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# Time is running out. No excuses to delay implementation of antimicrobial stewardship programmes: impact, sustainability, resilience and efficiency through an interrupted time series analysis (2017–2022)

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**Introduction:** The WHO declared antimicrobial resistance (AMR) a significant concern in 2014, sparking initiatives to ensure responsible antibiotic use. In human medicine, Antimicrobial Stewardship Programmes (ASPs) in hospitals play a pivotal role in combating AMR. Although evidence supports the effectiveness of ASPs in optimizing antimicrobial use, often the lack of resources becomes an excuse to limit their dissemination and use. This paper provides a comprehensive report on a 6-year analysis of an ASP implemented in a healthcare region in north-east Italy.

**Methods:** A retrospective data collection was conducted to assess the programme's impact on antibiotic consumption expressed as DDDs/100 patient-days, its sustainability over time, resilience during the COVID-19 pandemic and the efficiency of the ASP (relationship between workload and human resources).

**Results:** A substantial overall reduction in antibiotic consumption (−14%), particularly in fluoroquinolones (−64%) and carbapenems (−68%), was demonstrated, showcasing the programme's impact. Sustainability was confirmed through enduring trends in antibiotic consumption and ecological analysis over time. The ASP demonstrates resilience by maintaining positive trends even amid the challenging COVID-19 pandemic. Efficiency was underscored by an increase in on-site consultations despite consistent human resources until 2021.

**Conclusions:** This study offers insights into the prolonged success of a resource-efficient ASP, emphasizing the crucial role of long-term commitment in fostering responsible antibiotic use in the context of global health challenges such as AMR.

## Introduction

Less than a century has elapsed since the discovery of penicillin, and antimicrobial resistance (AMR) now poses a significant threat to antibiotic efficacy, prompting the WHO to declare it a global public health concern in 2014.[1] A strong effort for responsible use of antibiotics has arisen, leading to recommendations, guidelines, measures to control of antibiotics usage in all sectors connected with antibiotic misuse. In the realm of human medicine, antimicrobial stewardships (AMS) programmes (ASPs) in hospitals, together with infection and prevention control (IPC) measures, are part of the counter-measures needed for tackling AMR.

According to guidelines, every ASP must monitor antibiotic use and outcome.[2] Impact (or effectiveness) of AMS is measured through antibiotic consumption metrics, local trends of *Clostridioides difficile* infections (CDI) and AMR.[3] There are several parameters for evaluating antibiotic consumption, none of them complete or without drawbacks. The DDD over 100 patient-days (DDD-100 patient-days) is one of the most common variables to express in-hospital antibiotic consumption, which captures both antibiotic use and patient volume.[4] However, several factors, such as use of appropriate high doses of antibiotics or combination therapies, disadvantages use of DDDs.[5] For this reason, using DDDs in combination with other easy to obtain parameters assessing antibiotic exposure per-patient, such as point of prevalence surveys (PPS), can provide a more comprehensive picture of the actual antibiotic usage.[6]

Despite high-certainty evidence showing the effectiveness of ASPs in optimizing antimicrobial use,[7,8] there is scarce evidence of their prolonged effectiveness over years,[9] referred to as 'sustainability'. In the field of AMS, sustainability has been used to describe persistent effects of an ASP after the end of the active intervention,[10] or alternatively to denote economical sustainability.[11] In this paper we adhere to Moore *et al*. definition of sustainability: (i) after a defined period, (ii) the programme continues to be delivered and/or (iii) individual clinician behaviour change is maintained; (iv) the programme and individual behaviour may evolve or adapt while (v) continuing to produce benefits for individuals/system.[12]

Resilience is defined as 'the capacity of a system to absorb disturbance and reorganize while undergoing change to retain essentially the same function, structure, identity, and feedbacks'.[13] The COVID-19 pandemic adversely affected various healthcare aspects, including AMS.[14–17] Analysing antibiotic consumption during these years serves as a real-world 'stress-test' to assess the resilience of ASPs.

Efficiency pertains to the capability to use the available human resources to achieve the desired outcome. Both sustainability and resilience are closely linked to the balance between workload and dedicated human resources. Insufficient financial and human resources pose recognized barriers to AMS implementation.[18] A major obstacle to appropriate resource allocation is the lack of consensus and scientific evidence for minimum AMS staffing.[19] Then, detailed reporting of human resources needed for ASPs has been urgently advocated.[20]

The aim of this paper is to provide a detailed report on an ASP implemented in a healthcare area of north-east Italy, elucidating its impact, sustainability, resiliency and efficiency.

## Material and methods

Since July 2016, an ASP has been implemented in a healthcare area of north-east Italy, primarily focusing on the hub hospital and the major spoke hospital in the region.

### Study site

The ASP was implemented in the Pordenone healthcare area in the north-east of Italy, that serves almost 312 000 inhabitants. The local public health system comprises one hub hospital ('Hospital A', 600-beds), two spoke hospitals ('Hospital B', 200 beds and 'Hospital C', 76 beds), a network of low-intensity and long-term care facilities (around 175 beds, including one hospice), and 283 general practitioners providing primary care. Hospitals A and B are equipped with emergency departments, internal medicine wards, surgery wards and intensive care units (ICUs). No previous interventions had been conducted in the entire area.

### Design and setting of the intervention

The programme was initially conceived and executed by two infectious diseases (ID) specialists. The ASP aimed to be accessible, sustainable, flexible and widely accepted by the intervention targets. The programme was tailored to the specific healthcare area, considering the environmental setting as a crucial factor.

Before ASP initiation, an informal assessment phase (approximately 6 months) prioritized intervention goals. Several meetings were held during this phase to define the ASP team and to introduce the project to prescribers.

At the outset, general practitioners (GPs) were identified as significant antibiotic prescribers and they were actively involved in the presentation meetings to inform them about the option for remote consultations or outpatient referrals for complex cases. This initiative aimed to foster a strong link between the ID consultants and the primary-care physicians.

At the hospital level, the presence of the ID specialists provided a consultation service available in presence on all working days and via phone service on any other day. Following in-hospital direct observation of local prescription practices, antibiotic consumption data were analysed collaboratively with pharmacists, highlighting areas for improvement in antibiotic use.

A multifaceted set of interventions, employing behavioural change techniques (BCTs) targeting various behavioural components as described in Table 1 (education, persuasion, communication and service-provision were the main fields of intervention), was implemented. It was decided to limit the role of formulary restrictions to a small set of drugs (ceftaroline, ceftobiprole, cefiderocol, dalbavancin, oritavancin, ceftazidime/avibactam, ceftolozane/tazobactam), and a persuasive-oriented ASP was adopted to enhance and increase programme acceptance. Prospective audit and feedback (PAF) served as the primary form of antimicrobial guidance.

### Team composition

The stewardship team comprised two (later four) full-time ID consultants, supported by clinical microbiologists and pharmacists partly dedicated to the programme (see Table 6). In addition, there was active collaboration and interaction with the IPC team consisting of two nurses and one public health specialist.

### The ID consultant

In our ASP, the ID consultant played a pivotal role as the intermediary interacting directly among patients, prescribers and other team members. Prescribers' acceptance and feedback on programme efficacy and safety were considered crucial. The ID consultant's social characteristics were broadly discussed together to create a uniform interaction modality, consistent with personal attitudes of each professional. Key elements identified

**Table 1.** List of interventions classified according to COM-B model[a] and Behavioural Change Wheel (BCW)[a]

| | Example of targeted belief (from the prescriber perspective, except when explicitly stated) | BCT: physical/psychological capability (C), opportunity (O) and, reflective motivation (M) | Area of intervention (BCW)[a] | Intervention description |
|---|---|---|---|---|
| 1 | 'short AB courses are not safe'<br>'I am not conscious on the association between AB misuse and AMR rise'<br>'no alternatives to carbapenems exist'<br>'if my colleague use carbapenems I will do the same' | information about health consequences[C]<br>information about social and environmental consequences[C]<br>prompts/cues[C]<br>social comparison[O] | Education Persuasion | Educational activities<br>Meeting and courses on AMR and antimicrobial use for to hospital and primary-care practitioners; hospital meeting on new antibiotics and on specific ID (according to the main syndromes treated in the ward) |
| 2 | 'to prolong the AB prophylaxis is safer' | information about health consequences[O] | Education | Prophylaxis alignment<br>Creation and diffusion of guidelines on surgical prophylaxis, prophylaxis and pre-emptive therapy in open fractures |
| 3 | 'I have no pharmacokinetic competencies'<br>'I am afraid to cause damage with high doses of ABs'<br>'I don't request TDM because is too complicated to perform it as an out-of-the-institution service' | Prompt/cues[M]<br>Feedback on outcomes of behaviour[M]<br>Social support (practical)[O] | Education<br>Enablement | Pharmacokinetic appropriateness<br>Creation and diffusion of guidelines about antibiotic use in dialysis and pharmacokinetic optimization of antibiotic administration (reconstitution, dilution, infusion time, use of continuous infusion) shared with doctor and nurses; sensibilization about the use of therapeutic drug monitoring (TDM) for certain drugs (routinely recommended for long-term levofloxacin courses) |
| 4 | 'I am not aware if ASP is safe and effective'<br>'I don't know which is the target of antibiotic consumption';<br>'I do not believe that ASP will solve anything' | Feedback on outcome(s) of the behaviour[M]<br>Goal setting (behaviour)[M]<br>Credible source[M] | Enablement<br>Persuasion | Feedback and report<br>Periodic publication of local reports on AMR incidence (cumulative antibiograms) and antibiotic consumption; periodic meetings to discuss and comment on the reports |
| 5 | 'In absence of an ID specialist, I do not feel comfortable with a wait and see approach'<br>'I need assistance to choose appropriate ABs' | Social support (practical)[O]<br>Demonstration of the behaviour[C]<br>Social support (practical)[O] | Modelling<br>Enablement | On-demand consultations<br>• on-site consultations (8 hours per day and 5 days per week);<br>• remote consultations (12 hours per day and 7 days per week). |
| 6 | 'If I do not escalate immediately the therapy the outcome will be catastrophic'<br>'I will not stop early the ABs until I see ID specialist to do it without having worse outcomes' | Feedback on behaviour[M]<br>Demonstration of the behaviour[O] | Persuasion Modelling<br>Enablement<br>Training | Routine ID evaluations<br>Routine ward consultations in ICUs (twice per week), emergency medicine (once per week) and internal medicine (twice per week), with feedback and training of practitioners. |
| 6 | 'If I have access to the therapeutic pipeline, I would rather use novel beta-lactams than old ones because I believe they are more efficacious'<br>'I do not know the different subtypes of ESBL enzymes, but I would prefer using novel beta-lactams to be sure I am treating the patient' | | Restriction | Preauthorization for selected ABs<br>Preauthorization of use for ceftaroline, ceftobiprole, cefiderocol, dalbavancin, oritavancin, ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, imipenem/relebactam, tedizolid |
| 7 | 'It is better to check the urine cultures at the end of treatment', 'there is no role of prevention measures in UTIs' | Information about health consequences[C] | Enablement<br>Education | 'Integrative-health' and non-antibiotic therapies for chronic or recurrent conditions,<br>examples: |

*Continued*

**Table 1.** *Continued*

| | Example of targeted belief (from the prescriber perspective, except when explicitly stated) | BCT: physical/psychological capability (C), opportunity (O) and, reflective motivation (M) | Area of intervention (BCW)[a] | Intervention description |
|---|---|---|---|---|
| | 'There is no dedicated team for treating wounds so I have to decide alone if AB are beneficial or not for this condition'<br>'I do not believe that prevention measures may have a role in UTIs or chronic wounds'<br>'I feel anxious to not treat someone that have positive microbiological tests, such as urine cultures or wound-swabs' | Social support (practical)[O]<br>Demonstration of the behaviour[C]<br>Feedback on outcomes of behaviour[M] | | • recurrent UTIs: antibiotic-sparring bundle (water intake, dietary supplements, probiotics, physical activity)[b];<br>• chronic wounds: multidisciplinary team (vascular surgeon, plastic surgeon, diabetologist, ID specialist) with a dedicated wound-care specialist nurse, simplified access to the dermatological clinic for appropriate deep wound sampling for cultures. |
| 8 | 'I do not see any problem in using carbapenems and FQ for infections: they have excellent spectrum of activity and penetration in difficult sites';<br>'There are no alternatives to carbapenems in ESBL infections'<br>'I have no access to novel beta-lactams, so I must prescribe carbapenems for infections caused by multi-drug resistant Gram negatives' | Information about social and environmental consequences[C]<br>Credible source[C]<br>Social support (practical)[O] | Education<br>Persuasion<br>Enablement | Carbapenem and FQ sparing approach<br>• carbapenem-sparing approach: prefer combinations (i.e.: fosfomycin as companion drug) and/or alternative antibiotics (tigecycline or ceftolozane/tazobactam) in suspected or confirmed ESBL Gram-negative infections. This is warranted by rapid delivery of the molecules by the pharmacy and the availability of the ID specialist.<br>• FQ sparing approach: using alternatives (i.e. do not use FQ in ABSSSI or UTIs). |
| 9 | 'I wish I have updates on UTI treatment, otherwise I will use the old but gold FQs'<br>'It's easy to spare antibiotics in tertiary care: could you please tell me how to do it in primary care?'<br>'I have to manage the difficult ID cases as I can, because I cannot access to consultations'<br>'The general practitioner can manage just oral therapies, parenteral ABs are exclusively managed in the hospital' | Self-monitoring of behaviour[C]<br>Feedback on behaviour[C]<br>Social support (practical)[O]<br>Restructuring physical environment[O] | Training Education<br>Persuasion<br>Enablement | Link to primary care and GPs<br>Broad availability for remote consultations (12 hours per day and 7 days per week) for GPs, to ensure a direct link with the ID; periodic education activities focused on primary-care practice (UTI, acute respiratory illnesses); periodic feedback on ASP and results; 'AMS-oriented' lessons for the GPs residents during their education course; OPAT approach to involve GPs in the cure of complex ID cases |
| 10 | 'I rather do not use fosfomycin if it is labelled as resistant on the antibiogram, despite I don't know the analytic system reliability' [ID consultant point of view]<br>'I will report all the molecules I tested on the antibiogram' [Microbiologist point of view] | Prompts/cues[C]<br>Prompts/cues[C] | Education<br>Enablement | Team building, integration and reinforcement<br>Monthly meetings with the Microbiologists and ID specialists on common interest topics (i.e.: updates on EUCAST criteria, agreement for antibiogram profiles, discussion on diagnostic or clinical challenges, correct use of molecular microbiology), updates with the pharmacists about eventual drug-access criticisms. |
| 11 | 'If a patient has fever you have to put antibiotics, because no reliable biomarkers exist'<br>skills: 'There is no way to reduce AB therapy length or de-escalate AB'<br>'I wish to have a test that helps me to discriminate between fever caused by bacterial or viral infection') | Self-monitoring of behaviour[C]<br>Adding objects [diagnostic tools] to the environment[O]<br>Adding objects [diagnostic tools] to the environment[O]<br>Adding objects [diagnostic tools] to the environment[O] | Enablement<br>Training | Biomarkers,<br>use of:<br>• cytofluorimetric test (neutrophil CD64/monocyte CD169 activation) to discriminate between viral and bacterial infections;<br>• procalcitonin to guide antibiotic de-escalation;<br>• proADM as a prognostication marker. |

| | | | | |
|---|---|---|---|---|
| 12 | 'Contact precautions are not necessary because AMR rates are very low in our setting' | Adding objects [diagnostic tools] to the environment[O] | Enablement | Molecular and antigenic microbiology, use of: • molecular detection of resistance genes in surveillance rectal swabs; • nasal swab for common respiratory viruses in all patients with acute respiratory infections. |
| | 'If I have no etiologic test, I will assume that most of acute respiratory infections in the hospital have a bacterial origin' | Adding objects [diagnostic tools] to the environment[O] | | |
| 13 | 'I am not aware of the risk of transmission of bacteria through hands' | Information about social and environmental consequences[C] | Training Education Enablement Incentivization | IPC measures Hand-washing promotion (training and education, surveillance of compliance on IPC rules, measures of hand sanitizer consumption, putting hand sanitizer in every room); active surveillance of AMR-outbreaks or potentially contaminated patients ('contacts'); annual incidence of CDI; contact precautions for patients colonized by MRSA (and decolonization measures), VRE, ESBL and CPE. |
| | 'I am not sure how to wash properly my hands' | Demonstration of the behaviour[C] Instruction on how to perform the behaviour[C] | | |
| | 'Contact precautions are useless because I do not see many infections by ESBL' | Feedback on outcomes of behaviour[C] | | |
| | 'I will wash my hands before every patient's visit, if hand sanitizer would be available in every room' | Adding objects to the environment[O] | | |
| | 'If nobody checks if I am using contact precautions, it means it is no so important' | Feedback on the behaviour[C] | | |

AB, antibiotic; CDI, *Clostridium difficile* infections; ID, infectious diseases; UTI, urinary tract infection; ABSSSI, acute bacterial skin and skin structure infections.
[a]Michie S. *et al.*[21]
[b]Venturini S. *et al.*[22]

as ideal attributes of the ID consultants were: availability, proactivity, assertiveness, communication skills (avoiding aggressive or judgemental tones), strong mediation and collaboration skills. In instances of conflicting opinions, the emphasis was on reaching compromises for long-term collaborative maintenance. PAF was chosen for an educational approach during on-site consultations, presented in a written format to explain advice thoroughly. Adherence to real-life clinical settings, consideration of prescriber needs and active involvement in patient care were prioritized.

Facilitating intervention acceptance, consultants sometimes assumed responsibility for patients and their social networks, aiding clinicians in administrative tasks and ensuring drug or diagnostic tool availability through liaison with pharmacists and microbiologists. Prescribers appreciated frequent case re-evaluations, routine rounds and opportunities for informative discussions with patients and caregivers.

### *The microbiologists*

The microbiology was oriented towards constant and daily interaction with physicians from all hospital departments, including ID specialists. The key role of the microbiologist in our ASP was based on the promulgation of the concepts of pre-analytical appropriateness (through education on the sampling methods, appropriateness of microbiological samples and correct request for tests), on diagnostic appropriateness (correct choice, use and placement of diagnostic tests according to a concept of Diagnostic Stewardship[23]), and on the timely and exhaustive reporting of the results. Interpretative comments to the susceptibility report, including phenotypic insights into specific resistance mechanisms that affect the correct choice of antibiotic therapy (i.e. ESBL versus AMPc-producers *Enterobacterales*), expert opinion of microbiological results, customized antibiograms to guide prescription (susceptibility profile with unpublished molecules, such as vancomycin and teicoplanin for MSSA) and the possibility to test on request specific antibiotics were examples of the interactive activities carried out by microbiology. The microbiology laboratory was open 7 days a week for 24 hours a day. The microbiologist reported in real time through telephone communication and/or email notification a list of critical events established and agreed with the AMS team (i.e. growth of Gram-positive/-negative bacteria or moulds on blood cultures). Every year, the microbiologist of our hospital produced an epidemiological report on the trend of antibiotic resistance at a local level, and on the number of a list of monitored microorganisms (i.e. *Clostridioides difficile*, norovirus, MRSA) present throughout the hub hospital and in the peripheral facilities.

### *The pharmacists*

The hospital pharmacy played an active role in the ASP by collaborating with ID consultants to determine which drugs should only be dispensed with an ID authorization. They also tracked antibiotic consumption within the hospital for individual molecules or categories of antibiotics, and compiled these data in an annual report presented to the various departments. Additional activities included: collaboration with ID specialists to provide support and guidance for the reconstitution and optimal infusion methods of antibiotic; diffusion of internal guidelines on antibiotic use in dialysis and pharmacokinetic optimization of antibiotic administration;

fast revision of off-label indications in selected cases and procurement of specific antibiotics for long-term care facilities as directed by ID specialists. They also supported outpatient parenteral antimicrobial outpatient parenteral antimicrobial therapy by providing intravenous drugs, allowing the clinician to provide rapid discharge through early de-escalation. Furthermore, pharmacists conducted pharmacovigilance activities to monitor the safety and effectiveness of medications.

### *Intervention targets*

Primary targets were hospital medical doctors (prescribers). In parallel, an effort to empower IPC measures application involved all the staff, including doctors, nurses and assistants. Remote ID-consultation services were accessible to all area physicians, including GPs. Educational activities were extended to all staff. Originally, the AMS plan included expansion to the minor spoke hospital (Hospital C) and long-term facilities. Despite the increase of the pool of ID consultants, SARS-CoV-2 pandemic necessitated extra efforts for COVID-19 patient follow-up, delaying the extension project to 2024. To spare resources, the set of interventions was fully empowered at the hub hospital (Hospital A) and the largest spoke hospital of the designed healthcare area (Hospital B), making the main target the prescribers of hospitals A and B.

### *Data collection and design of the study*

We conducted an interrupted time series (2017–2022) with retrospectively collected data to assess the impact of a new AMS programme implemented in the healthcare area. The study was conducted in accordance with the Declaration of Helsinki. Because of the retrospective nature of data collection, ethics approval was waived for the study.

### *Parameters and measures*

(i) The impact of ASP was evaluated through antibiotic consumption (overall and single classes consumption of antibiotics, expressed in DDD/100 patient-days), prevalence of antimicrobial use (PPSs, according to European Centre for Disease Prevention and Control protocol were conducted every 2 years in our region[24]), adverse effects related to antibiotic consumption (CDI, rates expressed as ratio of positive tests over number of appropriate tested samples) and epidemiological data (AMR trends, cumulative antibiograms). Alert organisms undergoing surveillance were MRSA, VRE, ESBL-producing Enterobacterales and carbapenemase-producing Enterobacterales (CPE). The primary outcome involved an ecological time-trend analysis, adhering to the ORION statement.[25] See Supplementary Materials (available as Supplementary data at *JAC-AMR* Online) for a detailed description of the mentioned parameters.
(ii) Sustainability was graphically presented as persistent trends in antibiotic consumption and ecological analysis over time.
(iii) Resiliency was assessed by comparing antibiotic consumption trends between the pre-pandemic period (years 2018–2019) and the post-pandemic period (years 2020–21).
(iv) Efficiency was estimated through the relationship between workload and human resources over time. AMS activities are described in Table 1 but not all were measured or measurable. Measured process metrics were the yearly number of on-site consultations, educational meetings, internal protocols or guidelines produced (detailed description in Supplementary Materials, Table S2). Human resources were presented as full-time equivalents (FTE) dedicated specifically to AMS activities.

### *Data analysis*

A descriptive analysis of trends was performed for each outcome indicator on an annual basis. Comparisons were made comparing the period preceding the intervention ($t_0$: 2017) to a 6-years-after final-point ($t_6$: 2022). Graphics and linear trends were designed and calculated using Microsoft Excel.

## Results

The results of the ASP are summarized in Figure 1 and Tables 2–6.

### *Impact and sustainability*

Quantitative indicators of antibiotic consumption (Figure 1, numeric data in Supplementary Materials, Table S1) show a decrease (−14%) in overall use of antibiotics (expressed in DDD/100 patient-days). A strong decrease in the consumption of the fluoroquinolones (−64%) and carbapenems (−68%) was observed from 2017 to 2022. In the same period, a modest decrease in use of third-generation cephalosporin (−14%) and piperacillin-tazobactam (−7%) was observed, associated with a modest increase in amoxi-clavulanate use (+14%).

The PPS analysis performed in the years 2017, 2019 and 2021 (Table 2) showed a reduction in the number of hospitalized patients receiving antibiotics (from 41% to 36%) and a good appropriateness level on antibiotic use, stable over years.

Table 3 shows the comparison of alert organisms in our hospitals: VRE and CPE were a rare finding (less than 30 per year) and so they were expressed as absolute numbers. A decrease in MRSA (−5.2%) and ESBL (−3.2%) was observed during the observed period. This trend was not altered during the COVID-19 pandemic. CDI rates have been stable over the years.

### *Resilience*

Trend comparison of pre-pandemic (2018–19) and post-pandemic period (2020–21) are presented in Table 4. An improving trend in

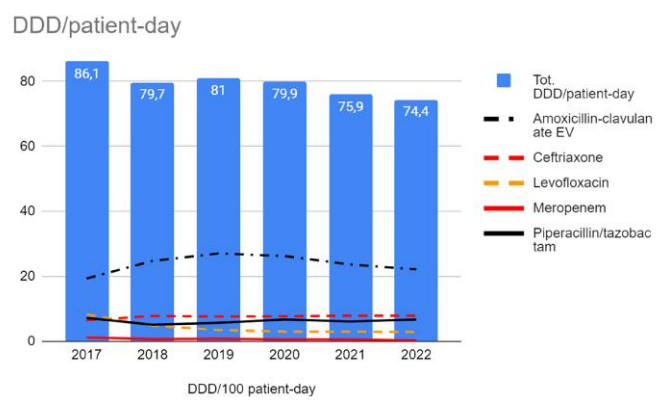


**Figure 1.** Antibiotic consumption expressed in DDD/100 patient-days.

**Table 2.** Antibiotic use prevalence and indication appropriateness (PPS)

| | 2017 ($n$=507) | 2019 ($n$=517) | 2021 ($n$=499) |
|---|---|---|---|
| Antibiotic prescription/ patient, *n* (%) | 211 (41.2%) | 196 (37.9%) | 179 (35.9%) |
| % confirmed or suspected bacterial infection | 74.6% | 83.6% | 82.5% |
| % surgical prophylaxis | 9.4% | 11.1% | 8.5% |
| % inappropriate (prophylaxis >24 h, no evidence of infection) | 15.9% | 5.3% | 8.9% |

overall antibiotic consumption is shown in the second period. Sustained but dampened reduction of III generation cephalosporins, fluoroquinolones and carbapenems is observed during the SARS-CoV-2 pandemic years.

### *Efficiency*

Process metrics are presented in Tables 5 and 6. An important increase in the number of on-site consultations per year from 2017 to 2022 (+138%) is displayed, despite a constant number of FTE ID consultants until 2021.

## Discussion

We have described a low-resource ASP based on behavioural change (BC) interventions, applied to a healthcare area of more than 300 000 inhabitants. The ASP was focused on hospitalized patients of the two hub hospitals in the area (A and B) but it was also accessible to other prescribers. The results of a 6-year analysis showed a reduction of the overall antibiotic consumption in the observed period, with a strong decrease in fluoroquinolones use and carbapenems, associated with a decreasing ecological time-trend of multi-drug microorganisms (ESBL and MRSA). The presented AMS was impactful both on antibiotic consumption and ecological trends. The improving consumption and ecological trends persisted over 6 years, demonstrating the programme sustainability. In the literature, few ASPs have a long follow-up, making difficult to assess long-term effects of AMS activities.[8] However, durability is pivotal, because compliance issues, trends inversion or unexpected negative consequences may appear in the long run.[26]

Appropriateness, antibiotic consumption and ecological trends were not reversed by the worst pandemic years (2020–2021), confirming a good performance of the ASP even during the dramatic challenges that occurred during COVID-19 pandemic. This shows that our ASP is robust and deep-seated in the healthcare area. Literature and national data showed an unjustified increase in hospital antimicrobial use associated with SARS-CoV-2 cases.[27–32] Our data are upstream and confirm the ASP resilience, even if our hospital was heavily and directly involved in managing SARS-CoV-2 patients.

In this paper, we gave a precise description of BC interventions implemented because, from our experience, targeted interventions are the key for an impactful, sustainable and resilient ASP. It is well known that antimicrobial use in hospitals is far from optimal: guidelines and general recommendations are usually insufficient to ensure appropriate antimicrobial use in daily practice.[33] The efficacy of ASP relies on many factors, most of them being irrational and qualitative, such as human factors (trusts and beliefs), highly dependent on the local context.[34–37] Furthermore, antimicrobial prescribing is always an ethical dilemma, where a careful balancing between the benefit for the patient and the good for the community is needed.[38] For all those reasons, BCT are really helpful in AMS.[39] BC models, such as the COM-B model, can provide a useful framework for a detailed design and structured reporting of ASP interventions.[8,39–42] Engagement to AMS activities from other clinical specialties is more likely to be achieved when interventions are specific and targeted,[43] and it is probably an underappreciated factor for a successful ASP. A recent survey aimed at identifying success factors in AMS, emphasized the importance of collaboration, trust and support among different professionals, roles and institutions.[44] Qualitative and narrative descriptions, together with traditional quantitative metrics, can provide a more complete understanding of successful ASPs.[45]

**Table 4.** Antibiotic consumption trend analysis expressed in DDD/100 patient-days

| | Pre-pandemic trend (2018–2019) | Pandemic trend (2020–2021) |
|---|---|---|
| DDD/100 patient-days | 1.3 | −4 |
| Amoxicillin-clavulanate IV | 2.3 | −2.6 |
| Third-generation cephalosporin | −0.9 | 0.1 |
| FQs | −1.83 | 0.02 |
| Carbapenems | −0.02 | 0.19 |
| Piperacillin/tazobactam | 0.6 | −0.6 |

**Table 3.** Alert microorganisms isolation in course of infection

| | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|
| MRSA, *n* (%) | 112 (20.6%) | 121 (19.7%) | 116 (18.1%) | 99 (19.4%) | 95 (16.2%) | 84 (15.4%) |
| VRE, *n* | 1 | 10 | 10 | 8 | 7 | 10 |
| ESBL, *n* (%) | 502 (12.5%) | 500 (10.8%) | 568 (11.7%) | 505 (10.1%) | 592 (10.5%) | 549 (9.3%) |
| CRE, *n* | 8 | 4 | 11 | 4 | 12 | 6 |
| CDI, % | 11.2% | 11.6% | 10.7% | 8.5% | 9.8% | 8.43% |

**Table 5.** Number of activities/year (annual variation %)

| | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|
| *N* on-site consultations | 1800 | 2411 (+34%) | 2647 (+10%) | 3479 (+31%) | 3417 (−2%) | 4283 (+25%) |
| *N* protocols | 2 | 5 | 3 | 3 | 4 | 3 |
| Educational meetings | 12 | 18 | 21 | 16 | 21 | 22 |
| Multidisciplinary meetings | 8 | 9 | 10 | 12 | 11 | 10 |

Phone consultations and informal consultations have a significant burden in the workload of AMS teams,[46,47] and that is confirmed in our experience. Remote consultations form a highly appreciated service by GPs[47] that improve accessibility and enhance collaboration between specialists.[48] A French study showed that a common motivation for phone consultations is to 'share the emotional risk during a difficult case', highlighting the psychological implications of antimicrobial prescription and the particular role of ID consultants.[49]

Resource allocation and workload need to be balanced to achieve efficiency. Despite that the absolute number of employed ID specialists grew in 2020 from two to four, the number of personnel actively dedicated for the AMS remained constant until 2021 because Hospital A became a referral centre for SARS-CoV-2 hospitalized patients and two (later three) ID specialists were dedicated for the management of those patients. The annual number of consultations is a raw data that estimates the working load. It does not include telephone consultations, informal advice, unstructured educational activities or other extra activities. It is also a surrogate parameter for ASP acceptance inside the hospital and the awareness for assistance need in antibiotic prescription. As shown in Table 5, the number of consultations increased over time, determining a significant working load. This is representative of good acceptance of our ASP but it is also an important point for the stakeholders: an increase in AMS resources over time should be considered to sustain the needs of prescribers. Because a recognized 'universal' staffing standard for AMS teams does not exist (2.0–6.7 FTE workers per 1000 acute-care beds is the range identified by one review), different attempts have been made to quantify the desirable or minimum human resources dedicated to ASP.[50–54] The Dutch consensus reports that the minimal staff requirements increase over time after initiation of an ASP, as an increase in stewardship activities is expected.[55] Then, long-term commitment by institutions is crucial to empower AMS teams and build AMS resilience.

In a frequently cited article, Petrak *et al*. asserted that ID consultants have a pivotal role, as they possess invaluable expertise in diagnosing and managing complex cases. They synthesize data to efficiently craft diagnostic and therapeutic plans, making them indispensable in the clinical arena.[56] Additionally, ID consultants play a crucial role as educators, enhancing healthcare quality by instructing various stakeholders and contribute to reducing inappropriate antibiotic use. The ability to effectively communicate their strengths to stakeholders is vital for recognition and success, emphasizing the importance of training dedicated and highly professional individuals. The AMS—as suggested in our paper—demonstrates the value of ID consultants to administrators, attending physicians and patients.

**Table 6.** FTE for core elements of AMS staff

| | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|
| ID consultants | 2 | 2 | 2 | 2 | 2 | 4 |
| Pharmacist | 0.3 | 0.4 | 0.4 | 0.6 | 0.8 | 0.8 |
| Microbiologist | 0.5 | 0.7 | 0.7 | 0.8 | 0.9 | 0.9 |

Our study has several strengths. The long duration of follow-up ensures appropriate outcome assessment. Persistence of ecological and antibiotic consumption trends over years, even during the COVID-19 pandemic, allows us to exclude major confounding factors in the data analysis (i.e. mean regression, temporary effects of the ASP, random variation of patterns over time).

Some limitations should be outlined. Electronic prescriptions are not available in our hospital and our AMS team did not include a data-manager and/or specific electronic tools for data collection. Thus, antibiotic consumption was determined using annual purchase data provided by pharmacists. This method may overestimate the overall antibiotic consumption (some amounts of drugs may be ordered but not consumed). However, it is unlikely that trends and proportional use of antibiotics would be affected by the use of purchase data. Microbiological and pharmaceutical data were provided on an annual basis. Thus, rapid fluctuations in antibiotic consumption or AMR are not provided. Also, our ASP lacks precise tracking of consultation effects on antibiotic prescriptions (for example: decrease in duration of treatment, escalation or early de-escalation, confirmation or discontinuation of ongoing treatment, not starting an antimicrobial therapy). Process metrics and outcome parameters are important to ameliorate the ASP, but data collection requires significant dedicated human and electronic resources that should be considered by policy makers. The shift to electronic records represents a unique opportunity to facilitate data collection and implement AMS aspects. We provided a detailed list of interventions and BCTs. This is useful to translate the results of our AMS. However, it is not possible to quantify the effect of single interventions. It must be considered that any BCT is targeted on specific beliefs and culture context. As shown for other BC experiences, i.e. the Matching Michigan 'paradox',[57] our results may be not reproducible in different cultural contexts.

## *Conclusions*

We have shown an ASP deeply embedded in the hospital cultural context, characterized by effectiveness (reduction of overall consumption of antibiotics and targeted antibiotics), sustainability (long-term effects), resiliency (trends that persisted over the years and during SARS-CoV-2 pandemic) and efficiency (increasing overall workload) in a resource-limited setting.

Resources for AMS are lacking in most countries, and the recent COVID-19 pandemic has shown the frailty of many ASPs and the importance of allocating resources in the field. Despite the demonstrable feasibility of implementing an ASP in low-resource settings,[58–60] as evidenced also by our work, it is crucial to ensure continuity of programmes by planning for resource implementation over the years. If ASPs prove effective even with a limited number of professionals, this should be seen as an opportunity to disseminate such programmes across any healthcare setting. Beyond economic considerations, the personal, social and human values of each team member should not be forgotten, as we believe they play a central role in the success of an ASP. The take-home message for stakeholders is that the scarcity of resources, rather than an excuse to delay the initiation of ASP, should be an impetus for selecting suitable and highly motivated personnel who can make a difference in the institution.

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## Transparency declarations

The authors declare no conflict of interests.

### Authors contributions

The study was designed by G.D.F. and S.V. M.A., G.B., B.B., C.Z., A.R. and M.Cr. obtained the data for the manuscript. The data analysis, the tables and figures were realized by G.D.F. All results and Supplementary Materials were revised by G.D.F., S.V. and M.A. The manuscript was drafted by G.D.F. (main author), S.V., M.A., B.B. and M.Cr. and was critically revised by the other authors (G.B., A.C., I.B., C.Z., A.R., G.T., M.Ch., E.F., M.T.). All authors approved the final manuscript for submission.

## Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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