Impact of clinical pharmacist intervention on antimicrobial use in a small 164-bed hospital

Pedro Mas-Morey,^{1,2} Alfonso Ballesteros-Fernández,³ Elisabet Sanmartin-Mestre,¹ Marta Valle^{2,4}

¹Department of Pharmacy, Hospital Quirón Salud Palmaplanas, Palma de Mallorca, Spain

²Department of Pharmacology, Therapeutics and Toxicology, Universitat Autònoma de Barcelona, Barcelona, Spain

³Department of Internal Medicine, Hospital Quirón Salud Palmaplanas, Palma de Mallorca, Spain

⁴Pharmacokinetic/Pharmacodynamic Modelling and Simulation, Sant Pau Biomedical Research Institute (IIB Sant Pau), Barcelona, Spain

Correspondence to

Dr Marta Valle, Pharmacokinetic/Pharmacodynamic Modelling and Simulation, Sant Pau Biomedical Research Institute (IIB Sant Pau), Av Sant Antoni M Claret 167, 08025 Barcelona, Spain; mvallec@santpau.cat

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ABSTRACT

Objectives To study the impact of clinical pharmacist interventions (PIs) on antimicrobial prescriptions in terms of physician acceptance rates, clinical benefits and antimicrobial use/cost outcomes.

Methods This study retrospectively analysed the impact of antimicrobial PIs over a 2-year period (October 2012 to October 2014) in a private non-teaching 164-bed hospital without a formal antimicrobial stewardship programme. Excluded from the study were outpatients and patients admitted to the intensive care unit or the emergency department. The PIs focused on appropriate indication and appropriate dosage; drug adverse events, allergies, intolerance and interactions; sequential therapy; therapeutic de-escalation; excessive duration of treatment and therapeutic drug monitoring. Carbapenems and linezolid were classified as special-vigilance drugs. Amoxicillin-clavulanic, piperacillin-tazobactam and vancomycin were classified as preferred drugs. Clinical benefits evaluated in accordance with internal guidelines, were classified as enhancing appropriate antimicrobial prescription or potentially reducing toxicity. Antimicrobial use and expenditure were compared with that of the previous 2-year period.

Results 386 PIs were implemented in 303 patients. The overall acceptance rate was 83.4%. The acceptance rate for appropriate prescription PIs was significantly lower than for toxicity PIs (73.7% vs 90.9%; $p < 0.0001$). Significant reductions in the use of special-vigilance drugs (from 39.9 (22.2–86.0) to 28.0 (6.0–43.4) defined daily doses (DDD)/1000 patient-days; $p = 0.0003$) were seen and increases in the use of piperacillin-tazobactam (from 13.2 (0–22.9) to 17.2 (6.9–44.8) DDD/1000 patient-days; $p = 0.007$) and of cephalosporins (from 123.5 (61.8–196.6) to 149.1 (80.3–228.2) DDD/1000 patient-days; $p = 0.027$). Overall cost savings were 5.1%.

Conclusions PIs on antimicrobial prescriptions may be effective in enhancing appropriate use of antimicrobials, reducing their toxicity, reducing the use of special-vigilance drugs and reducing overall antimicrobial cost.

INTRODUCTION

Rational use of antimicrobial drugs is of paramount importance in avoiding antimicrobial resistance (AMR), one of the greatest threats to public health worldwide, due to its associated morbidity, mortality and healthcare costs.¹ The development and distribution of clinical practice guidelines adapted to local needs and adherence to them is essential to prevent the emergence of AMR and to ensure judicious use of antimicrobials,² yet a

multicentre study has shown that 37.8% of antibiotic use in European hospitals does not comply with local guidelines.³ Antibiotic resistance rates vary in Europe, with the highest rates reported for Greece, Portugal, Italy and Spain, where antibiotic consumption is higher than for their northern counterparts.⁴

Antimicrobial stewardship programmes (ASPs) are a promising strategy for dealing with AMR.⁵ An ASP is defined as an ongoing effort by a healthcare institution to optimise antimicrobial use by hospitalised patients in order to improve patient outcomes, reduce adverse events associated with antimicrobial use (including AMR) and ensure cost-effective treatment.⁶ It is less likely that small community hospitals can implement a formal ASP, so they continue to represent one of the last frontiers for ASPs.⁷ In small hospitals without a formal ASP, the clinical pharmacist can play a key role in monitoring antimicrobial prescriptions and in advising and educating medical and nursing staff.⁸ Such clinical pharmacist interventions (PIs) can optimise antimicrobial use, improve outcomes, promote rational prescribing, reduce inappropriate use and, ultimately, potentially slow down the spread of AMR.⁹ The importance of PIs in validating medication has been previously documented, with systemic antimicrobials named as one of the drug categories with the highest frequency of PIs.¹⁰

There are two main classes of antibiotics: narrow-spectrum antibiotics, which target specific bacteria (identified through laboratory methods using patient swabs), and broad-spectrum antibiotics, which are presumably active against multiple bacteria. Increased antibiotic consumption accelerates the development of resistance, where bacteria mutate making the antibiotics less effective; consequently, antibiotic monitoring is of paramount importance. Although ASPs can address rational antimicrobial use overall or specific antimicrobials,¹¹ the initial primary goal should be to monitor the laboratory report on bacteria and to recommend narrow-spectrum antibiotics. The purpose is to prevent indiscriminate use of broad-spectrum antibiotics that are active against multidrug-resistant bacteria, so that these drugs can be kept in reserve as last-resort antibiotics.¹²

Carbapenems and linezolid are broad-spectrum antibiotics used to fight multidrug-resistant microorganisms. Carbapenems, in particular, are usually reserved as a last-resort treatment against multidrug-resistant Gram-negative bacilli. However, several studies have shown a significant correlation between recent use of certain antibiotics, including

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carbapenems, and the development of resistance to these antibiotics.^{13 14} In several parts of the world carbapenemase-encoding genes have become endemic, which suggests the urgency of rationalising the use of carbapenems.¹⁵ Indeed, a link between restrictions imposed on carbapenem use and lower incidence rates for carbapenem-resistant pathogens has been shown.^{16 17}

Concerns about linezolid are focused on the emergence of linezolid-resistant *Staphylococcus* (mainly isolated from patients in North America and Europe). Linezolid is highly active against most staphylococci, is crucial to the treatment of serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and is the only oral-formulation antibiotic suitable for MRSA treatment. Judicious use of this antibiotic is therefore essential for the preservation of its antimicrobial activity.¹⁸

Ideally, pharmaceutical care should focus on certain antibiotics, and also monitor all antimicrobials (antibiotics, antifungals, antivirals). However, small hospitals, which tend to struggle with resources, may focus particularly on those drugs for which rational use is urgently needed, such as carbapenems and linezolid, in order to address antibiotic resistance.^{11 12}

Our objective was to analyse, in a small 164-bed southern European hospital without a formal ASP, the impact of PIs on antimicrobial prescriptions as shown by physician acceptance rates, clinical benefits and antimicrobial use/cost.

PATIENTS AND METHODS

Setting

This study retrospectively analysed the impact of PIs on antimicrobial prescriptions in a private non-teaching 164-bed hospital without a formal ASP over a period of 2 years (15 October 2012 to 14 October 2014).

Patients

All patients (including paediatrics) admitted to inpatient services were included in the analysis. Excluded were outpatients and patients admitted to the intensive care unit (ICU) or the emergency department because of the small number of pharmacists in the hospital. For data analysis, any discharged patient who was subsequently readmitted was considered as a new patient.

Antimicrobials

Linezolid (oxazolidinone) and carbapenems (doripenem, ertapenem, imipenem, meropenem) were classified as special-vigilance drugs intended only to be used as last-resort antibiotics and their prescription was carefully evaluated following international guidelines (no pre-authorisation or formulary restriction forms were in use in the hospital). Two penicillins (amoxicillin-clavulanic and piperacillin-tazobactam) and a glycopeptide (vancomycin, which was preferred over linezolid for treatment of MRSA) were included in the group of preferred drugs and a final group of other antimicrobials included quinolones (levofloxacin ciprofloxacin and moxifloxacin), other penicillins (ampicillin, aztreonam and cloxacillin), macrolides (azithromycin, erythromycin and clarithromycin), cephalosporins (cefazolin, cefuroxime, cefotaxime, ceftriaxone, ceftazidime, cefepime and cefditoren), aminoglycosides (gentamicin, amikacin and tobramycin), lincosamides (clindamycin), tetracyclins (tigecycline and doxycycline), antivirals (acyclovir, ganciclovir, famciclovir, valganciclovir, brivudine and antiretrovirals) and antifungals (fluconazole and voriconazole) and other antibiotics (dapto-mycin, fosfomycin, colistin, rifampicin, trimethoprim/sulfa-methoxazole and metronidazole).

Antimicrobial interventions by pharmacists

The PIs focused on the following aspects of antimicrobial prescriptions: appropriate indication and appropriate dosage; drug adverse events, allergies, intolerance and interactions; sequential therapy (a switch from parenteral to oral administration); therapeutic de-escalation (a switch in antibiotic to target a narrower antimicrobial activity spectrum); excessive duration of treatment; and therapeutic drug monitoring of antimicrobial plasma concentrations for those drugs with a narrow therapeutic index and an analytical method available at the hospital (vancomycin, gentamicin, amikacin and tobramycin). PIs involving a change in antimicrobial agent or discontinuation of treatment due to excessive therapy duration were first discussed with an internal medicine physician. When a PI was considered necessary, the clinical pharmacist or internal medicine physician verbally proposed the recommendation to the attending physician.

PIs were classified by type as follows: dose adjustment or interval modification with reason given (kidney impairment, obesity, or other); drug change due to inappropriateness; sequential treatment; de-escalation of treatment; discontinuation due to excessive duration; discontinuation because no indication to proceed; and other. For clinical benefits, PIs were classified as implemented to ensure appropriate antimicrobial prescription or to reduce toxicity. This classification was generated by the clinical pharmacist on the basis of internal guidelines. PI benefits considered to ensure appropriate antimicrobial prescription were as follows: substitution with a more appropriate antimicrobial; therapeutic de-escalation; dose increases for any reason or interval modification; dosage changes for pharmacokinetic/pharmacodynamic reasons; a switch from intravenous to oral administration and correction of a drug-drug interaction that might reduce efficacy. PI benefits considered to reduce toxicity were as follows: dose reductions or interval modification; shortened treatment duration; avoidance of possible adverse events; allergies or intolerances; and a lack of indication for continued treatment.

Data collection

From 15 October 2012, following a strategy similar to a prospective audit and feedback, the clinical pharmacist started to perform and record PIs in antimicrobial prescriptions. Every day (Monday–Friday) the clinical pharmacist received an automated report on all hospitalised patients who had received antimicrobials in the previous 24 hours. The report included information on admission date, antimicrobial agent, drug form and dose, date of first administration, patient weight and height and patient location in the hospital. Patient medical histories, laboratory reports and microbiological reports were also used as sources of information. When necessary, creatinine clearance was calculated in adult patients using the Cockcroft–Gault equation. Patients were followed up until discharge.

The proposed PI, the physician's acceptance or rejection of the recommendation and the reason for rejection were recorded in the pharmacy department database. PIs were not recorded in patient medical records.

Data collected for each patient from the pharmacy system included demographic and clinical data, including age, sex, admitting service and diagnosis on admission.

Data on antimicrobial use/cost were obtained from the pharmacy department's database. For the intervention period, data were collected during the 2 years running from 15 October 2012 to 14 October 2014. We also collected data for the 2 years before the intervention (the pre-intervention period).

To evaluate changes in antimicrobial use, we used median monthly defined daily dose (DDD) per 1000 patient-days of intravenous antimicrobials, and to evaluate cost outcomes, we compared intravenous antimicrobial costs for special-vigilance drugs, preferred drugs and other antimicrobials. Since sequential treatment was encouraged during the intervention period, the direct costs of oral amoxicillin-clavulanic, levofloxacin and ciprofloxacin were also taken into account. To avoid price distortions arising from contract price changes or the release of generic versions of antimicrobials, we used Spanish retail sales prices for 2014 for both periods.

Statistical analysis

The statistical analysis was performed using G-STAT 2.0 (GlaxoSmithKline). Key patient data such as age, sex, admitting service and diagnosis on admission were descriptively reported as median (range) and frequency. Descriptive statistics regarding PIs and acceptance were reported as the number and frequency. Chi squared analyses were used to compare physician acceptance rates for PIs aimed at reducing toxicity and PIs aimed at ensuring appropriate antimicrobial prescription. Because the use and cost of some groups were not normally distributed the Mann-Whitney U (Wilcoxon) test was used to compare median monthly antimicrobial use and cost per 1000 patient-days in the pre-intervention and intervention periods. For all comparisons significance was set at <0.05 .

RESULTS

A total of 303 patients were included: median age 78 (range 10–100) years and similar percentages of men and women (50.2% men). These patients were primarily admitted via the internal medicine service (52.2%), followed by pneumology (10.9%), cardiology (7.9%), general surgery (6.9%), urology (5.9%), neurology (5.6%), orthopaedic surgery and traumatology (5.3%), digestive (2.3%) and other services (including paediatrics) (3.0%). Diagnoses on admission were lower respiratory tract infection (33.3%), urinary tract infection or pyelonephritis (17.2%), intra-abdominal infection (14.2%), skin and soft tissue infection (13.5%), bacteraemia or sepsis (9.2%), osteoarticular infection (2.3%), central nervous system infection (1.7%), endovascular infection (1.7%), fever of unknown origin (1.0%) and other diagnoses (2.3%). Antibiotic prophylaxis for surgical procedures was the indication for 11 patients (3.6%).

A total of 386 PIs were implemented (one–seven per patient). PIs associated with quinolones, penicillins, carbapenems and cephalosporins accounted for over three-quarters of all recommendations (table 1). The intravenous administration route required the highest number of interventions ($n=317$, 82.1%). Dose adjustments or interval modifications accounted for nearly two-thirds of all PIs and dose adjustment or interval modification due to kidney impairment was the single most frequently performed PI (table 2).

The overall acceptance rate for the 386 implemented PIs was 83.4% ($n=322$). The main reason for rejecting a PI was hospital discharge very soon after the recommendation ($n=16$). PIs for dose adjustment or interval modification due to obesity had the lowest acceptance rate (46.5%). Just under 31% of the PIs were first discussed with the internal medicine physician.

The percentages for clinical benefit were similar, at 43.3% for PIs aimed at ensuring appropriate antimicrobial prescription and 56.7% for PIs aimed at reducing toxicity. The acceptance rates for PIs referring to appropriate antimicrobial prescription and to toxicity were 73.7% and 90.9%, respectively (χ^2 , $p<0.0001$).

Table 1 Clinical pharmacist interventions by antimicrobial group and physician acceptance rate

Antimicrobial group	N (%)	Acceptance (%)
Quinolones	106 (27.5)	81 (76.4)
Penicillins	102 (26.4)	88 (86.3)
Carbapenems	49 (12.7)	41 (83.7)
Cephalosporins	37 (9.6)	28 (75.7)
Aminoglycosides	18 (4.7)	15 (83.3)
Antivirals	13 (3.4)	13 (100)
Oxazolidinones	12 (3.1)	11 (91.7)
Glycopeptides	7 (1.8)	7 (100)
Macrolides	7 (1.8)	7 (100)
Lincosamides	6 (1.6)	6 (100)
Antifungals	6 (1.6)	5 (83.3)
Tetracyclines	4 (1.0)	3 (75)
Other	19 (4.9)	17 (89.5)
Total	386 (100)	322 (83.4)

No adverse events were noted after implementing a PI in any patient.

Table 3 shows that in the intervention period there was a statistically significant reduction in the use of special-vigilance drugs, with the exception of meropenem.

Conversely, there were significant increases in use of piperacillin-tazobactam (from 13.2 (0–22.9) to 17.2 (6.9–44.8) DDD/1000 patient-days; $p=0.007$) and the cephalosporins (from 123.5 (61.8–196.6) to 149.1 (80.3–228.2) DDD/1000 patient-days; $p=0.027$) and a decrease in ampicillin use (from 12.4 (0–40.1) to 12.1 (0–27.1) DDD/1000 patient-days; $p=0.047$). No significant changes were seen for any other antimicrobials. Changes in use patterns overall translated into a 33% reduction in expenditure on special-vigilance drugs (from €255980 to €170633), a 23% increase in expenditure on preferred drugs (from €109499 to €135054), an 11% increase in expenditure on other antimicrobial drugs (from €249742 to €277246) and, finally, a small increase in expenditure on oral antimicrobials (from €7946 to €8231). Total cost savings were €32003, representing a 5.1% decrease in overall expenditure. Expressed another way, the median monthly antimicrobial cost

Table 2 Pharmacist interventions by intervention type and physician acceptance rate

Pharmacist interventions (n=386)	N (%)	Acceptance (%)
Drug dose adjustment or interval modification due to kidney impairment	134 (34.7)	124 (92.5)
Drug dose adjustment or interval modification due to obesity	43 (11.1)	20 (46.5)
Drug dose adjustment or interval modification for other reasons*	47 (12.2)	42 (89.4)
Discontinuation due to excessive duration	47 (12.2)	39 (83.0)
Drug change due to inappropriateness	47 (12.2)	43 (91.5)
Sequential therapy	37 (9.6)	28 (75.7)
Discontinuation due to no indication to proceed	13 (3.4)	13 (100)
Therapy de-escalation	12 (3.1)	7 (58.3)
Others†	6 (1.6)	6 (100)

*Drug dose adjustment or interval modification for other reasons: pharmacokinetic/pharmacodynamic parameters or recommended dose/interval modification according to clinical guidelines.

†Others: drug administration recommendation, adverse events/allergies information, pharmacological interaction.

Table 3 Median monthly defined daily dose per 1000 patient-days of intravenous antimicrobials in the pre-intervention and intervention periods

Variable	Pre-intervention median (range)	Intervention median (range)	p Value
Total special-vigilance drugs	39.9 (22.2–86.0)	28.0 (6.03–43.4)	0.0003
Linezolid	4.9 (0–16.1)	4.8 (0–8.4)	0.036
Doripenem	1.6 (0–14)	0 (0–3.2)	0.0009
Ertapenem	7.4 (0–24.7)	2.4 (0–14.5)	0.0003
Imipenem	6.3 (0–21.6)	2.4 (0–11.3)	0.006
Meropenem	19.8 (6.2–34.6)	17.5 (1.2–30.1)	0.47
Total preferred drugs	161.4 (96.7–278.5)	152.1 (105.7–235.5)	0.92
Total other antimicrobials	247.8 (177.7–334.0)	268.8 (209.8–394.4)	0.10

All p values calculated using the Mann-Whitney U (Wilcoxon) test.

fell from €6329 (range €4845–9875) to €5950 (range €3713–8483) per 1000 patient-days ($p=0.27$).

DISCUSSION

We measured the impact of antimicrobial interventions by the clinical pharmacist at a small community hospital without a formal ASP, which, with under 200 beds, is representative of a setting where further information on ASPs is much needed. We observed a good acceptance rate for the proposed interventions and report an overall reduction in the use of special-vigilance drugs (carbapenems and linezolid) and a parallel increase in the use of piperacillin-tazobactam and the cephalosporins, with no associated adverse events. The changes might have produced clinical benefits, such as enhanced appropriate antimicrobial prescription and reduced toxicity, and also resulted in a fall in total expenditure on antimicrobial drugs. Importantly, patients' characteristics and hospital activity remained stable during both pre-intervention and intervention periods.

PIs and physician acceptance rates

In this study, as in other similar studies,¹⁹ the most frequently proposed PI was antimicrobial dose adjustment or interval modification due to kidney dysfunction. In view of these results, and because PIs in patients with chronic kidney conditions seem to have a direct positive impact on patient outcomes,²⁰ we suggest that attending physicians should receive pharmacological training about the dosage for patients with impaired kidney function. In view of the high prevalence of these interventions, we also suggest that randomised controlled clinical studies need to be performed to evaluate the clinical and economic outcomes of PIs for patients with kidney dysfunction.

We observed a high acceptance rate (83.4%) for the proposed PIs, which is corroborated by results reported by other studies carried out in small- to medium-sized hospitals implementing ASP recommendations.^{21–22} Interestingly, the acceptance rate was significantly higher for interventions that potentially reduced toxicity than for interventions aimed at ensuring appropriate antimicrobial prescription—a result also corroborated elsewhere.²³ We suggest that this is because attending physicians feel more confident in the proposed changes when there is a sign of toxicity than when dose reductions or therapeutic de-escalations are suggested. The lowest acceptance rate was for PIs reflecting drug dose adjustments or interval modification due to obesity (46.5%), probably because attending physicians considered that a dose increase might result in a higher risk of an adverse event. This problem of antibiotic underdosage also needs to be studied, as it may enhance antibiotic resistance through bacterial exposure to subtherapeutic concentrations.²⁴ Therapeutic de-escalation also requires further study, as, after considering microbiological

culture results, treatment for patients, can potentially be streamlined with less expensive or less toxic drugs.

Antimicrobial use/cost outcomes

The high acceptance rate reported in this study led to a reduction in total antimicrobial expenditure, mostly due to reduced use of linezolid and of most carbapenems. Expenditure on special-vigilance drugs was reduced by a third overall, implying savings for the hospital and the healthcare system, but more importantly, benefiting society, as these drugs can then be reserved as a last-resort therapeutic option, reducing the risk of escalating drug resistance. However, restricting specific antimicrobial classes may result in increased use of other drugs and, consequently, in an increased risk of the development of resistance by the corresponding pathogens (the squeezed-balloon effect).²⁵

Although we did not specifically restrict the use of any antimicrobial, the reduction in use of special-vigilance drugs was accompanied by a significant increase in use of piperacillin-tazobactam and the cephalosporins. A number of studies conducted in small- to medium-sized hospitals operating formal ASPs have reported similar findings: a decrease in the use of carbapenems which correlated with an increased use of piperacillin-tazobactam,²⁶ and decreased use of other antimicrobials, including antipseudomonal carbapenems and linezolid, associated with a significant surge in the use of cefazolin.²¹ In our study the increase in cephalosporins could be explained by the reduction in the use of linezolid, carbapenems and ampicillin. Overall cost savings reported in both these studies were higher than those reported in our study, possibly because these studies referred to multidisciplinary formal ASPs focusing on reducing use of all antimicrobial agents (and not just special-vigilance drugs). Our antimicrobial use/cost analysis was based on whole-hospital expenditure, so we can assume that cost savings would have been greater had we included ICU patients in the intervention.

Limitations

As far as we are aware, and as indicated by the fact that no adverse effects were reported, no intervention was harmful for the patient. Nevertheless, this study has some limitations. First, we did not evaluate whether our recommendations affected clinical outcomes, such as length of stay, mortality or readmission rates. Such outcomes are rarely evaluated in a context of ASP recommendations, but when reported, have mostly been non-significant.^{5,27,28} Consequently, we assume that our interventions were unlikely to have had an impact on these outcomes.

Second, antimicrobials such as anidulafungin, voriconazole, daptomycin, tigecycline and colistin were not considered in

the use/cost analysis since they are mainly used in ICU patients (excluded from our study). Third, in evaluating the cost of antimicrobials, although we adjusted prices to a single year (as recommended by experts to account for changing prices), in our final analysis we did not take into account clinical pharmacist and personnel time investment in recording and implementing PIs.²⁹ Lastly, not compared were microbiologic outcomes (improvements in certain antimicrobial resistance patterns, or differences in the incidence of resistant microorganisms—for example, carbapenem-resistant pathogens or linezolid-resistant *Staphylococcus* and *C. difficile*) between pre-intervention and intervention periods. It is unlikely, however, that our interventions affected these outcomes, given the relatively small number of recommendations implemented and bearing in mind the presence of confounding factors such as other infection control measures.³⁰

Apart from these limitations, the validity of our study is supported by the finding that the use of special-vigilance drugs was significantly reduced and that the PIs may have increased appropriate antimicrobial prescription or reduced drug toxicity without resulting in any adverse event.

CONCLUSION

Clinical PIs in antimicrobial prescriptions have been shown to be effective in enhancing appropriate use of antimicrobials and reducing their toxicity, which may improve patient care. The reduction in the use of special-vigilance drugs (broad-spectrum antibiotics) seen in this study is expected to reduce antibiotic resistance since these drugs can be kept in reserve as last-resort antibiotics. The PIs and the high acceptance rate by the physicians led to a reduction in total antimicrobial expenditure, which is especially relevant in small hospitals which tend to struggle with financial resources.

What this paper adds

What is already known on this subject?

- In large hospitals, the importance of an antimicrobial stewardship programme (in which a pharmacist is a member of the team) in improving patients outcomes, reducing adverse events associated with antimicrobial use (including antimicrobial resistance) and ensuring cost-effective treatment, has been highlighted.
- Small- to medium-sized hospitals (fewer than 500 beds) tend to struggle with financial and human resources and, consequently, are less likely to develop such a programme.

What this study adds?

- Clinical pharmacist interventions in antimicrobial prescriptions have been shown to be effective in enhancing appropriate use of antimicrobials and reducing their toxicity, which may improve patient care.
- The reduction in the use of special-vigilance drugs (broad-spectrum antibiotics) observed in this study is expected to reduce antibiotic resistance since these drugs can be reserved as last-resort antibiotics.
- Pharmacist interventions and the high acceptance rate of physicians led to a reduction in total antimicrobial expenditure.

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Contributors All authors have participated in at least one of the following: conception and design of the project, analysis and interpretation of the data or writing. In addition all the authors have made a substantial contribution to drafting or critical revision of the manuscript for important intellectual content.

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