (estimate overall effect -26.5 DOTs*1000PDs/month, P= 0.016);

- significant downward trend in the post-intervention Watch antimicrobials consumption, decreasing by -14.4 DOTs*1000PDs/month (P=0.046)

- increasing consumption of Reserve antimicrobials (+10.2 DOTs*1000PDs/month, P= 0.0198) in the post-intervention period, resulting in an overall estimate effect of +10.5 DOTs*1000PDs/month (P= 0.021).

*Figure 11. Access, Watch and Reserve antimicrobials consumption in the General Surgery Unit (DOTs *1000PDs)*



Considering individual antibiotics, amoxicillin/clavulanate consumption increased from 151.5 to 242 DOTs*1000PDs (+ 90,5 DOTs, +60%) and consumption of piperacillin/tazobactam equally decreased from 288.8 to 193.6 DOTs*1000PDs (-95.22 DOTs, -33%). Expenditure for new cephalosporins targeting MDR gram-negative bacteria was consistently higher in the post-intervention period (+2040.6 Euro *1000PDs) representing the major cause of the increase in total ATC J01 expenditures from 8088.9 to 10.135.6 Euro *1000PDs (+2046.7 Euro*1000PDs, +25%). Significant inversion in overall expenditures trend toward increasing expenditures (change in slope +1280.4 Euro/*1000PDs/month, P=0.032) and decreasing post-intervention trend for fluoroquinolones expenditures emerged when ITS analysis was performed. Detailed data on antimicrobial consumption indicators and ITS analysis parameters for General Surgery are provided in Tables 9 and 10.

Table 9: General surgery, antimicrobial consumption (DOTs per 1000PDs) of ATC-J01 antimicrobial agents

DOT *1000PDs	Pre-intervention (%)	Post-intervention (%)	Δ (%)
Daptomycin	14,61 (1,8%)	16,74 (2,3%)	2,13 (15%)
Fosfomycin	0,79 (0,1%)	2,15 (0,3%)	1,36 (171%)

Linezolid	11,73 (1,5%)	11,33 (1,6%)	-0,40 (-3%)
Amikacin	0,59 (0,1%)	4,00 (0,6%)	3,41 (573%)
Gentamicin	4,82 (0,6%)	16,25 (2,2%)	11,43 (237%)
Ertapenem	0,84 (0,1%)	5,91 (0,8%)	5,08 (606%)
Imipenem + Cilastatin	6,08 (0,8%)	-	- 6,08 (-100%)
Meropenem	42,16 (5,3%)	58,46 (8,0%)	16,30 (39%)
Ceftobiprole medocaril	-	0,88 (0,1%)	0,88
Cefazolin	13,94 (1,7%)	20,92 (2,9%)	6,97 (50%)
Cefotaxime	6,79 (0,8%)	2,52 (0,3%)	- 4,27 (-63%)
Ceftazidime	12,23 (1,5%)	11,54 (1,6%)	- 0,69 (-6%)
Ceftazidime + Avibactam	0,11 (0,0%)	8,01 (1,1%)	7,90 (7073%)
Ceftriaxone	21,21 (2,7%)	4,74 (0,7%)	- 16,47 (-78%)
Cefepime	0,96 (0,1%)	- (0,0%)	- 0,96 (-100%)
Metronidazole	52,94 (6,6%)	20,15 (2,8%)	-32,79 (-62%)
Ciprofloxacin	77,83 (9,7%)	16,21 (2,2%)	-61,62 (-79%)
Levofloxacin	10,91 (1,4%)	1,49 (0,2%)	-9,43 (-86%)
Vancomycin	53,52 (6,7%)	45,91 (6,3%)	-7,60 (-14%)
Clindamycina	2,65 (0,3%)	9,12 (1,3%)	6,47 (245%)
Azitromicin	-	0,27 (0,0%)	0,27
Clarithromicin	1,31 (0,2%)	1,09 (0,1%)	- 0,22 (-17%)
Aztreonam	-	0,70 (0,1%)	0,70
Ampicillin	-	0,37 (0,1%)	0,37
Piperacillin	1,03 (0,1%)	- (0,0%)	- 1,03 (-100%)
Amoxicillin + clavulanate	151,51 (19,0%)	242,30 (33,3%)	90,80 (60%)
Ampicillin + Sulbactam	0,78 (0,1%)	1,61 (0,2%)	0,83 (106%)

Piperacillin + Tazobactam	288,82 (36,2%)	193,60 (26,6%)	- 95,22 (-33%)
Oxacilline	0,71 (0, 1%)	0,08 (0,0%)	- 0,63 (-89%)
Colistin	2,03 (0,3%)	3,97 (0,5%)	1,93 (95%)
Trimethoprim-sulphametoxazole	2,18 (0,3%)	1,40 (0,2%)	- 0,78 (-36%)
Doxiciclin	0,78 (0,1%)	0,35 (0,0%)	- 0,42 (-54%)
Tigecyclin	13,65 (1,7%)	25,28 (3,5%)	11,63 (85%)
TOTAL	**798,73**	**727,51**	**- 71,22** **(-9%)**
Fluoroquinolones	88,75 (11,1%)	17,70 (2,4%)	- 71,05 (-80%)
Carbapenems	49,07 (6,1%)	64,37 (8,8%)	15,30 (31%)
Anti-MRSA agents*	231,69 (29,0%)	318,70 (43,8%)	87,01 (38%)
Access	230,8 (29%)	316,55 (45,5%)	86,75 (-37%)
Watch	524,36 (65,6%)	343,47 (47%)	-180.89 (-34,5%%)
Reserve	42,86 (5,4%)	67,48 (9,3%)	24,68 (58%)
Overall JO1 Expenditures € x1000PDs	8.088,86	10.135,60	2.046,74 (25%)
Fluoroquinolones Expenditures € x1000PDs	107,16 (1,3%)	21,61 (0,2%)	-85,55 (-10%)
Carbapenems Expenditures € x1000PDs	879,60 (10,9%)	748,33 (7,4%)	-131,28 (-123%))
New Cephalosporins Expenditures € x1000PDs	9,09 (0,1%)	2.049,69 (20,2%)	2.040,60 (22446%)
* ***Vancomycin + teicoplanin + daptomycin + linezolid + ceftaroline + ceftobiprole***			

Table 10: General Surgery, Defining parameters of the interrupted time series analysis of antibiotic consumption.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
DDDs x1000PDs (95% CI) *P-value*	821.7 (665.4; 978.1) *NA*	2.8 (-21.2; 26.9) *P: 0.809*	-89.1 (-358.2; 180.1) *P: 0.498*	4.98 (-26.8; 36.7) *P: 0.747*	7.8 (-14.2; 29.8) *P: 0.4681*
DOTs x1000PDs (95% CI) *P-value*	821.2 (747.9; 894.5) *NA*	-4.1 (-16.9; 8.7) *P: 0.513*	-13.0 (-176.7; 150.7) *P: 0.870*	-1.7 (-24.0; 20.7) *P: 0.879*	-5.7 (-25.0; 13.5) *P: 0.5413*
LOTs x1000PDs (95% CI) *P-value*	614.5 (567.9; 661.2)	-0.7 (-10.8; 9.3) P*: 0.880*	1.6 (-120.2; 123.3)	-6.2 (-21.2; 8.8) *P: 0.398*	-7 (-18.3; 4.4) *P: 0.2175*

	NA		*P: 0.979*		
Fluoroquinolone DOTs x1000PDs (95% CI) *P-value*	97.1 (57.6; 136.5) *NA*	-1.5 (-6.0 ;3) *P: 0.490*	-47.3 (-83.5; -11.1) ***P: 0.013***	-1.0 (-5.7; 3.6) *P: 0.653*	-2.5 (-4.4; -0.7) ***P: 0.0092***
Carbapenems DOTs x1000PDs (95% CI) *P-value*	49.8 (23.1; 76.4) *NA*	-0.1 (-5.1; 4.8) *P: 0.957*	29.5 (-18.1; 77.1) *P: 0.211*	-2.3 (-9.6; 5.19) *P: 0.522*	-2.4 (-7.4; 2.6) *P: 0.3215*
Anti-MRSA DOTs x1000PDs (95% CI) *P-value*	89.5 (59.7; 119.3) *NA*	-1.8 (-6.2; 2.8) *P: 0.427*	-15.9 (-65.8; 34) *P: 0.513*	5.8 (-1.7; 13.3) *P: 0.121*	4.0563 (-2.1; 10.2) *P: 0.1824*
Fluoroquinolone DDDs x1000PDs (95% CI) *P-value*	102.3 (50.8; 153.8) *NA*	-1.4 (-7.2; 4.5) *P: 0.633*	-51.6 (-97.2; -6.0) ***P: 0.028***	-1.7 (-7.6; 4.3) *P: 0.570*	-3.0 (-5.6; -0.4) ***P: 0.0249***
Carbapenems DDDs x1000PDs (95% CI) *P-value*	56.8 (13.4; 100.1) *NA*	-0.6 (-7.4; 6.2) *P: 0.863*	32.4 (-24.6; 89.3) *P: 0.249*	-1.8 (-11.1; 7.5) *P: 0.7*	-2.4 (-8.0; 3.3) *P: 0.3962*
Anti-MRSA DDDs x1000PDs (95% CI) *P-value*	104.5 (58.3; 150.7) *NA*	-0.0 (-8.9; 8.8) *P: 0.994*	-65.4 (-155.2; 24.5) *P: 0.145*	12.0 (-0.07; 24.1) *P: 0.051*	12.0 (3.0; 21) **P: 0.0114**
ACCESS DOTs x1000PDs (95% CI) *P-value*	94.6 (-36.6; 225.8) *NA*	24.9 (6.9; 42.9) ***P: 0.009***	-66.1 (-235.9; 103.6) *P: 0.426*	-26.5 (-47.6; -5.5) ***P: 0.016***	-1.6 (-12.0; 8.8) *P: 0.7513*
WATCH DOTs x1000PDs (95% CI) *P-value*	682.4 (570.9; 793.9) *NA*	-28.9 (-49.9; -7.8) ***P: 0.010***	85.3 (-115.5; 286.1) *P: 0.386*	14.5 (-11.8; 40.8) *P: 0.263*	-14.4 (-28.4; -0.3) ***P: 0.0457***
RESERVE DOTs x1000PDs (95% CI) *P-value*	43.8 (25.7; 61.8) *NA*	-0.3 (-2.6; 2.0) *P: 0.794*	-30.2 (-61.7; 1.3) *P: 0.060*	10.5 (1.8; 19.2) ***P: 0.021***	10.2 (1.8; 18.6) ***P: 0.0198***
Overall JO1 Expenditures € x1000PDs	9342.5 (6050.5; 12634.5) *NA*	-227.9 (-657.5; 201.6) *P: 0.281*	-2260 (-7783.2; 3263.3) *P: 0.403*	+ 1280.4 (120.1; 2440.6) ***P: 0.032***	1052.4 (-27.1; 2131.9) *P: 0.0555*
Fluoroquinolones Expenditures € x1000PDs	137.3 (47.9; 226.7) *NA*	-5.5 (-16.7; 5.7) *P: 0.319*	-30.7 (-108.1; 46.8) *P: 0.418*	2 (-9.2; 13.2) *P: 0.718*	-3.5 (-5.9; -1.2) ***P: 0.0053***
Carbapenems Expenditures € x1000PDs	1397.6 (713.5; 2081.7) *NA*	-94.2 (-193.4; 5) *P: 0.061*	638.2 (-180.7; 1457.1) *P: 0.120*	65.6 (-54.9; 186.0) *P: 0.270*	-28.6 (-94.1; 36.9) *P: 0.3735*
New Cephalosporins Expenditures € x1000PDs	-9.8 (-26.9; 7.3) *NA*	3.4 (-1.6; 8.5) *P: 0.171*	-228.4 (-3245.8; 2789.1) *P: 0.876*	405.1 (-169.4; 979.59 *P: 0.157*	408.5 (-165.9; 982.9) *P: 0.1536*

During the 24 observed months, 4193 patients were admitted to the General Surgery ward, resulting in 23815 patient days. Length of hospital stay was substantially stable across the two periods (5.9 and 5.4 days, no significant trends or change in level or slope identified by ITSA). In-hospital mortality kept significant decreasing trend across the two periods (pre-intervention -0.2 death/100admission/month P=0.021; post-intervention -0.1 death/100admission/month, P=0.016) with mortality of 2.2% in the former and 1.8% in the latter period. Blood-stream infection showed statistically significant but minimal increasing trends in both pre- (+0.4

BSI/100admissions/month, P=0.014) and post-intervention period (+0.3 BSI/100 admissions/month, P=0.01), but AMS implementation was associated with an immediate reduction in level of consumption in level (-3.7 BSI/100admissions, P= 0.016); BSI caused by gram-negative bacteria had the same trend (pre-int. : +02 BSI/100admissions/month, P=0.021; post-int. : +0.2 BSI/100admissions/month, P<0.001; change in level -2.1 BSI/100 admissions, P=0.034).

CDI was a rare event with 4 diagnoses evenly distributed across the two periods. Thirty-two BSI caused by third-generation cephalosporin-resistant occurred, representing approximately one-fourth of total gram-negative BSI. Carbapenem-resistant bacteria BSI were 2 in the pre- and 8 in the post-intervention period, incidence per 100 admissions being 0.1% and 0.38%, respectively.

Table 11: General Surgery, Clinical and microbiological indicators

	Pre-intervention	Post-intervention	Overall
Patient Days (PDs) (n=23814)	12404	11411	23815
Admission (n=4193)	2087	2106	4193
Length of Hospital Stay (days, mean)	5.9	5.4	5.7
In-hospital mortality (n=77)	2.2%(45)	1.5% (32)	1.8%
Bloodstream Infections, incidence (n=250)	5.5% (115)	6.4% (135)	6%
C.difficile Infections incidence (n=4)	0.05% (1)	0.14% (3)	0.10%
Gram-positive BSI incidence (n= 98)	2.2% (46)	2.5% (52)	2.3%
Gram-negative BSI incidence (n=135)	2.8% (59)	3.6% (76)	3.2%
Third-generation cephalosporin-resistant BSI incidence (n32) [prevalence of gram-negative BSI]	0.7% (14) [24%]	0.9% (18) [24%]	0.8% [24%]
Carbapenem Resistant BSI incidence (n10) [prevalence of gram-negative BSI]	0.1 % (2) [3.4%]	0.38% (8) [10.5%]	0.24% [7.4%]

Table 12: General Surgery, defining parameters of the interrupted time series analysis of clinical outcomes.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
Length of Hospital stay (95% CI) *P-value*	6.0 (5.1;7) *NA*	0.0 (-0.1; 0.1) *P: 0.962*	-0.5 (-1.4; 0.5) *P: 0.297*	-0.03 (-0.1; 0.09) *P: 0.658*	-0.02 (-0.1; 0.02) *P 0.2986*
Admission (95% CI) *P-value*	181.2 (167.5; 194.9 *NA*	-1.3 (-3.4; 0.7) *0.195*	21.2 (-6.1; 48.4) P: 0.121	-0.7 (-4.3; 3) *P: 0.701*	-2.0 (-4.9; 0.9) *P: 0.1603*
Mortality (death/100admission) (95% CI) *P-value*	3.3 (2.3; 4.3) *NA*	-0.2 (-0.4; -0.04) ***P: 0.021***	1.5 (-0.3; 3.4) P: 0.098	0.1 (-0.08; 0.3) *P: 0.274*	-0.1 (-0.2; -0.03) ***P: 0.0159***
Bloodstream Infections (/100 admission) (95% CI) *P-value*	3.4 (1.5; 5.4) *NA*	0.4 (0.09; 0.7) ***P: 0.014***	-3.7 (-6.7; -0.8) ***P: 0.016***	-0.07 (-0.4; 0.29) *P: 0.679*	0.3 (0.1; 0.6) ***P: 0.01***
Gram positive BSI (/100 admission) (95% CI) *P-value*	1.6 (0.2; 2.9) *NA*	0.13 (-0.07; 0.33) *P: 0.198*	-0.99 (-2.5; 0.6) *P: 0.203*	-0.07 (-0.3; 0.2) *P: 0.619*	0.1 (-0.1; 0.2) *P: 0.4715*
Gram negative BSI (/100 admission) (95% CI) *P-value*	1.6 (0.5; 2.6) *NA*	0.2 (0.04; 0.4) ***P: 0.021***	-2.1 (-4.1 -0.2) ***P: 0.034***	0.006 (-0.2; 0.2) *P: 0.952*	0.2 (0.13; 0.4) ***P: 0.0003***
Third-generation cephalosporin-resistant BSI (/100 admission) (95% CI) *P-value*	0.1 (-0.5; 0.7) *NA*	0.12 (0.0; 0.2) ***P: 0.050***	-0.3 (-1.9; 1.4) *P: 0.746*	-0.16 (-0.3; 0.003) *P: 0.053*	-0.06 (-0.2; 0.1) *P: 0.4556*

Traumatology

Traumatology was involved in SAVE AMS intervention since November 2018 (pre-intervention period: November 2018-October 2018; post-intervention period: November 2018-October 2019). Twelve senior and 23 junior surgeons prescribing antimicrobials to the hospitalized patients were involved. Guidelines for SAP and empirical antimicrobial therapy were approved and disseminated in February 2019. Audit for evaluating antimicrobial prescription appropriateness was performed from May to August.

Prescribing Appropriateness

Fourteen audits were performed weekly since May 2019 and antimicrobials prescribed to 189 patients were reviewed for appropriateness. The overall prevalence of patients receiving at least one antibiotic was 27% (189 out of 692 hospitalized patients), substantially stable across the whole audit period. 62% of prescriptions were aimed at SAP, the25% represent empirical therapy and 12% targeted antibiotic treatment.

First- and second-generation cephalosporin represented the most prescribed agent, accounting for 50% of reviewed prescriptions; Beta-lactams/beta-lactamase inhibitors were frequently employed (24% of the total) with amoxicillin/clavulanate representing individually 18% of prescriptions. Anti-MRSA agents were prescribed in 13% of the case (daptomycin 6%, vancomycin 5%, linezolid 2%). Third generation and antipseudomonal-cephalosporins were prescribed to the 4% and meropenem to the 2% of patients, respectively. Reported primary sources of infection were Bone and Joint in 43% of cases, skin and soft-tissue in 27%, lung in 13% and urinary tract in 7% of cases; Primary bacteremia occurred in 13% of observed patients and no clear localization was reported for 5% of prescription.

The overall appropriateness of prescription was 75% and a trend towards improvement was observed after the first month of audits. For SAP, 29% of prescriptions (34 out of 118) were deemed inappropriate: 26 for excessive duration, 5 because of use of prophylaxis when not recommended, 3 for

incorrect choice of antimicrobial; 65% of SAP prescriptions were correctly administered only once.

Thirty-one per cent of empirical therapy were inappropriate (15/48): 9 as unnecessary starting of antibiotics, 2 for excessive duration and 4 because the choice of antimicrobial deviates from guidelines.

Figure 13 Prevalence of patients receiving antibiotics in the Traumatology unit.

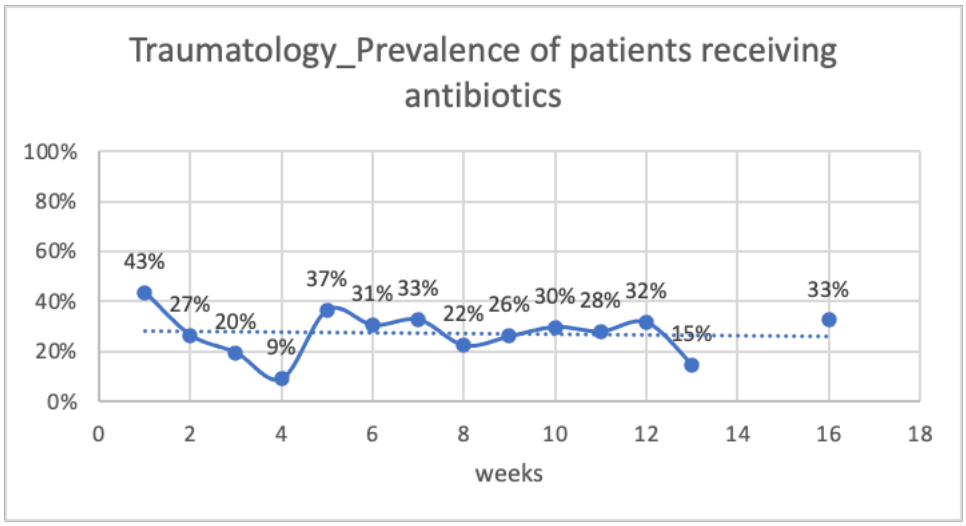
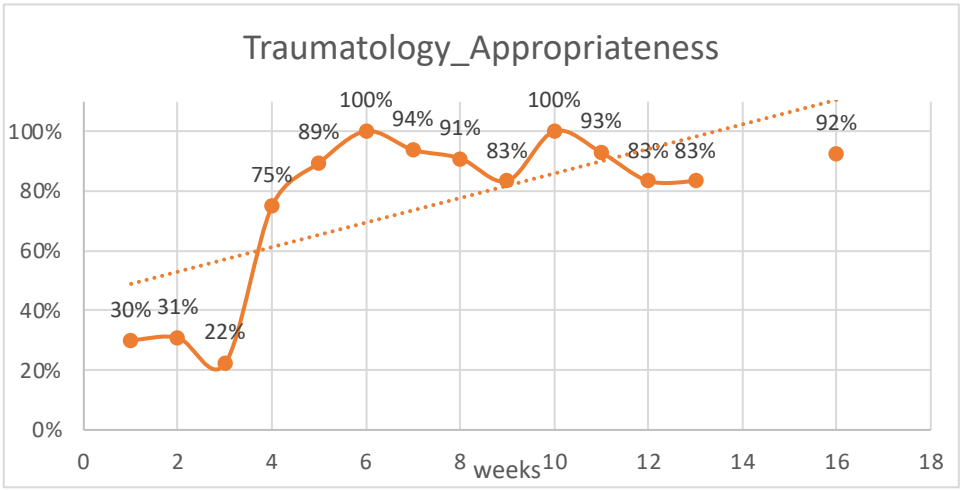


Figure 14 Prescribing appropriateness in the Traumatology unit.

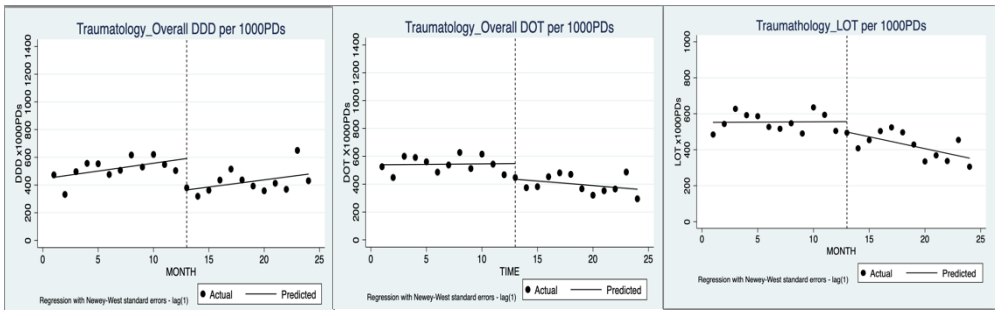


Antimicrobial Consumption

Total consumption of ATC J01, measured as normalized DOTs (DOTs*1000PDs) antimicrobials was lower in the post-intervention period (408.7 vs 543 4, -134.7 DOTs, -24.8%); fluoroquinolones (12.1 vs 31.8, -19.7 DOTs, -61.9%) consumption also reduced compared to the pre-intervention while carbapenems usage was stable (9.2 vs 9.8, -0.6 DOTs) and anti-MRSA

agent slightly increased (52 vs 44.5, +7.5 DOTs, + 16.9%). ITS analysis estimated a change in level of -226.6 DDDs*1000PDs (P< 0.01) and -111.6 DOTs*1000PDs (P=0.032) associated with the intervention implementation and identified a significant reduction in LOTs over time in the post intervention period (-13.2 LOT*1000PDs/month, P=0.006).

*Figure 15. ITSA of the overall antimicrobial consumption n the Traumatology unit(DDDs, DOTs, and LOTs*1000PDs).*



The consumption of fluoroquinolones exhibited statistically significant decreasing trends in the pre-intervention periods (-2.5 DOTs*1000PDs/month, P= 0.025; -2.4 DDDs*1000PDs/month, P= 0.004) with significant, positive, change in slope associated with the intervention due to stabilization of consumption (no significant trend identified) in the post-intervention period. Increasing consumption of anti-MRSA agent was also confirmed by ITS analysis that revealed a significant upward post-intervention trend (+4.1 DOTs*1000PDs/month, P=0.0059) reversing downward pre-intervention trend and thus resulting in an estimate overall effect of +7.5 DOTs*1000PDs/month (P=0.001). Stratifying usage data using the WHO AWaRe classification, consumption of antimicrobials included in the Access (265.9 vs 367.4, -110.5 DOTs, -27.6%) and Watch (111.6 vs 153 3, -41.7 DOTs, -27.2%) classes was lower in the post-intervention period while Reserve antimicrobials consumption showed a considerable increase (33.8 vs 22.5, +11.37 DOTs, +50%). When analyzed with the ITS, Access DOTs showed significant change in level (-96.9 DOTs*1000PDs, P= 0.021) associated with decreasing trend (-14.2 DOTs*1000PDs/month, P<0.001) in the post-period, with an estimate overall effect of -25.2 DOTs*1000PDs/month (P=0.001). Watch antimicrobials consumption showed a significant upward post-intervention trend at a rate of 6.0

DOTs*1000PDs/month (P=0.047) reversing the pre-intervention downward trend (change in slope +17.8 DOTs/PDs/month, P=0.004).

Reverse increased consumption resulted in a significant increasing post-intervention trend with 4.3 DOTs*1000PDs employed every month in the post-intervention period (P<0.001).

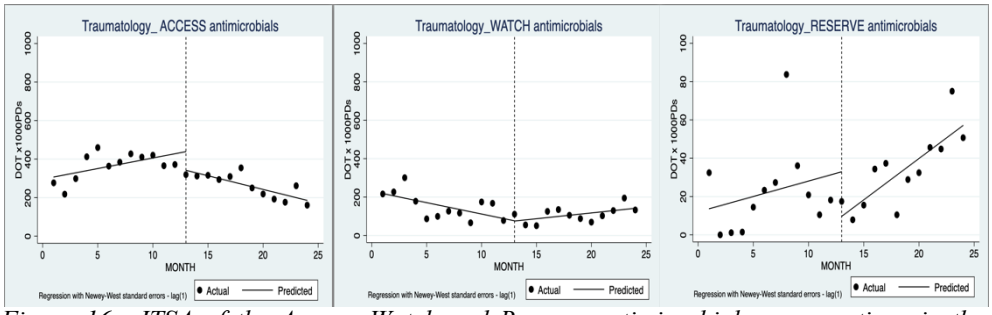


*Figure 16. ITSA of the Access, Watch and Reserve antimicrobial consumption in the Traumatology unit (DOTs *1000PDs*

Among Access antimicrobials, cefazolin showed the most extensive reduction (162.7 vs 251.6, -89 DOTs, -35.4%) in the post-intervention period. Fluoroquinolones were responsible for half the reduction observed in the watch agents, with a reduction in third-generation cephalosporin and piperacillin/tazobactam also contributing. Daptomycin was the only antimicrobial in the Reserve class showing increased consumption in the post-intervention period (+16.0 DOT*1000PDs, +217.7%). Data on the expenditures due to antimicrobials purchasing were not available for this unit.

Table 13: Traumatology, antimicrobial consumption (DOTs per 1000PDs) of ATC-J01 antimicrobial agents

DOT *1000PDs	**Pre-intervention**	**Post-intervention**	**absolute difference**
Amikacin	1,56 (0.29%)	0,78 (0,19%)	- 0,78 (-49,9%)
Gentamicin	4,25 **(**0,78%	0,74 (0,18%)	- 3,51 (-82,6%)
Daptomycin	7,36 (1,36%)	23,39 (5,72%)	16,03 (217,7%)
Fosfomicina	1,47 (0,27%)	2,56 (0,63%)	1,09 (74,3%)
Linezolid	7,27 (1,34%)	5,87 (1,44%)	-1,40 (-19,3%)
Teicoplanin	0,99 (0,18%)	2,07 (0,51%)	1,07 (107,7%)

Vancomycin	28,87 (5,31%)	20,69 (5,06%)	- 8,19 (-28,3%)
Meropenem	9,84 (1,81%)	9,22 (2,26%)	- 0,62 (-6,3%)
Cefazolina	251,64 (46,31%)	162,67 (39,80%)	- 88,97 (- 35,4%)
Cefepime	0,81 (0,15%)	1,57 (0,39%)	0,76 (94,1%)
Cefotaxime	4,67 (0,86%)	0,68 (0,17%)	- 3,99 (-85,4%)
Ceftazidime	3,51 (0,65%)	5,10 (1,25%)	1,59 (45,5%)
Ceftazidime + avibactam	2,33 (0,43%)	0,20 (0,05%)	- 2,13 (-91,4%)
Ceftriaxone	15,22 (2,80%)	8,71 (2,13%)	- 6,51 (- 42,8%)
Metronidazole	0,99 (0,18%)	2,73 (0,67%)	1,73 (174,0%)
Nitrofurantoine	3,77 (0,69%)	0,56 (0,14%)	- 3,21 (- 85,2%)
Ciprofloxacin	21,96 (4,04%)	9,06 (2,22%)	- 12,90 (- 58,7%)
Levofloxacin	9,85 (1,81%)	3,05 (0,75%)	- 6,80 (- 69,1%)
Clindamycin	0,65 (0,12%)	3,41 (0,83%)	2,75 (421,6%)
Azitromicin	-	0,08 (0,02%)	0,08
Clarithromicin	2,00 (0,37%)	1,14 (0,28%)	- 0,86 (-43,1%)
Amoxicillin	0,36 (0,07%)	0,62 (0,15%)	0,26 (70,8%)
Ampicillin	0,12 (0,02%)	-	- 0,12 (- 100,0%)
Amoxicillin + clavulanate	100,03 (18,41%)	85,73 (20,98%)	- 14,30 (- 14,3%)
ampicillina + sulbactam	1,07 (0,20%)	1,75 (0,43%)	0,68 (63,3%)
Piperacillin + tazobactam	55,54 (10,22%)	50,22 (12,29%)	- 5,31 (- 9,6%)
Oxacillinw	1,16 (0,21%)	2,19 (0,54%)	1,03 (89,3%)
Colistine	2,67 (0,49%)	1,80 (0,44%)	- 0,87 (- 32,4%)
Trimethoprim + sulphametoxazole	0,79 (0,15%)	4,73 (1,16%)	3,94 (500,3%)
Doxiciclin	0,99 (0,18%)	-	- 0,99 (- 100,0%)
Minocyclin	0,33 0(,06%)	-	- 0,33 (- 100,0%)

Tigecyclina	1,02 (0,19%)	-	- 1,02 (-100,0%)
TOTAL	**543,39**	**408,68**	**- 134,71** **(- 24,8%)**
Fluoroquinolones	31,81 (5,85%)	12,11 (2,96%)	- 19,70 (- 61,9%)
Carbapenems	9,84 (1,81%)	9,22 (2,26%)	- 0,62 (- 6,3%)
Anti-MRSA agents	44,51 (8,19%)	52,02 (12,73%)	7,51 (16,9%)
Access	367,40 (67,61%)	265,90 (65,06%)	- 101,50 (- 27,6%)
Watch	153,26 (28,21%)	111,60 (27,31%)	- 41,66 (- 27,2%)
Reserve	22,45 (4,13%)	33,82 (8,28%)	11,37 (50,7%)
* ***Vancomycin + teicoplanin + daptomycin + linezolid + ceftaroline + ceftobiprole***			

Table 14: Traumatology, Defining parameters of the interrupted time series analysis of antibiotic consumption.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
DDDs x1000PDs (95% CI) *P-value*	455.38 (370.8; 540.0) *NA*	11.3 (-0.97; 23.6) **P: 0.069**	-226.6 (-333.1; -120) ***P: 0.000***	-0.97 (-17.8; 15.9) *P: 0.906*	10.4 (-1.5; 22.2) *P: 0.0832*
DOTs x1000PDs (95% CI) *P-value*	539.7 (470.9; 608.5) *NA*	0.7 (-10.1; 11.5) *P: 0.897*	-111.6 (-212.6; -0.5) ***P: 0.032***	-7.2 (-21.4; 6.9) *P: 0.299*	-6.6 (-16.1; 3) *P: 0.1671*
LOTs x1000PDs (95% CI) *P-value*	552.1 (481.3; 622.9) *NA*	0.3 (-10.1; 10.8) *P: 0.948*	-57.6 (-156; 40.7) *P: 0.236*	-13.5 (-27.3; 0.2 *P: 0.053*	-13.2 (-22.1; -4.3) ***P: 0.0056***
Fluoroquinolone DOTs x1000PDs (95% CI) *P-value*	45.8 (29.7; 61.8) *NA*	-2.5 (-4.7; -0.3) ***P: 0.025***	-8.4 (-33.0; 16.2) *P: 0.484*	3.4 (0.4; 6.4) ***P: 0.028***	0.9 (-1.4; 3.1) *P: 0.4420*
Carbapenems DOTs x1000PDs (95% CI) *P-value*	5.3 (12; 8.6) *NA*	0.8 (0.1; 1.5) ***P: 0.026***	-2.7 (-20; 14.7) *P: 0.753*	-1.4 (-4.6; 1.4) *P: 0.302*	-0.6 (-3.1; 1.9) *P: 0.6188*
Anti-MRSA DOTs x1000PDs (95% CI) *P-value*	63.2 (40.2; 86.3) *NA*	-3.4 (-6.1; -0.7) ***P: 0.017***	7.9 (-19.2; 35) *P: 0.550*	7.5 (3.6; 11.5) ***P: 0.001***	4.1 (1.3; 6.9) **P*: 0.0059***
Fluoroquinolone DDDs x1000PDs (95% CI) *P-value*	38 (28.4; 49.1) *NA*	-2.4 (-3.9; -0.85) ***P: 0.004***	-7.6 (-29.0; 13.8) *P: 0.465*	4.2 (1.6; 6.8) ***P: 0.003***	1.8 (-0.4; 4.0) *P: 0.102*
Carbapenems DDDs x1000PDs (95% CI) *P-value*	4.3 (-0.6; 9.3) *NA*	0.96 (-0.4; 2.3) P: 0.160	-9.3 (-26.9; 8.30) *P: 0.284*	-0.7 (-2.5; 1.2) *P: 0.453*	0.3 *(-1.0; 1.6)* P: 0.6632

Anti-MRSA DDDs x1000PDs (95% CI) *P-value*	44.2 (29.1; 59.3) *NA*	-1.7 (-3.4; 0.05) *P: 0.057*	-14 (-41.0; 13.2) *P: 0.296*	7.5 (1.7; 13.3) ***P: 0.013***	5.9 *(0.2; 11.3)* *P: 0.0362*
ACCESS DOTs x1000PDs (95% CI) *P-value*	307 (210; 404) *NA*	11 (-1.9; 23.9) *P 0.091*	-96.91493 (-177.5; -16.3) ***P: 0.021***	-25.2 (-39.3; -11.0) ***P: 0.001***	-14.2 (-19.1; -9.3) ***P: 0.0000***
WATCH DOTs x1000PDs (95% CI) *P-value*	17.8 (6.4; 29.3) *NA*	-11.8 (-21.8; -1.9) ***P: 0.022***	-1.2 (-83.1; 80.8) *P: 0.977*	*17.8 (6.4; 29.3)* ***P: 0.004***	*6.0 (0.1; 12)* ***P: 0.0467***
RESERVE DOTs x1000PDs (95% CI) *P-value*	13.6 (-7.4; 34.6) *NA*	1.6 (-2.0; 5.2) *P: 0.365*	-23.3 (-57.9; 11.3) *P: 0.175*	2.7 (-1.1; 6.6) *P: 0.158*	4.3 (2.7; 5.9) ***P: 0.0000***

The traumatology ward underwent a considerable re-organization during the first months of the post-intervention period with an increase in bed and change in patient case-mix. Patient volumes significantly e progressively increased in the post-intervention period. The medical staff was also expanding. Patients admitted to the ward were 2006 in the pre- and 2647 in the post-intervention period (9388 PDs vs 13187 PDs). LOS significantly increased in the post-intervention period (0.1 day/month, P=0.02) resulting in an average LOS of 5.4 days in the post-intervention vs 4.7 days in the former one. No significant variation in mortality trend or level occurred, with mortality rate consistently low across the two periods (pre-intervention:0.6%; post-intervention 0.76%). C.*difficile* infections were rare although 4 cases were diagnosed in the post-intervention compared to only one in the previous period. BSI incidence was higher in the post-intervention period (21 BSI, 0.8% of admitted patients vs 11 BSI, 0.5%) but no significant increasing trend nor change in level emerged when the ITS analysis was performed.

Table 15: Traumatology, Clinical and microbiological indicators

	Pre-intervention	Post-intervention	Overall
Patient Days (PDs) (n=23575)	9388	14187	23575
Admission (n=4653)	2006	2647	4653
Length of Hospital Stay (mean, days)	4.7	5.4	5.1
In-hospital mortality (n=32)	0.60% (12)	0.76% (20)	0.69%
Bloodstream Infections, incidence (n=45)	0.5% (11)	1.3% (34)	1 %
C.*difficile* Infections incidence (n=5)	0.05% (1)	0.15% (4)	0.11%
Gram-positive BSI incidence (n= 27)	0.3% (6)	0.8% (21)	0.6%
Gram-negative BSI	0.2% (4)	0.4% (10)	0.3%

incidence (n=14)			
Third-generation cephalosporin-resistant BSI incidence (n=3) [prevalence of gram-negative BSI]	0.05% (1) [25%]	0.08% (18) [20%]	0.06% [21%]
Carbapenem Resistant BSI incidence (n=1) [prevalence of gram-negative BSI]	0.05% (2) [3.4%]	- (0) [-]	0.02% [0.02%]

Table 16: Traumatology, defining parameters of the interrupted time series analysis of clinical outcomes.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
Length of Hospital stay (95% CI) *P-value*	4.7 (4.2; 5.3) *NA*	-0.01 (-0.1; 0 .1) *P: 0.784*	0.2 (-0.5; 0.9) *P: 0.576*	0.1 (-0.01; 0.2) *P. 0.073*	0.1 (0.01; 0.2) ***P: 0.0253***
Admission (95% CI) *P-value*	179.9 (166.8; 193.0) *NA*	-2.3 (-5.2; 0.6) *P: 0.114*	22.4 (-13.6; 58.4) *P: 0.208*	10.7 (6; 15.4) P**: 0.000**	8.4 (4.5; 12.2) ***P: 0.0002***
Mortality (death/100admission) (95% CI) *P-value*	0.6 (0.1; 1.0) *NA*	0.01 (-0.08; 0.1 *P: 0.867*	0.09 (-0.8; 1.0) *P: 0.839*	-0.0 (-0.12; 0.1) *P: 0.936*	0.003 (-0.07; 0.08) *P: 0.9378*
Bloodstream Infections (/100 admission) (95% CI) *P-value*	0.55 (0.16; 0.9) *NA*	0.003 (-0.1; 0.1) P: 0.959	0 .9 (-0.4; 2.3) P: 0.170	-0.03 (-0.25; 0.2) 0.825	-0.02 (-0.2; 0.2) *P: 0.8268*
Gram positive BSI (/100 admission) (95% CI) *P-value*	0.5 (-0.005; 0.9) *NA*	-0.03 (-0.1; 0 .04) P: 0.392	0.9 (-0.1; 1.9) P: 0.071	-0.001 (-0.16; 0.15) P: 0.991	-0.03 (-0.17; 0.1) *P: 0.6612*
Gram negative BSI (/100 admission) (95% CI) *P-value*	0.12 (0.2; 0.5) *NA*	0.01 (-0.03; 0.06) P: 0.562	0.1 (-0.3; 0.6) p: 0.525	-0.02 (-0.1; 0.06) P: 0.623	-0.01 (-0.06; 0.05) *P: 0.8372*

Cardiac Surgery and Cardiothoracic Intensive Care Units

The SAVE intervention was implemented simultaneously in the Cardiac Surgery and Cardiothoracic Intensive care units due to the close collaboration and high rate of patients co-managed by the two units. The intensive observational and educational phase started in April 2019. The Post-intervention period, initially planned to be completed in March 2020, was prematurely interrupted in February 2020 as the Covid-19 pandemic forced an impactful re-organization of the two wards with reduction of the activity and change in the patient's case-mix (pre-intervention period: April 2018-March 2019; post-intervention period: April 2019-February 2020). Thirty-one surgeons (13 senior and 11 junior doctors) and 18 anesthesiologists (12 senior and 6 junior doctors during their cardiothoracic rotation) prescribing antimicrobials to the hospitalized patients were involved in the two wards.

Guidelines for SAP and empirical antimicrobial therapy were approved and disseminated in September 2019. Audits evaluating the appropriateness of the antimicrobial prescriptions were performed from November 2019 to January 2020 in the Cardiac Surgery ward and December to February (6) in the Cardiothoracic ICU.

Feedback was provided directly to ward staff during routinely consulting activities.

Prescribing Appropriateness

Four audits were performed monthly in the period November 2019 to January 2020 in the surgery ward and six bi-weekly (December to February) in the ICU.

In the surgical ward, the total reviewed prescriptions were 28 (22 patients). The overall prevalence of patients prescribed with at least one antibiotic was 22.2% (22 out of 99 hospitalized patients). Nine percent of the total prescriptions addressed SAP, 32% represented empirical therapy and 46% was aimed at targeted antibiotic treatment. Two patients received medical prophylaxis being immunocompromised. Piperacillin/tazobactam was prescribed in 26% of cases and ant-MRSA drugs accounted for 30% of the

prescriptions (daptomycin 17%, vancomycin 13%). Considering only therapeutical prescriptions, 5 prescriptions (27%) targeted cardio-circulatory system infections and 5 primary bacteremias; pneumonia, Urinary-tract infection and skin and soft-tissue infections were the referred reason for two prescriptions (9%) each one. Overall, 86% of the prescriptions were appropriate, one empirical therapy was deemed unnecessary and one empirical, as well as one targeted treatment, exceeded in duration. The 77% (15 out of 22) of patients prescribed antibiotics received at least one infectious disease consultation during antibiotic therapy.

In the ICU 56 prescriptions to 40 patients were audited. Patients prescribed with at least one antibiotic were 74% of the total (54 patients hospitalized in the 6 observed days), with pointily prevalence ranging from 100% to 44%. Fourteen patients received antibiotics for SAP (35%), 15 (37.5%) received empirical therapy and 6 (15%) targeted treatment. Beta-lactams/beta-lactamase inhibitors association accounted for 34% of prescriptions (piperacillin/tazobactam 31%), anti-MRSA agents for 44% (vancomycin 19%, linezolid 16%, and daptomycin 9%), meropenem for 16%, and third-generation cephalosporins for 6%. The most frequent referred diagnosis was pneumonia 25%, followed by primary bacteremia (15%), cardio-circulatory system infection (8%), and SSTI 3%. In 13% of cases, no clear source of infection could be identified. Appropriateness was close to 100% with only two prescriptions (one SAP and one empirical therapy) judged excessive in duration. Seventeen out of 40 patients (42.5%) received at least one infectious disease consultation addressing antibiotic treatment.

Figure 17. Prevalence of patients receiving antibiotics in the Cardiothoracic area

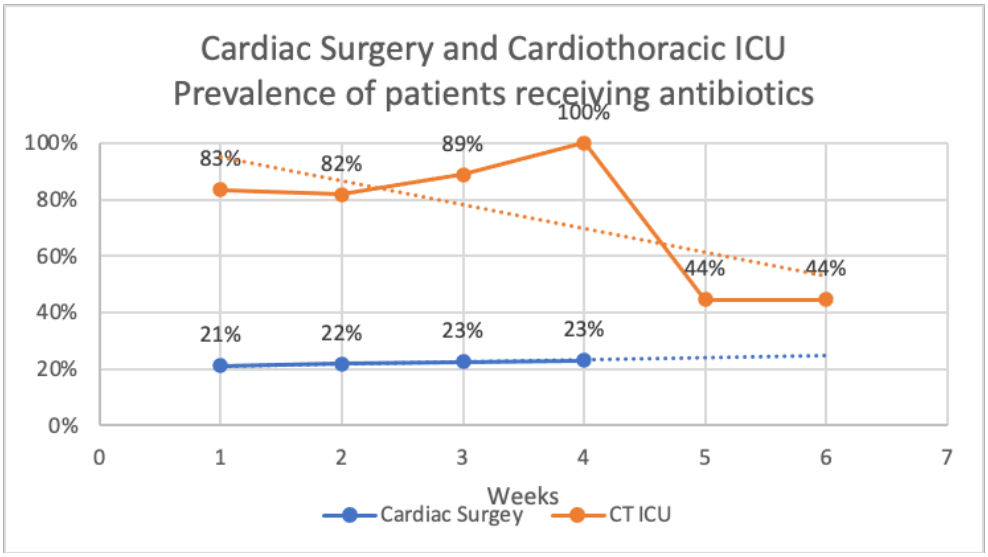
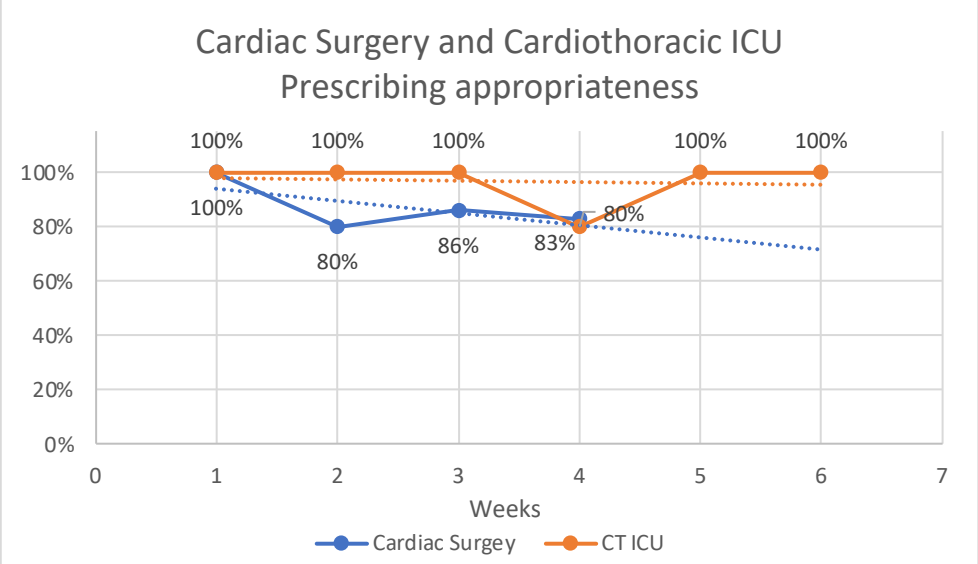


Figure 18. Prescribing appropriateness in the Cardiothoracic area



Antimicrobial Consumption

Cardiac Surgery

Total consumption of antimicrobials, normalized as DOT per 1000 PDs was lower during the post-intervention period (360,76 vs 571,56, -210.8 DOTs, -36.9%); observing the selected sub-classes, anti-MRSA agents showed the most substantial absolute reduction (77,2 vs 130,4, -53.1 DOTs, - 40,8%), followed by carbapenems (13,1 vs 61,1, - 47,9 DOTs, -78,5%) and

fluoroquinolones (5.3 vs 21.6, -16.4 DOTs, -75.6%). Consumption of antimicrobials included in the Access WHO class was higher in the post-intervention period (136.2 vs 111.8, +24.4 DOTs, + 21.8%) while the opposite occurred for the ones included in the Watch (164.9 vs 287, -122.1 DOTs, -42.6%) and in the Reserve classes (59.0 vs 171.7, -112.7 DOTS, -65.6%). Absolute consumption of first and second generation cephalosporins (mainly prescribed for SAP) was stable across the two periods (53.8 vs 58.7, -4.9 DOTs, -8.4%).

Relative composition of consumption considerably changed between the two periods with Access antimicrobials shifting from 19.6% to 37.7% and the Reserve ones from 30.0% to 16.4% in the pre-and post-intervention period, respectively. Carbapenems also dropped from 10.7% to 3.6% of the total.

Access antimicrobials increased consumption was due to amoxicillin/clavulanate (+ 14.3 DOTs per 1000PDs) and cefazolin (+15.6 DOTs per 1000PDs). Among Watch agents, meropenem (- 47.2 DOTS per 1000PDs), cephalosporins (- 37.3 DOTs per 1000PDs), piperacillin/tazobactam (- 26.1 DOTs per 1000PDs), and fluoroquinolones (-16.4 DOTs per 1000PDs) showed lower consumption in the post-intervention. Linezolid (- 29.5 DOTs per 1000PDs), daptomycin (- 25.1 DOTs per 1000PDs), ceftazidime-avibactam (-22.7 DOTs per 1000PDs) and tigecycline (-20.0 DOTs per 1000PDs) equally contributed to the observed reduction in consumption of the Reserve class. Complete data on consumption of ATC-J01 agents in the Cardiac Surgery unit are provided in table 17.

Table 17: Cardiac Surgery, antimicrobial consumption (DOTs per 1000PDs) of ATC-J01 antimicrobial agents

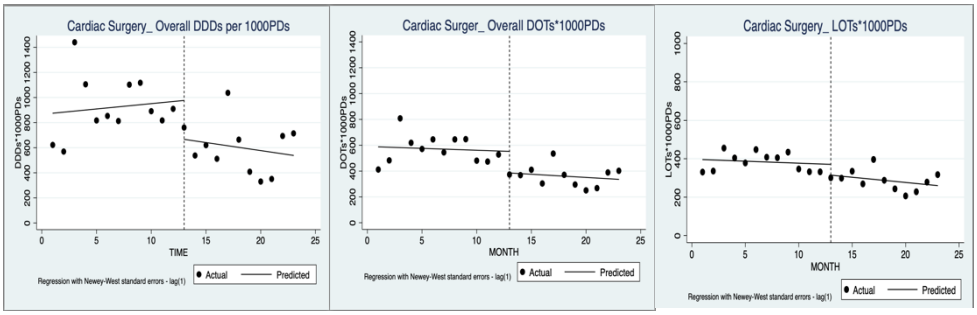
DOTs x1000PDs	*Pre-Intervention (%)*	*Post-intervention (%)*	*Δ (%)*
Minocyclin	*-* *(0,0%)*	*0,54* *(0,1%)*	*0,54* *-*
Tigecyclina	*20,76* *(3,6%)*	*0,75* *(0,2%)*	*- 20,01* *(-96,4%)*
Ampicillin	*12,53* *(2,2%)*	*6,94* *(1,9%)*	*- 5,59* *(-44,6%)*
Amoxicillin	*0,95* *(0,2%)*	*1,88* *(0,5%)*	*0,92* *(97,0%)*
Piperacillin	*-* *(0,0%)*	*0,23* *(0,1%)*	*0,23* *-*
Penicillin	*0,10* *(0,0%)*	*-* *(0,0%)*	*- 0,10* *(-100,0%)*
Oxacillin	*4,33* *(0,8%)*	*7,17* *(2,0%)*	*2,84* *(65,6%)*
Amoxicillin + clavulanate	*16,52* *(2,9%)*	*30,79* *(8,5%)*	*14,27* *(86,4%)*

Piperacillin + Tazobactam	*83,94 (14,7%)*	*57,83 (16,0%)*	*- 26,11 (-31,1%)*
Cefazolin	*9,79 (1,7%)*	*25,43 (7,0%)*	*15,64 (159,7%)*
Cefuroxime	*48,88 (8,6%)*	*28,32 (7,9%)*	*- 20,55 (-42,1%)*
Cefotaxime	*1,72 (0,3%)*	*0,64 (0,2%)*	*- 1,08 (-62,9%)*
Ceftazidime	*13,82 (2,4%)*	*12,67 (3,5%)*	*- 1,15 (-8,3%)*
Ceftriaxone	*28,11 (4,9%)*	*16,97 (4,7%)*	*- 11,14 (-39,6%)*
Ceftazidime + Avibactam	*28,26 (4,9%)*	*5,55 (1,5%)*	*- 22,71 (-80,3%)*
Cefepime	*4,01 (0,7%)*	*0,32 (0,1%)*	*- 3,69 (-92,0%)*
Meropenem	*59,75 (10,5%)*	*12,56 (3,5%)*	*- 47,19 (-79,0%)*
Ertapenem	*0,31 (0,1%)*	*- (0,0%)*	*- 0,31 (-100,0%)*
Imipenem + Cilastatin	*0,99 (0,2%)*	*0,55 (0,2%)*	*- 0,44 (-44,6%)*
Ceftobiprole medocaril	*4,30 (0,8%)*	*- (0,0%)*	*- 4,30 (-100,0%)*
Ceftaroline fosamil	*1,35 (0,2%)*	*1,16 (0,3%)*	*- 0,19 (-13,8%)*
Trimethoprim +Sulphametoxazole	*48,33 (8,5%)*	*17,97 (5,0%)*	*- 30,36 (-62,8%)*
Clarithromicin	*0,51 (0,1%)*	*-*	*- 0,51 (-100,0%)*
Clindamycin	*3,13 (0,5%)*	*3,48 (1,0%)*	*0,34 (11,0%)*
Gentamicin	*8,05 (1,4%)*	*9,39 (2,6%)*	*1,34 (16,7%)*
Amikacin	*0,20 (0,0%)*	*- (0,0%)*	*- 0,20 (-100,0%)*
Ciprofloxacin	*9,58 (1,7%)*	*3,23 (0,9%)*	*- 6,35 (-66,3%)*
Levofloxacin	*12,06 (2,1%)*	*2,06 (0,6%)*	*- 10,01 (-82,9%)*
Vancomycin	*20,07 (3,5%)*	*25,56 (7,1%)*	*5,49 (27,4%)*
Teicoplanin	*0,10 (0,0%)*	*0,43 (0,1%)*	*0,33 (320,9%)*
Colistin	*4,06 (0,7%)*	*-*	*- 4,06 (- 100,%)*
Metronidazole	*0,41 (0,1%)*	*1,27 (0,4%)*	*0,86 (210,1%)*
Nitrofurantoine	*10,54 (1,8%)*	*35,34 (9,8%)*	*24,80 (235,3%)*
Fosfomycin	*8,38 (1,5%)*	*0,98 (0,3%)*	*- 7,40 (-88,3%)*
Linezolid	*38,07 (6,7%)*	*8,56 (2,4%)*	*- 29,51 (-77,5%)*
Daptomycin	*66,52 (11,6%)*	*41,48 (11,5%)*	*- 25,03 (-37,6%)*
Total	***571,56***	***360,76***	***- 210,80 (-36,9%)***
Fluoroquinolones	*21,64 (3,8%)*	*5,29 (1,5%)*	*- 16,36 (-75,6%)*
Carbapenemes	*61,05 (10,7%)*	*13,12 (3,6%)*	*-47,94 (-78,5%)*
Anti-MRSA agents*	*130,41 (22,8%)*	*77,19 (21,4%)*	*- 53,21 (-40,8%)*
Aware	*111,76 (19,6%)*	*136,17 (37,7%)*	*24,42 (21,8%)*
Watch	*286,99 (50,2%)*	*164,85 (45,7%)*	*- 122,13 (-42,6%)*
Reserve	*171,70 (30,0%)*	*59,02 (16,4%)*	*- 112,67 (-65,6%)*
Prophylaxis (I and II generation cephalosporins)	*58,67 (10,3%)*	*53,75 (14,9%)*	*- 4,92 (-8,4%)*
TOTAL without proph	*512,90 (89,7%)*	*307,01 (85,1%)*	*- 205,89 (-40,1%)*
Overall JO1 Expenditures	24.280	13.262	*-11.018*

€ x1000PDs			*(-45.4%)*
Fluoroquinolones Expenditures € x1000PDs	14 (0,1%)	9 *(0,1%)*	*-5 (-36.4%)*
Carbapenems Expenditures € x1000PDs	888 (3,7%)	238 (1,8%)	*-650 (-73,2%)*
New Cephalosporins Expenditures € x1000PDs	5.438 (22,4%)	3.451 (26%)	*-1987 (-36,5%)*
* ***Vancomycin + teicoplanin + daptomycin + linezolid + ceftaroline + ceftobiprole***			

The Interrupted time series analysis showed a statistically significant drop in the level of consumption, associated with the AMS intervention implementation (- 310.0 DDDs*1000PDs, P= 0.043; -167 DOTs*1000PDs P= 0.027) but no variations in the consumption trends nor downward trends in the post-intervention period occurred. LOTs were stable across the whole 24-months period.

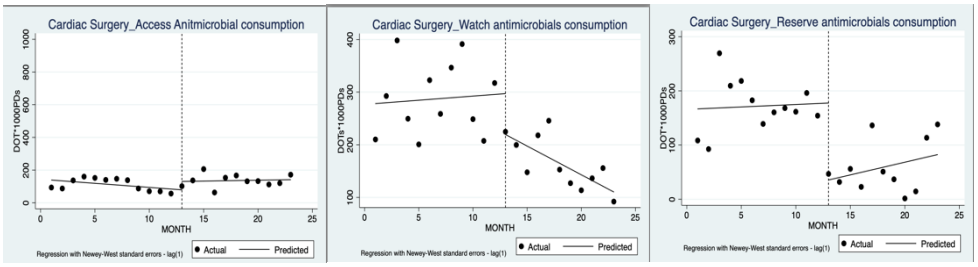
*Figure 19. ITSA of Overall antimicrobial consumption in Cardiac Surgery (DDDs, DOTs, and LOTs*1000PDs)*



Fluoroquinolone consumption was already significantly decreasing in the pre-intervention period (-3.0 DOTs *1000PDs/month P< 0.001; – 4.1 DDDs *1000PDs/month, P=0.001) then stabilized as demonstrated by significant, positive, change in slope. Carbapenems showed a change in level associated with intervention implementation (- 54.5 DOTs*1000PDs, P=0.010; - 115.3 DDDs*1000PDs, P=0.022) but, as for overall consumption, no statistically significant trends towards reduced consumption could be observed thereafter. Anti-MRSA agents also showed an immediate change in level associated with intervention implementation when considering DDDs (-173.6 DDs*1000PDs, P=0.041) but not for DOTs. Watch class antimicrobials post-intervention trend was significantly decreasing at the rate of -10.9 DOTs*1000PDs/month (P<0.001), while Reserve antimicrobials consumption had an important change in the level of -141.9

DOTs*1000PDs (P<0.001) and no significant post-intervention slope nor change in it.

*Figure 20. ITSA of Access, Watch, and Reserve antimicrobials consumption in Cardiac Surgery (DOTs *1000PDs)*



Overall J01 antimicrobials expenditures were significantly increasing in the pre-intervention period (+ 1261.7 Euro*1000PDs/month, P=0.046); the intervention was associated with a significant change in the level of - 22238.7 Euro*1000PDs (P< 0.001) that was also significant when considering expenditures for carbapenems (- 946.1 Euro*1000PDs, P= 0.022) and new cephalosporines (-8094 Euro*1000PDs, P= 0.045). No significant post-intervention trend or change in slope comparing the two periods could be observed in the expenditures for overall and sub-classes antimicrobials.

Results of the ITS analysis relative to antibiotic consumption in the Cardiac Surgery department are summarized in table 18.

Table 18: Cardiac Surgery, defining parameters of the interrupted time series analysis of antibiotic consumption.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
DDDs x1000PDs (95% CI) *P-value*	874.8 (484.6; 1265.1) *NA*	8.5 (-40.1; 57.4) *P: 0.720*	-310.0 (-608.4; -11.6) ***P: 0.043***	-21.3 (-80.8; 38.2)) *P: 0.462*	-12.8 (-47.3; 21.7 *P: 0.0.4469*
DOTs x1000PDs (95% CI) *P-value*	587.7 (402.7; 772.5) *NA*	-2.9 (-27.7; 21.9) *P: 0.808*	-167 (-312.8; -21.2) ***P: 0.027***	-2.0 (-29.8; 25.7) *P: 0.879*	-5 (-17.3; 7.4) *P: 0.411*
LOTs x1000PDs (95% CI) *P-value*	395.5 (322.2; 468.8) *NA*	-2.1 (-13.0; 8.9) *P: 0.698*	-56.2 (-9.3; 14.8) *P: 0.159*	-3.4 (-17.5; 10.8) *P: 0.623*	-5.4 (--14.1; 3.2) *P: 0.204*
Fluoroquinolone DOTs x1000PDs (95% CI) *P-value*	38.2 (27.3; 49) *NA*	-3.0 (--4.2; -1.8) ***P: 0.000***	+2.7 (-9.3; 14.8) *P: 0.638*	+3.1 (1.5; 4.6) ***P: 0.001***	0.01 (-1.0; 1.1) *P: 0.881*
Carbapenems DOTs x1000PDs (95% CI) *P-value*	57.4 (10.4; 104.3) *NA*	0.7 (-5.5; 6.8) *P: 0.833*	-54.5 (-94.1; -14.8) ***P: 0.010***	-0.2 (-6.9; 6.5) *P: 0.0.942*	0.4 (-2.9; 3.7) *P: 0.783*
Anti-MRSA DOTs x1000PDs (95% CI) *P-value*	135.6 (48.6; 222.5) *NA*	-0.9 (-11.0; 9.2) *P: 848*	-60.6 (-125.1; 3.8) *P: 0.064*	3.6 (-9.5; 16.7) *P: 0.568*	2.7 -5.7; 11.1) *P: 0.510*

Fluoroquinolone DDDs x1000PDs (95% CI) *P-value*	53.1 (35.7; 70.5) *NA*	-4.1 (-6.3; -1.8) ***P: 0.001***	-0.1 (-20.9; 20.7) *P: 0.990*	5 (1.9; 8) ***P: 0.003***	0.9 -1.2; 2.9) *P: 0.387*
Carbapenems DDDs x1000PDs (95% CI) *P-value*	64.5 (-0.3; 129.4) *NA*	8.3 -0.1; 16.8) *P: 0.052*	-115.3 (-212.2; -18.3) ***P: 0.022***	-13.5 (-26.7; -0.4) ***P: 0.044***	-5.2 (-16.3; 5.9) *P: 0.343*
Anti-MRSA DDDs x1000PDs (95% CI) *P-value*	241.5 (49.5; 433.5) *NA*	4.9 (-17.5; 27.4) P: 0.651	-173.6 (-339.7; -7.4) **P: 0.041**	-3.6 (-26.4; 33.7) *P: 0.802*	8.6 (-12.0; 29.2) P: 0.395
ACCESS DOTs x1000PDs (95% CI) *P-value*	139.2 (81.3; 197.1) *NA*	-5 (-12.8; 2.8) *P: 0.198*	-51.5 (-9; 112) *P: 0.091*	-6.1 -4.3; 16.5) *P: 0.237*	-1-1 (-5.2; 7.4) *P: 0.724*
WATCH DOTs x1000PDs (95% CI) *P-value*	278.4 (198.4; 358.3) *NA*	1.6 (-10.5; 13.7) *P: 0.789*	-77.8 (-173.8; 18.3) *P: 0.106*	-12.5 (-25.6; 0.6 *P: 0.061*	-10.9 -15.8; -6.0) ***P: 0.0002***
RESERVE DOTs x1000PDs (95% CI) *P-value*	166.8 (81.3; 252.3) *NA*	0.9 (-9.3; 11.1) *P: 0.856*	-141.9 (--195.3; -88.6) ***P: 0.000***	3.8 (-9.9; 17.4) *P: 0.569*	4.7 (-4.6; 13.9) *P: 0.302*
Overall JO1 Expenditures € x1000PDs	17340.7 (7782.4; 26898.9) *NA*	1261.7 (24.6; 2498.7) ***P: 0.046***	-22238.7 (--30638.1; -13839) ***P: 0.000***	-1126 (-3077.6; 825.7) *P: 0.242*	135.7 (-1.35; 1624.0) *P: 0.851*
Fluoroquinolones Expenditures € x1000PDs	19.9 (9.8; 30.0) *NA*	-1.14 (-2.8; 0.5) *P: 0.174*	-8.1 (-27.9; 11.6) *P: 0.399*	3.2 (-0.9; 7.4) *P: 0.116*	2.1 (-1.7; 6.1) *P: 0.265*
Carbapenems Expenditures € x1000PDs	517 (-89.5; 1123.3) *NA*	67.5 (-10.1; 145.2) *P: 0.084*	- 946.1 (-1739.1; -153.1) ***P: 0.022***	-105.9 (-217.1; 6.7) *P: 0.064*	-37.7 (--126.8; 51.5) *P: 0.388*
New Cephalosporins Expenditures € x1000PDs	2107 (-1361; 5575) *NA*	605.7 (-72.6; 1284) *P: 0.077*	-8094 (-16007.1; 182.1) ***P: 0.045***	-559.8 (-1360.9; 5574.9) *P: 0.0.219*	45.8 (--779.1; 870.8) *P: 0.909*

Cardiothoracic ICU

The total consumption of antimicrobials in cardiothoracic ICU (expressed as DDDs per 1000 PDs) showed a lower level in the post-intervention period compared to the previous one (1271.9 vs 1607.3, -335.4 DDDs, -20.9%). Lower consumption was also observed for anti-MRSA antibiotics (256.7 vs 334,1 -77.4 DDDs, -23.2%), carbapenems (64.6 vs 116.1, -51.6 DDDs, -44.4%) and fluoroquinolones (10.6 vs 35.5, -24.9 DDDs, -70.3%). Adopting the WHO AWaRe classification for stratifying consumption, Access antimicrobials usage resulted higher in the post-intervention period (346 vs 151, +194.9 DDDs, +129.1%), while Watch and Reserve consumption levels lowered (Watch 679.5 vs 1033.8, -354.3 DDDs, -34.3%; Reserve 222.2 vs 410.2, -188 DDDs, -45.8%); this resulted in variation of relative composition of the total consumption with Access antimicrobials shifting from the 9.4% to the 27.2% and Reserve oppositely from the 25.5% to the 17.5% of the total, while Watch only slightly reduced (64.3% to 53.4% of the total). Complete

data on the consumption of ATC-J01 agents in the Cardiothoracic ICU are provided in table 19.

Table 19: Cardiothoracic ICU, antimicrobial consumption (DDDs per 1000PDs) of ATC-J01 antimicrobial agents

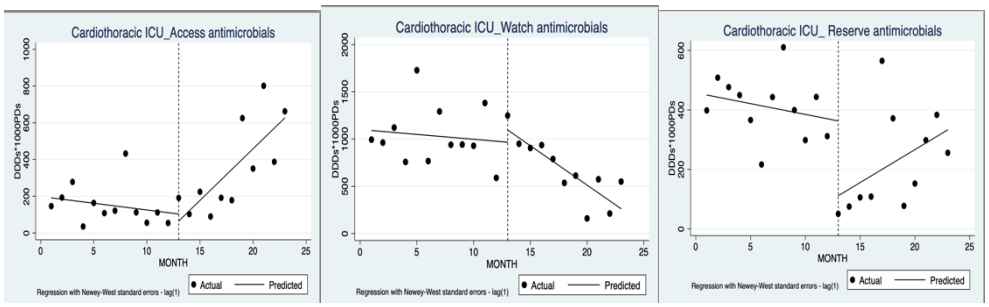
DDDs x1000PDs	*Pre-Intervention (%)*	*Post-intervention (%)*	*Δ (%)*
Fosfomycin	18,14 (-1,1%)	7,23 (0,6%)	- 10,91 (-60,1%)
Linezolid	71,38 (4,4%)	50,51 (4,0%)	-20,87 (-29,2%)
Daptomycin	216,91 (13,5%)	146,59 (11,5%)	-70,32 (-32,4%)
Tedizolid	- (0,0%)	2,16 (0,2%)	2,16
Vancomycin	34,18 (2,1%)	46,76 (3,7%)	12,58 (36,8%)
Teicoplanin	7,93 (0,5%)	- 3,52 (-0,3%)	- 11,45 (-144,3%)
Colistin	28,96 (1,8%)	- (0,0%)	- 28,96 (-100,0%)
Meropenem	116,14 (7,2%)	64,60 (5,1%)	- 51,55 (-44,4%)
Ceftobiprole medocaril	3,69 (0,2%)	5,86 (0,5%)	2,17 (58,8%)
Ceftaroline fosamil	-	8,36 (0,7%)	8,36
Cefazoline	32,98 (2,1%)	249,74 (19,6%)	216,75 (657,2%)
Cefuroxime	610,75 (38,0%)	328,11 (25,8%)	- 282,64 (-46,3%)
Cefotaxime	10,07 (0,6%)	4,67 (0,4%)	- 5,41 (-53,7%)
Ceftazidime	26,20 (1,6%)	5,48 (0,4%)	-20,73 (-79,1%)
Ceftriaxone	43,57 (2,7%)	53,17 (4,2%)	9,59 (22,0%)
Ceftazidime + Avibactam	29,77 (1,9%)	- (0,0%)	-29,77 (-100,0%)
Cefepime	8,42 (0,5%)	- (0,0%)	- 8,42 (-100,0%)
Gentamicin	23,35 (1,5%)	4,70 (0,4%)	- 18,65 (-79,9%)
Amikacin	- (0,0%)	5,46 (0,4%)	5,46
Ampicillin	29,43 (1,8%)	18,01 (1,4%)	- 11,42 (-38,8%)
Piperacillin	- (0,0%)	2,38 (0,2%)	2,38
Amoxicillin + clavulanate	5,58 (0,3%)	22,69 (1,8%)	17,11 (306,5%)
Piperacillin + Tazobactam	137,81 (8,6%)	155,90 (12,3%)	18,09 (13,1%)
Oxacillin	12,27 (0,8%)	24,31 (1,9%)	12,04 (98,1%)
Ciprofloxacin	14,56 (0,9%)	1,53 (0,1%)	- 13,03 (-89,5%)
Levofloxacin	20,90 (1,3%)	9,01 (0,7%)	- 11,89 (-56,9%)
Clindamycin	20,86 (1,3%)	16,84 (1,3%)	- 4,02 (-19,3%)
Clarithromicin	3,26 (0,2%)	4,40 (0,3%)	1,14 (35,0%)
Azitromicin	- (0,0%)	6,99 (0,5%)	6,99
Trimethorpim + sulphametoxazole	38,83 (2,4%)	21,22 (1,7%)	- 17,61 (-45,4%)
Doxicyclin	- (0,0%)	7,30 (0,6%)	7,30

Tigecyclin	41,32 (2,6%)	1,47 (0,1%)	- 39,86 (-96,4%)
TOTAL	**1.607,28**	**1.271,91**	**- 335,36 (-20,9%)**
Fluoroquinolones	35,46 (2,2%)	10,55 (0,8%)	- 24,91 (-70,3%)
Carbapenems	116,14 (7,2%)	64,60 (5,1%)	- 51,55 (-44,4%)
Anti-MRSA agents*	334,09 (20,8%)	256,73 (20,2%)	- 77,37 (-23,2%)
Access	151.0 (9.4%)	346 (27,2%)	194.9 (129.1%)
Watch	1033.8 (64.3%)	679.5 (53.4%)	- 354.3 (-34.3%)
Reserve	410,18 (25,5%)	222.2 (17,5%)	- 188 (-45,8%)
Overall JO1 Expenditures € x1000PDs	37.400,27	20.636,50	- 16.763,77 (-44,8%)
Fluoroquinolones Expenditures € x1000PDs	42,53 (0,1%)	8,11 (0,0%)	- 34,42 (-80,9%)
Carbapenems Expenditures € x1000PDs	924,19 (2,5%)	550,20 (2,7%)	- 373,99 (-40,5%)
New Cephalosporins Expenditures € x1000PDs	7.269,61 (19,4%)	1.413,23 (6,8%)	- 5.856,38 (-80,6%)
* ***Vancomycin + teicoplanin + daptomycin + linezolid + ceftaroline + ceftobiprole***			

The impact of the AMS intervention was evaluated by ITS analysis: although showing a consistent downward slope, neither the pre- nor the post-intervention trend in overall consumption reached statistical significance. Variation in slope across the two periods was also non-significant. Carbapenems and anti-MRSA antimicrobials were both observed to drop with a significant change in level after intervention implementation (carbapenems: -72.1 DDDs*1000PDs, P=0.013; anti-MRSA: -241.9 DDDs*1000PDs, P=0.003) but no change in slope nor sustained decreasing trends in the post-intervention periods occurred. Increase in the consumption of antimicrobials included in the Access class was due to a significant upward slope in the post-intervention period (+ 56.2 DDDs*1000PDs/month, P<0.001) with an estimated overall effect of + 63.5 DDDs*1000PDs/month (P<0.001) when considering the downward pre-intervention slope; the AMS intervention was oppositely associated with a significant decrease in consumption of Watch antimicrobials in the post-intervention period (-83 DDDs*1000PDs/month, P<0.001) that magnified the already present downward trend of the pre-intervention, with an estimated total effect of – 73.1 DDDs*1000PDs/month (P=0.002). Reserve antimicrobials showed a significant drop in the level of consumption (-251.6 DDDs*1000PDs/, P=0.007) but a significant upward post-intervention trend +22.2 DDDs*1000PDs/month (P=0.012) resulting in

a change in slope of +29.4 DDDs*1000PDs/month (P=0.007) when considering the downward, although non-significant, pre-intervention trend.

*Figure 21: ITSA of the Access, Watch and Reserve antimicrobials consumption in the Cardiothoracic ICU, (DDDs*1000PDs)*



ITS analysis of expenditures revealed only a significant drop in the level of carbapenem-associated costs (-562.5 DDDs*1000PDs, P=0.014). Results of the ITS analysis relative to antibiotic consumption in the Cardiothoracic ICU are summarized in table 20.

Table 20: Cardiothoracic ICU, defining parameters of the interrupted time series analysis of antibiotic consumption.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
DDDs x1000PDs (95% CI) *P-value*	1758.4 (1518.6; 1998.3) *NA*	-27.5 (-72.8; 17.9) *P: 0.220*	-128.6 (--603.9; 346.8) *P: 0.578*	21.8 (-25.1;68.8) *P: 0.342*	-5.6 (-37.7; -26.4) *P: 0.7168*
Fluoroquinolone DDDs x1000PDs (95% CI) *P-value*	52.9 (-43.3; 149.2) *NA*	-3.2 (--13.3; 6.9) *P: 0.517*	-16.9 (-65.9; 32.2) *P: 0.480*	5.7 (-5.2;16.6) *P: 0.285*	2.5 -1.9; 6.9) *P: 0.245*
Carbapenems DDDs x1000PDs (95% CI) *P-value*	104.6 (56.0; 153.3) *NA*	2.1 (-4.7; 8.8) *P: 0.524*	-72.1 (-127.2; -17.1) ***P: 0.013***	-0.7 (-10.7; 9.3) *P: 0.886*	1.4 (-5.2; 8.1) *P: 0.663*
Anti-MRSA DDDs x1000PDs (95% CI) *P-value*	282.0 (194.1; 370.0) *NA*	9.4 (-1.1; 20.0) *P: 0.076*	-241.9 (-389.8; -94) ***P: 0.003***	11.1 (-8-8; 31.1) *P: 0.257*	20.6 (4.8; 36.4) ***P: 0.013***
ACCESS DDDs x1000PDs (95% CI) *P-value*	191.3 (122.9; 259.7) *NA*	-7.3 (-19.1; 4.5) *P: 0.210*	-38 (--221.7; 144.6) *P: 0.664*	63.5 (42.3; 84.7) ***P: 0.000***	56.2 (36.8; 75.6) ***P: 0.000***
WATCH DDDs x1000PDs (95% CI) *P-value*	1090.0 (879.3; 1301.9) *NA*	-10.3 (-46.4; 25.8) *P: 0.556*	129.8 (-232.2; 491.8) *P: 0.426*	-73.1 (-114.6; -31.5) ***P: 0.002***	-83 (-114; -52.2) ***P: 0.0000***
RESERVE DDDs x1000PDs (95% CI) *P-value*	450.0; (371.1; 528.9) *NA*	-7.3 (-17.2; 2.7) *P: 0.145*	-251.6 (-425.9; -77.3) ***P: 0.007***	29.4 (9.1; 49.7) ***P: 0.007***	22.2 (5.4; 38.9) ***P: 0.012***
Overall JO1 Expenditures € x1000PDs	43104.1 (33860; 52348) *NA*	-1037.1 (-2404.4; 330.3) *P: 0.129*	-11152.85 (-23840; 1534) *P: 0.081*	966.4 (-720.9; 2653.7) *P: 0.245*	-70-7 (-932.6; 791.2) *P: 0.866*

Fluoroquinolones Expenditures € x1000PDs	57.7 (-50.0; 165.4) *NA*	-2.8 (-14; 8.5) *P: 0.613*	-19.6 (-80.8; 41.7) *P: 0.512*	3.5 (-8.1; 15.1) *P: 0.532*	0.7 (-3.1; 4.6) *P: 0.683*
Carbapenems Expenditures € x1000PDs	838.3 (456.7; 1219.9) *NA*	15.6 (-37.8; 69) *P: 0.547*	-562.5 (-997.5; -127.5) ***P: 0.014***	-4.9 (-83.0; 73.2) *P: 0.896*	10.7 (-40.5; 61.8) *P: 0.667*
New Cephalosporins Expenditures € x1000PDs	10365.4 (-4670.8; 16060) *NA*	-562.9 (-1216.6; 90.8) *P: 0.087*	-3610.9 (-7955.7; 733.9) *P: 0.098*	562.9 (-90.8; 1216.6) *P: 0.087*	0.0 (-0.0; 0.0) *P: 1.000*

Clinical and microbiological outcomes

Cardiac Surgery

During the whole observed period (23 months), 4147 patients were admitted to the cardiac surgery ward (2108 in the pre-intervention and 2039 in the post-intervention period, monthly mean 180 patients/month); the mean length of hospital stay was substantially stable (4.6 and 4.2 days in the pre-and post-intervention period, respectively) across the two periods as confirmed by the ITS analysis, that couldn't identify any significant trend. Mortality was low in both periods (0.2% vs 0.3) with ITS analysis not identifying any significant variation.

Only 4 C.*difficile* infections were diagnosed during 23 months, they were evenly distributed in the two periods. Bloodstream infections were 60 (incidence per 100 admitted patients= 2.8%) in the pre-intervention year and 35 (incidence per 100 admitted patients= 5.21%) in the post-intervention one, with the pre-intervention starting level estimated at 3.1 BSI/100 admitted patients, and no significant trend emerging at the ITS analysis. Gram-positive bacteria were responsible for 38 and 20 BSI (63.3% and 57% of the total BSI, incidence per 100 admitted patients = 1.8% and 1%) in the pre-and post-intervention period, respectively; as for total BSI, ITS analysis didn't detect significant trends nor change in slope when considering individually BSI caused by gram-positive and gram-negative bacteria. Bacteriemic infections caused by MDR gram-negative were rare, but CRE-BSI accounted for one-third of BSI caused by gram-negative in both periods. Clinical and microbiological indicators and results of the ITS analysis relative to the clinical and microbiological data are summarized in Tables 21 and 22.

Table 21: Cardiac Surgery, Clinical and microbiological indicators

	Pre-intervention	Post-intervention	Overall

Patient Days (PDs) (n=18158)	9643	8515	18158
Admission (n=4147)	2108	2039	4147
Length of Hospital Stay (days, mean)	4.6	4.2	4.4
In-hospital mortality (n=11)	0.2% (5)	0.3% (6)	0.3%
Bloodstream Infections, incidence (n=95)	2.8% (60)	1.7% (35)	2.3%
C.*difficile* Infections incidence (n=4)	0.09% (2)	0.10% (2)	0.10%
Gram-positive BSI incidence (n= 58)	1.8% (38)	1.0% (20)	1.4%
Gram-negative BSI incidence (n=29)	0.7% (15)	0.7% (14)	0.7%
Third-generation cephalosporin-resistant BSI incidence (n=1) [prevalence of gram-negative BSI]	- (0) [-]	0.0 % (1) [7%]	0.0 % (1) [3%]
Carbapenem Resistant BSI incidence (n=10) [prevalence of gram-negative BSI]	0.24% (5) [33.3%]	0.25% (5) [35.7%]	0.24% [34.5%]

Table 22: Cardiac Surgery, defining parameters of the interrupted time series analysis of clinical outcomes.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope
Length of Hospital stay (95% CI) *P-value*	4.3 (4.1; 4.6) *NA*	0.04 (-0.01; 0.1) *P: 0.125*	-0.5 (-1.3; 0.3) *P: 0.193*	-0.08 (--0.2; 0.01) *P: 0.086*	-0.04 (-0.11; 0.04) *P: 0.361*
Admission (95% CI) *P-value*	172.4 (158.2; 186.5) *NA*	0.6 (-1.7; 3) *P: 0.604*	0.6 (-24.5; 25.7) *P: 0.960*	0.4 (-2.3;3.1) *P: 0.740*	1.0 (-0.5; 2.6) *P: 0.1821*
Mortality (death/100admission) (95% CI) *P-value*	0.2 (-0.07; 0.5) *NA*	0.0 (-0.06; 0.06) *P: 0.980*	-0.1 (-0.7; 0.9) *P: 0.753*	-0.02 (-0.13; 0.1) *P: 0.778*	-0.01 (-0.1; 0.07) *P: 0.5*
Bloodstream Infections (/100 admission) (95% CI) *P-value*	3.1 (2.2; 4) *NA*	-0.04 (-0.2; 0.1) *P: 0.621*	-0.7; (-2.6; 1.1) *P: 0.407*	0.19 (-0.2; 0.25) *P: 0.860*	-0.02 (-0.2; 0.1) *P: 0.771*
Gram positive BSI (/100 admission) (95% CI) *P-value*	2.0 (01.5; 2.6) *NA*	-0.04 (-0.1; 0.06) *P: 0.398*	-0.3 (-1.3;0.6) *P: 0.502*	-0.01 (-0.14; 0.11) *P: 0.855*	-0.05 (-0.15; 0.05) *P: 0.304*
Gram negative BSI (/100 admission) (95% CI) *P-value*	0.6 (0.2; 1.1) *NA*	0.01 (-0.6;0.08) *P: 0.721*	-0.14 *(-1.2; 0.88)* *P: 0.772*	-0.0 (-0.13; 0.13) *P: 0.962*	-0.01 (-0.1; 0.1) *P: 0.857*

Cardiothoracic ICU

During the whole observed period (23 months), 2249 patients were admitted to the cardiothoracic ICU (1165 in the pre-intervention and 1084 in the post-intervention period, monthly mean 180 patients/month); Mean length of hospital stay was short in the two periods (3.1 and 2.8 days in the pre-and post-intervention period, respectively); the ITS analysis revealed a significant change in the level of -0.5 days after intervention implementation. In-hospital mortality was 2.3%in the pre-intervention and 3.2 in the post-intervention; ITS analysis showed a significant inversion in slope from up-to downward after SAVE implementation (-0.5 death*100 patients/month P=0.003)

Only 2 C.*difficile* infections were observed, evenly distributed in the two periods. Ninety-one bloodstream infections occurred across the two periods, 38 in the pre-intervention year and 53 in the post-intervention one (incidence per 100 admitted patients= 3.3 and 5.21%). Gram-positive bacteria were responsible for 21 and 30 BSI (55.5% and 56.6% of the total BSI, incidence per 100 admitted patients = 1.8% and 2.8%) in the pre-and post-intervention period, respectively; as for total BSI, ITS analysis didn't detect significant trends nor change in slope when considering individually BSI caused by gram-positive bacteria, while for gram-negative, a slightly decreasing post-intervention trend emerged (-0.2 BSI*100patient/month, P=0.04) resulting in an estimated total effect as a change in slope of -0.4 BSI*100patients/month, P=0.03). Bloodstream infections caused by MDR gram-negative bacteria were 18, 9 caused by third-generation cephalosporin-resistant and 9 by carbapenem-resistant bacteria. These latter accounted for more than one-fourth of total gram-negative BSI. Clinical and microbiological indicators and results of the ITS analysis relative to the clinical and microbiological data are summarized in Tables 23 and 24.

Table 23: Cardiothoracic ICU, Clinical and microbiological indicators

	Pre-intervention	Post-intervention	Overall
Patient Days (PDs) (n=6557)	3564	2993	6557
Admission (n=2249)	1165	1084	2249
Length of Hospital Stay (days, mean)	3.1	2.8	2.9
In-hospital mortality (n=62)	2.3% (27)	3.2% (35)	2.8%
Bloodstream Infections, incidence (n=91)	3.3% (38)	4.9% (53)	4.0%
C.difficile Infections incidence (n=2)	0.17% (2)	- (0)	0.09%
Gram-positive BSI incidence (n= 51)	1.8% (21)	2.8% (30)	2.3%
Gram-negative BSI incidence (n=34)	1.9% (22)	1.1% (12)	1.5%
Third-generation cephalosporin-resistant BSI incidence (n=9) [prevalence of gram-negative BSI]	0.3% (4) [18%]	0.5% (5) [42%]	0.4% [26%]
Carbapenem Resistant BSI incidence (n=9) [prevalence of gram-negative BSI]	0.52% (6) [27.3%]	0.28% (3) [25.0%]	0.40% [26.5%]

Table 24: Cardiothoracic ICU, defining parameters of the interrupted time series analysis of clinical outcomes.

	Starting level	Pre-intervention slope	Change in level	Change in slope	Post-Intervention slope

Length of Hospital stay (95% CI) *P-value*	3.0 (-0.02; 0.05) *NA*	0.01 (-0.02; 0.05) *P: 0.438*	-0.5 (-0.9; -0.03) ***P: 0.0.037***	0.0 (-0.06; 0.07) *P: 0.916*	0.02 (-0.04; 0.08) *P: 0.581*
Admissions (95% CI) *P-value*	95.1 (84.7; 105.6) *NA*	0.4 (-1.0; 1.7) *P: 0.598*	3.2 (--7.8; 14.1) *P: 0.553*	-1.2 (-3; 0.7) *P: 0.200*	-0.8 (-2; 0.4) *P: 0.173*
Mortality (death/100admission) (95% CI) *P-value*	0.3 (-0.8; 1.3) *P: 0.135*	0.4 (0.2; 0.6) ***P: 0.000***	-0.8 (-2.7; 1.2) *P: 0.416*	-0.5 (-0.8; -0.2) ***P: 0.003***	- 0.1 (-0.4; 0.1) *P: 0.215*
Bloodstream Infections (/100 admission) (95% CI) *P-value*	2.2 (-0.04; 4.4) *NA*	0.2 (-0.08; 0.5) *P: 0.144*	-0.3 (-3.9; 3.3) *P: 0.865*	-0.08 (-0.6; 0.4) *P: 0.747*	0.12 (-0.3; 0.5) *P: 0.486*
Gram positive BSI (/100 admission) (95% CI) *P-value*	1.4 (0.0; 2.8) *NA*	0.1 (-0.1; 0.3) *P: 0.405*	-0.3 (-2.8; 2.2) *P: 0.789*	0.1 (-0.2; 0.4) *P: 0.624*	0.2 (-0.1; 0.4) *P: 0.0.163*
Gram negative BSI (/100 admission) (95% CI) *P-value*	0.9 (-0.4;2.2) *NA*	0.2 (-0.06; 0.4) *P: 0.128*	-1.0 *(-3.7; 1.7)* *P: 0.441*	-0.4 (-0.7; -0.03) ***P: 0.030***	-0.2 (-0.4; -0.01) ***P: 0.040***

DISCUSSION

SAVE was conceived as a hospital-wide quality improvement project aimed at curbing antibiotic overuse and optimizing prescribing behaviours in a large tertiary care hospital in Northern Italy. The core intervention adopted an enabling approach based on-field training, shared guidelines editing, educational activities, and audit and feedback process. The original plan was to gradually implement the core intervention in the whole medical and surgical areas over three years starting from April 2018. Four medical wards were firstly involved in 2018 and the intervention resulted in a sustained reduction in antibiotic consumption, mortality, and length of hospital stay in that setting (44). Since October 2018 surgical departments were also involved and this far 5 surgical wards and one surgical ICU had completed the 12 months post-intervention follow-up. Since March 2020 the covid-19 pandemic caused an important disruption of the daily clinical practice in the targeted hospital, with a considerable reduction in surgical activities that was limited to urgent procedures when the pandemic waves reached their peak. For this reason, the whole project plan was rescheduled, and follow-up of 2 of the already involved wards was prematurely interrupted at the 11th-month post-intervention, as variation in clinical activities and patient case-mix introduced too many confounders to proceed with the analysis.

Prescribing appropriateness

The prevalence of patients receiving at least one antibiotic ranged from 22% to 63.5% across the 5 surgical wards and reached 74% in the Cardiothoracic ICU. The variation was primary due to different surgical activities performed: lower prevalence was observed in Traumatology and Cardiac Surgery (27 and 22% respectively) where clean surgery was prevalently performed; Urology and General Surgery, where most of the patients underwent contaminated or dirty surgery and a considerable rate of patients had an infection as the principal cause of hospitalization, showed higher levels (63.5% and 43%). Three out of 4 individual wards showed lower prevalence when compared to the one collected during the 2017 hospital PPS (traumatology SAVE 27%,

and cardiac Surgery SAVE 22% vs AOVR-PPS Specialized Surgery 42.13%; General Surgery SAVE 43.8% vs AOVR-PPS 58.6%) while a higher prevalence was observed for Urology (SAVE 63.5% vs AOVR-PPS Specialized Surgery 42.13%) and the Cardiothoracic ICU (SAVE 74% vs AOVR-PPS Specialized ICU 63.16%).

This data, the mean prevalence across surgical areas being 40%, suggests a reduced prevalence compared to the Italian 2016 PPS data reporting a mean prevalence of 51% in the whole surgical area. The ICU prevalence appears higher than the one reported in the Italian PPS (64.3%) but this latter involved only a minority of large size hospitals (i.e. more than 500 beds) thus not directly suitable for benchmarking consumption of a highly specialized ICU.

Post-intervention overall prescribing appropriateness was above 70% in all the involved wards; SAP appropriateness was 68.5% (295 out of 311 prescriptions) with individual wards ranging from 62% to 100%. As appropriateness was evaluated in terms of adherence to the guidelines developed during the intervention for SAP and empirical treatment, no pre-intervention data are available for comparison. However, the post-intervention level of compliance appears satisfactory when compared to the literature.

Segala et al. described a long-term (2013-2019) enabling, audit and feedback based, AMS intervention targeting SAP in the whole surgical area of a tertiary care Italian hospital. The intervention resulted in improved appropriateness of SAP prescription with a post-intervention guideline adherence of 57.9% (221 out of 382 prescriptions reviewed) (50). In a 3-years, retrospective AMS study, conducted in a German hospital and targeting Intra-abdominal Infections, the rate of patients receiving post-operative antibiotics significantly decrease from 56.8 to the 45.2%. The rate of inappropriate indications for therapy also decreases from 17.4% to 8.1%) (51).

In a recent systematic review, improved compliance to SAP recommendations was observed in 12 out of 14 AMS studies targeting adherence to SAP protocols across a wide range of surgical specialities; the post-intervention adherence ranged from 52.1 to 86.6%; a protective effect on SSI incidence could be detected for 4 interventions that employed audit

and feedback techniques as a complementary strategy to protocols implementation. (52)

Elevate compliance was in particular observed in our study for recommendation on SAP duration considering that more than 65% of the courses were administered for 24 hours or less compared to 2016 European PPS showing more than 60% of surgical prophylaxis courses in Italy and more than the 50% in Europe lasting more than 1 day. (53)

Antimicrobial Consumption

All the surgical units where the AMS was implemented showed lower raw antimicrobial usage levels in the post-intervention year, with clean surgeries (traumatology, cardiac surgery and cardiothoracic ICU) showing a more prominent (above the 20% of the pre-intervention level) relative reduction. The extent of this reduction appears unrelated to the overall hospital antimicrobial consumption variation as in the period 2017-2020 the overall annual normalized antimicrobial consumption (DDDs per 1000PDs), was substantially stable (752.8, 778.5, 715,7, 780,7; annual variation + 3.5%, -8.1%, +9.1%). The ITS analysis confirmed an association between consumption reduction and the SAVE intervention implementation in Traumatology, Urology, and Cardiac Surgery.

The fluoroquinolones consumption dropped by more than 70% of the baselines, thus the PNCAR requirement of a 5% reduction in the period 2016-2020 was overly accomplished; the whole hospital consumption annual variation didn't exceed - 40% and then stabilized in the period 2019-2020. The ITS analysis identified a significant progressive reduction in consumption in the post-intervention period in the two wards showing higher pre-intervention consumption (Urology and General Surgery); the introduction of empirical antibiotic therapy guidelines, never proposing these agents as first-line therapy, could have played a role in this result.

The consumption variation was proportional to baseline levels also for carbapenems, with Cardiac Surgery and Cardiothoracic ICU showing greater reduction in raw data (Cardiothoracic ICU: -44%, -51,5 DDDs*1000PDs, post-intervention mean 64.6 DDDs*1000PDs; Cardiac surgery: -78.5%, -47.9 DOTs*1000PDs, post-intervention mean 13.12 DOTs*1000PDs) and a

significant drop in consumption level associated with AMS implementation in the ITS analysis. In the Urology ward, although raw consumption data showed decreased normalized consumption (-36%), the ITS analysis showed a significant positive change in slope for DDDs only, comparing the two periods; this suggests a variation in the dosage choice more than an actual increase in patients' exposure to the drug. In the General surgery carbapenem consumption slightly increased in the post-intervention period (+ 31%, +15.3 DOTs*1000PDs, post-intervention mean 64,4 DOTs*10000PDs), probably due to combined introduction of ertapenem as SAP for the high-risk procedure in patients colonized by ESBL-producing gram-negative bacteria and frequent prescription of meropenem as empirical therapy in patients colonized; nevertheless, the ITS analysis didn't confirm a time association between guidelines implementation and consumption variation. The whole hospital carbapenems consumption showed considerable reduction in the period 2017-2019 (annual variation – 24,4%, -9,1%), then stabilized in 2020. A persuasive AMS intervention targeting specifically carbapenem consumption as a response to a KPC outbreak in a Vascular Surgery unit showed a level change in carbapenem consumption of -111.4 DDDsx1000PDs without increasing the overall antibiotic consumption (54). In a prospective study addressing long-lasting antimicrobial therapy, a multidisciplinary team led by surgeons was effective in decreasing consumption of carbapenems with combined imipenem-cystatin + meropenem DDDs x1000PDs decreased from 23.9 to 8.16 (-63%) across 32 months but the reported rate of MDR isolates was lower than the one we observed in the General Surgery department. (55)

Anti-MRSA antimicrobials consumption showed a significant increase over time in Traumatology and General Surgery resulting in higher usage levels in the post-intervention period (approximately +10%); considering the high prescribing appropriateness recorded, this could be an expression of improvement in early empirical coverage when SSI was suspected. Oppositely, a considerable decrease in consumption of these antimicrobials (greater than the 20%) was observed in Cardiac Surgery and Cardiothoracic ICU, where an immediate change in consumption level occurred in association with SAVE intervention start; confident de-escalation practice,

reinforced by a daily clinical discussion with the ID specialist, had probably led to shorter empirical coverage, also considering low incidence of gram-positive caused BSI, with no significant variation over time.

Similarly to our intervention, Feihl et al. succeed in a 25% reduction of overall antimicrobials consumption in a German orthopaedic unit specialized in peri-prosthetic joint infections (PJIs) (from 129.078 DDDs/100 PDs to 96.826 DDDs/100 PDs) after implementing an AMS project. The intervention was based on orthopaedics and ID specialist joint development of a local guideline for SAP and diagnostic algorithm for PJI management, educational workshop and regular multidisciplinary ward rounds. The most consistent reduction was observed for clindamycin and second-generation cephalosporins as expected for the new SAP policy introduced, while amino- and narrow-spectrum penicillins usage increased due to improvement in de-escalation and targeted therapy. (56)

In their quality-improvement AMS project targeting IAI, Surat et al. obtained a reduction in the overall antimicrobial consumption from 47.0 to 42.2 DOT per 100 PDs, with more considerable reduction occurring in fluoroquinolones, and third-generation cephalosporins but no variation in ureidopenicillins consumption. (51)

Consumption stratification by the WHO AWaRe antimicrobial classes offers further useful insights on the impact of the AMS intervention:

- A desirable shift from prescribing Watch to Access antimicrobials occurred, principally with increased usage of amoxicillin/clavulanate instead of piperacillin/tazobactam and third and fourth generation cephalosporins for community-acquired infections, as recommended by the newly introduced guidelines. Lower consumption of watch agents resulted from a significant decreasing post-intervention trend in 3 out of 5 wards.
- Antimicrobials included in the Reserve antimicrobial classes showed a close to 30% increase in the post-intervention consumption in Traumatology and the General Surgery unit; ITS analysis identified a significant post-intervention upward consumption trend in both the wards. In the first case, daptomycin was the main drive of sura ge in consumption and this has to be attributed to change in patient case-

mix, with an increased rate of elderly and frail patients with Chronic Kidney disease limiting the use of vancomycin for anti-MRSA coverage. In General, Surgery, where Carbapenem-resistant *Enterobacteriaceae* colonization and infection were endemic before the intervention and high rate of SSI occurs, the availability of a new and effective drug against these pathogens led to the wide use of ceftazidime/avibactam soon after it became available.

In the cardiothoracic area, where AMS intervention was implemented more than a year after new-cephalosporins Italian registration, a huge decrease in consumption was observed, with an impressive drop in the level of consumption corresponding to the introduction of the AMS intervention. Reduction in both high-cost anti-MRSA agent and ceftazidime/avibactam consumption contributed, but this desirable effect tend to vanish rapidly when the intensive observational phase ended.

Expenditures due to J01 antimicrobials appears lower in the post-intervention year in all the wards but General Surgery, where the cost increase was coincident with the expenditures for new-cephalosporins (ceftazidime/avibactam and ceftolozane/tazobactam); in this ward SAVE intervention implementation started soon after the ceftazidime/avibactam approval by the Italian drug organization, with the drug representing the new first-line option for KPC-producing Enterobacteriaceae as already discussed above; Total antimicrobial costs reduction ranged from 25 to 45% resulting higher than the reduction occurred yearly in the whole hospital antimicrobial expenditures (2017-2018: -9%, 2018-2019: -12,3%, 2019-2020: -3,2%). ITS analysis confirmed a temporal association between intervention implementation and variation in overall consumption trends only for the Cardiac Surgery (negative change in level), where analogue findings emerged considering individually carbapenems and new cephalosporins expenditures. Significant variation in the post-intervention trend of carbapenems also emerged for the Cardiothoracic ICU where a negative change in level (towards reduced costs) occurred while, quite surprising considering the raw

data, a positive change in level after the AMS intervention emerged in urology.

The number of admissions in each ward was analyzed by ITSA to evaluate possibly confounding; a significant post-intervention increase in the number of patients admitted to the Traumatology ward (+8.4 patients/month) was identified associated with a significant increase in LOS (+0.1 day/month) in the same period. As the ward re-organization led to the hospitalization of all the orthogeriatric patients in this ward while half of them were previously hospitalized in another unit, this result is most probably the effect of a change in the patient case-mix rather than of the AMS intervention. No significant increase in mortality trend could be identified, indeed a significant trend towards mortality reduction was preserved in General Surgery (-0.1 death*100admissions/month) and reversion of the pre-intervention upward slope (total effect: -0.5 death*100admissions/month) emerged in the Cardiothoracic ICU. In the same surgical units, a significant trend towards reduction of BSI caused by gram-negative bacteria emerged (-2.1 BSI*100admissions as an immediate change in level in General Surgery and – 0.2 BSI*100admissions/month as the post-intervention slope in Cardiothoracic ICU). These findings appear promising but the number of events, as well as the effect size of variations, was minimal, thus, considering even all the potential confounders, a conclusion about a protective effect of the SAVE AMS intervention could not be drawn. A prolonged follow-up and a larger sample size would be needed to confirm these results.

In a meta-analysis published in 2014 ASPs was found to have a protective effect, effectively decreasing the incidence of CDI. This effect was particularly evident for geriatric patients, with restrictive policies resulting min ore effective than persuasive ones. (36)

In our study, *C.difficile* infection occurred extremely rarely during the whole pre- and post-intervention period, the incidence ranging from 0.07 to 0.11 infection/100 admission. The limited number of events (less than 1 per month in all the involved units) prevented us to perform the ITS analysis as originally planned. The rate of CDI where comparable to the one reported by Feihl et al. in their intervention (AOVR 17 cases in 86204 PDs; Feihl et al.

16 cases in 50161 PDs); they were also unable to demonstrate a significant variation in the incidence after the AMS intervention implementation, due to the low rate of infection and the small cohort they considered. (56)
A comprehensive evaluation of the clinical outcomes suggests a substantial safety of our intervention with no adverse events emerging. No reliable trends could be identified for microbiological outcomes and in particular for MDR infections, as the rate of BSI were too low. Including isolates from other samples, and in particular SSI, a deeper analysis of prevalence data, and prolonging the follow-up period would increase sensibility for an AMS impact on MDR and CDI infections, although confounders are several and difficult to neutralize.

The SAVE intervention was faithful to an AMS paradigm aimed at improving the current and future patients' care through the empowerment of non-ID specialist prescribers, able to also increase the latter's professionalism and job satisfaction. A holistic approach was adopted, with educational and clinical training on the field encompassing all the multiple aspects of antimicrobials prescribing, rather than focusing on a single specific task (e.g. SAP or carbapenems overuse).
The tailored and flexible approach adopted in the educational and training activities in the surgical wards went along with the cogent methodology to evaluate the AMS intervention effectiveness. As suggested by literature (57) multiple outcome measures were included: process measures (i.e. antimicrobials usage indicators), clinical and microbiological measures, financial measures, and appropriateness measures. Moreover, for each category, a comprehensive set of indicators was selected to increase the detecting power for both desirable and unattended consequences. Adherence to antimicrobials usage and microbiological indicators proposed by the ARCH consensus for the hospital setting was complete for the essential ones with also some desirable ones included when the hospital performance and surveillance systems made the data available (49). Consumption was extracted and reported for all the individual antimicrobial agents included in the ATCJ01 group to avoid neglecting a possible "squeezing the balloon" effect. Being an RCT not feasible for pragmatical and ethical issues, an ITS

design with ARIMA models was employed as strongly recommended to limit Bias and in particular random time effects. (57, 58) To note, to our best knowledge very few AMS studies specifically focusing on surgical wards employed ITS as a statistical model. (55, 56)

Although we agree about the many advantages of this quasi-experimental design approach and its statistical power, especially if compared to uncontrolled before-after design, some unresolved issues in its application to AMS intervention emerged in our analysis:

- usually, at least 12 pre- and 12 post-intervention time points are required, with no major confounding occurring to disrupt the values of observation. Even not considering extraordinary events, such as the covid-19 pandemic, abruptly interrupting data continuity, the hospital organization is nowadays fluid, with wards and staff incurring infrequent and not always preventable re-organization and change in patient management.
- most of the authors recommend collecting at least 100 events for time points, to obtain a reliable regression trend. If this value seems rational and affordable for some traditional AMS metrics, such as antimicrobial consumption or prescriptions, this is hardly affordable for most of the microbiological and clinical outcomes when the units of analysis are represented by a single hospital ward. Being the analysis of multiple wards as a whole to increase the sample size, a possible solution for that, artefacts trends could emerge, due to random sum effect; in contrast, oppositely trends in different settings could be neglected due to reciprocal neutralization.
- ITS analysis, to be meaningful, requires that desirable direction trends for the selected outcome indicators have been defined *a priori.* This is the case of AMS interventions focusing on a single and precise outcome (e.g. reduction of a specific antimicrobial class as a response to an outbreak of MDR or improving SAP appropriateness). In our study, an overall reduction in antimicrobial consumption was advisable due to current overuse but specific antimicrobial classes and single-agent shift in use need to be analyzed case by case, ITS analysis alone, if not interpreted based on normalized raw consumption data,

wouldn't be reliable and informative about the actual impact of the intervention.

Moreover, as AMS deals primary with appropriate antimicrobial use, and then with a decrease in use as an indirect indicator, the wards that have already righteous prescribing habits could be penalized by the analysis. Indeed, when the baseline antimicrobial consumption or MDR incidence is already low or decreasing in time, stabilization of consumption level, rather than reduction, could be the expression of optimal use, limited to actual indication as by guidelines or narrow-spectrum targeted therapy. Thus, a positive change in slope between the pre-and post-intervention period needs to be regarded as favourable.

In addition to the methodological challenges, the major limitation of our study was the impossibility to employ SSI as a clinical outcome indicator, as it would be expected in an AMS intervention focusing on surgical area and pursuing a multifaceted improvement in antimicrobials prescribing and infection management practice. Unfortunately, formal surveillance for SSI was not in place in our institution when the AMS intervention started; some of the involved wards, especially the ones in the cardiothoracic areas, collected some data on SSI, even in the context of multicenter surveillance initiatives, but lack of standardizations and limited access to data preclude their analysis in this study. Since 2020, the Veneto Region introduced mandatory reporting for HAI for all the local hospital, thus this valuable indicator would be included in the next SAVE project analysis.

Another legitimate concern could be the sustainability of our intervention, meaning both sustained results over time and the amount of resources employed. Two FTE ID specialists were employed in the period October 2018-June 2020 to train prescribers on the field, coordinate AMS team activities and educational workshops, and perform audit and feedback, data extraction and analysis. Several ID trainees and the other AMS team members (microbiologists, IPC practitioners, pharmacists) also contribute, as a part of their routinary task (no protected time or economic compensation provided). As claimed by literature, the inclusion of a dedicated IT expert in AMS

activities is advisable especially in the complex modern hospital institution, where abilities to merge and filter a huge amount of data from different software and database is essential; in addition, collection and reporting of antimicrobial consumption and microbiology and clinical data should occur on a periodical and stable base aimed at hospital performance evaluation. These precautions would preserve ID specialists and other health professionals for clinical and coordination tasks, thus improving resource allocation. An audit and feedback approach was employed to strengthen prescriber confidence and generate virtuous circles by positive reinforcement of correct habits, early correction of misconstrues and barriers, and building trustful professional relationships. Duration of post-intervention follow-up needs to be prolonged to ascertain that the improvements achieved in antibiotics consumption would be maintained when time distance from implementation increases, in our case the hospital organization disruption due to covid-19 pandemic played a major role in preventing further follow-up. However, the availability of post-intervention consumption and appropriateness data in association offers a valid comparison to critically evaluate up-to-date consumption and appropriateness data after a time gap and decide whether an educational reprise or a training refresh including shared clinical rounds would be required to preserve the improvements achieved.

The save project was designed as an AMS intervention addressing the hospital as a whole; the same approach was adopted for the medical and surgical areas, with specific adaptation for the single units. The extent of consumption reduction observed in the surgical area, although promising, are somehow limited compared to the achievements in the medical ones (44) Higher intrinsic complexity of the surgical setting, including socio-relational determinants of prescribing behaviours probably played a not negligible role (59-61). Some adjustments could be applied to the original protocol taking some peculiarities into account: less familiarity with antimicrobials in general, increased concerns about LOS and prolongation of stay due to infectious complications, high turn-over of the staff even in brief periods. Moreover, in addition to evaluating the impact of the intervention implementation on prescribers' behaviour, temporal trends provided by ITS

analysis, in association with audit data, could be also helpful to re-think and improve ID consultation service activities: in less complex settings, optimal results could be obtained with guidelines development and periodical adherence evaluation thus fostering surgeons autonomy in the simpler task (SAP and empirical therapy for not-critical patients) and reserving consultation only for complex cases and targeted therapy. On the contrary, observing an abrupt reduction in consumption soon after AMS implementation with a subsequent upward trend associated with a high rate of ID consultation for antimicrobial prescriptions in the audits (e.g. the cardiothoracic area), suggest the need for periodical (e.g. biweekly) shared clinical rounds with a pro-active review of antimicrobial therapy ongoing rather than traditional, on-demand consultation service.

CONCLUSION

An enabling AMS intervention aimed at improving the quality of care across the entire surgical pathway can enhance prescribing appropriateness and safely achieve valuable variation in overall and selected antibiotic classes consumption levels. As great variability exists across the several surgical specialities in terms of patient case-mix, surgical procedures performed, relational dynamics, adopting a tailored approach in the intervention implementation represents a key element for the success and sustainability of the intervention.

A more prolonged follow-up and an adequate and meaningful aggregation of data are required to be able to detect variation in incidence and prevalence of infection caused by antimicrobial-resistant bacteria.

To be able to correctly interpret ITS Analysis results desirable variation in terms of main targeted antimicrobials class consumption should be pre-defined and baseline levels of consumption, before the intervention implementation, should be taken into account.

The study results also provide useful insights prompting a reorganization of the ID consultation service to adequately address the peculiarity of the prescribing practice in the surgical areas.

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