


BMJ Open Infectious diseases experts as part of the antibiotic stewardship team in primary care: protocol for a cluster-randomised blinded study (IDASP)

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ABSTRACT

Introduction Antibiotic overuse is directly related to antibiotic resistance, and primary care is one of the main reasons for this overuse. This study aims to demonstrate that including experts on infectious diseases (ID) within the antimicrobial stewardship (AMS) programme team in primary care settings achieves higher reductions in overall antibiotic consumption and increases the quality of prescription.

Methods and analysis A multicentre, cluster-randomised, blinded clinical trial will be conducted between 2021 and 2023. Six primary care centres will be randomly assigned to an advanced or a standard AMS programme. The advanced AMS programme will consist of a standard AMS programme combined with the possibility that general practitioners (GP) will discuss patients' therapies with ID experts telephonically during working days and biweekly meetings. The main endpoint will be overall antibiotic consumption, defined as daily defined dose per 1000 inhabitants per day (DHD). Secondary end-points will be: (1) unnecessary antibiotic prescriptions in patients diagnosed with upper respiratory tract or urinary tract infection, (2) adequacy of antibiotic prescription, (3) reattendance to GP or emergency room within 30 days after the initial GP visit and (4) hospital admissions for any reason within 30 days after the GP visit. Two secondary endpoints (unnecessary antibiotic therapy and adequacy of therapy) will be evaluated by blinded investigators.

We will select three clusters (centres) per arm (coverage of 147 644 inhabitants) which will allow the rejection of the null hypothesis of equal consumption with a power of 80%, assuming a moderate intracluster correlation of 0.2, an intracluster variance of 4 and a mean difference of 1 DHD. The type I error will be set at 5%.

Ethics and dissemination The protocol was reviewed and approved by local ethics committees. The results of this study will be published in peer-reviewed journals and presented at medical conferences.

Trial registration number NCT04848883

Strengths and limitations of this study

- This is a multicentre randomised study.
- The quality of prescription will be blindly assessed.
- A cluster-randomised design has been selected to reduce the effect of patient contamination within the centre.
- In Spain, COVID-19 has increased virtual general practitioner visits, which might influence the effect of this intervention on antibiotic consumption.
- As our secondary outcomes will be assessed through point prevalence surveys, the final sample may be small to detect differences between groups.

INTRODUCTION

The rapid spread of untreatable multidrug-resistant (MDR) bacteria poses a serious threat to global public health^{1,2} causing up to 33 000 attributable deaths annually.³ By 2050, global estimates predict that bacterial resistance will be responsible for 10 million deaths every year, and healthcare costs will exceed €80 billion.⁴

Antimicrobial resistance is directly associated with antimicrobial misuse, which mostly refers to unnecessary antibiotic prescriptions.^{5–7} According to the WHO, country-level efforts to reduce unnecessary antimicrobial consumption are keys to preventing the worldwide rise of MDR bacteria.⁸

Spain is among the European countries with the highest rates of antibiotic consumption. In 2019, the average consumption of antibiotics was 24.7, defined daily doses per 1000 inhabitants per day (DHD), most of which (23.1 DHD) was consumed in the primary care setting.⁹ Moreover, the Spanish National Health System reported that 430 million antibiotic prescriptions

were dispensed from outpatient pharmacies, 30% of which were inappropriate.¹⁰ In the primary care setting, these inappropriate prescriptions are mostly driven by antibiotic misuse for treating non-bacterial respiratory tract infections, and by using broad-spectrum antibiotics for treating infections for which a narrower spectrum of antibiotics is indicated.¹¹⁻¹³ Additionally, another cause of concern at the primary care level is overtreatment of asymptomatic bacteriuria, particularly in older patients.^{14 15}

Different antimicrobial stewardship (AMS) programmes have shown their efficacy in reducing antibiotic consumption in both the hospital and primary care settings. Many of the successful experiences included multidisciplinary teams, which also increased the quality of antibiotic prescriptions.¹⁶⁻¹⁹

The European Society of Clinical Microbiology and Infectious Diseases has recently elaborated a consensus document stating that healthcare providers who prescribe antibiotics should know about infectious diseases (ID).²⁰ In this regard, different societies recommend including experts in ID in their AMS programme teams; however, these recommendations are particularly focussed on hospital settings.^{21 22}

This study aims to assess the impact of including ID experts within the AMS programme team in the primary care setting on antibiotic consumption and prescription quality in patients diagnosed with upper respiratory tract and urinary tract infections.

Hypothesis

Centres including ID experts as part of their primary care AMS (advanced AMS) programme teams will enhance general practitioner (GP) knowledge and skills on prescribing, which will decrease antibiotic consumption and improve the quality of prescription. Improvement will be achieved without increasing the number of patients who revisit the GP attend the emergency room or need hospitalisation within 30 days after the initial GP visit.

Primary objective

- ▶ To assess the impact of the advanced AMS programme on overall antibiotic consumption.

Secondary objectives

Selected to assess the quality of prescription and safety of the advanced AMS programme:

- ▶ The unnecessary antibiotic prescriptions in diagnosed upper respiratory and urinary tract infections.
- ▶ The adequacy of antibiotic prescriptions.
- ▶ The total number of patients who re-attend to GPs or emergency rooms within 30 days after the initial GP visit.
- ▶ The number of hospital admissions within 30 days after the initial GP visit.

METHODS AND ANALYSIS

Study design and setting

A multicentre blinded clinical trial will be conducted at six centres of the Delta of Llobregat primary care section in the southern metropolitan health area of Barcelona (Spain) from June 2021 to April 2023. This healthcare section covers a total population of 402 657 inhabitants (census 31 December 2020), and has an overall of 18 primary care centres, a community hospital and a tertiary university referral hospital, Hospital Universitari de Bellvitge (HUB). The microbiological laboratory is the same for all Delta healthcare areas and it is located in HUB. The participating centres have research experience and accepted the invitation to participate in the study.

This cluster-randomised trial uses primary care centres as a unit of analysis to avoid intracentre contamination.

Participants

The intervention is targeted at GPs who treat adult patients from the six participating primary care centres. To obtain information about the quality of prescription and safety outcomes, we will collect clinical data from the medical records of patients who fulfil the following inclusion criteria: older than 14 years, and diagnosed with upper respiratory tract (pharyngoamygdalitis, sinusitis and otitis) or urinary tract infection (cystitis, prostatitis and pyelonephritis). Patients with indwelling urinary catheter or congenital urinary tract abnormalities will be excluded.

Eligible patients will be identified according to the International Classification of Diseases (ICD)-10 CM codes as follows:

Upper respiratory tract infection: J00, J01, J02, J03, J04, J05, J06, J31, J39, H60, H62, H65, H66, H67, H83 and H92.

Urinary tract infection: N10, N30, N39, N41, R82 and O23.

Online supplemental appendix 1 shows the detailed ICD-10 code list.

Patients could be included more than once if the GP visit occurred 30 days or more after a previous medical visit.

Study timeline

The study will be composed of two main periods. From June 2021 to March 2022, all the centres will enforce the standard AMS programme. On 1 April 2022, centres will be randomly assigned to receive the advanced AMS programme (intervention group) or to continue the standard AMS programme (control group). This period spans 12 months (figure 1).

As the first 4 months will aim to increase the knowledge and acceptance of the AMS programme among the GPs; therefore, data from these 4 months will be excluded from the final analysis.

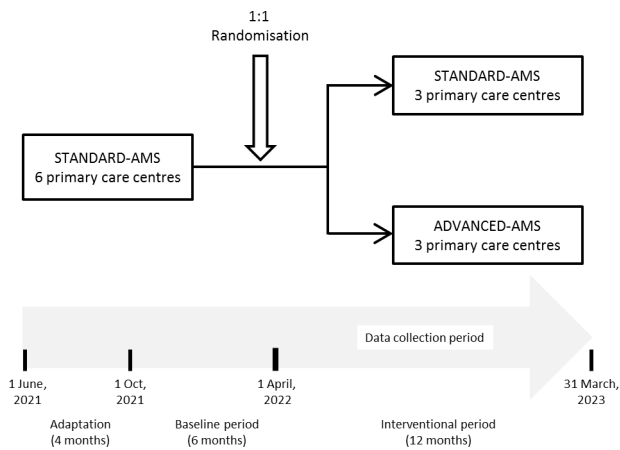


Figure 1 Clinical trial randomisation and study timeline. AMS, antimicrobial stewardship.

Components of the AMS

- ▶ Educational campaign. To improve the knowledge about the importance of antibiotic use and the potential harms from its misuse, we will develop educational materials targeted at both patients and GPs. Information will be released through digital toolkits on social media, healthcare centres' televisions and print materials. The campaign will start on October 2021 and will last the entire study period (online supplemental appendix 2 shows some social media images and messages of the campaign).
- ▶ Updated Empirical Antibiotic Guidelines. Local guidelines will be updated according to bacterial antibiotic susceptibility patterns and embedded within the electronic prescription support tool of primary care to enhance guideline compliance (online supplemental appendix 3 shows the updated guidelines)
- ▶ Promotion of delayed antibiotic prescriptions. It involves only patients diagnosed with upper respiratory tract infections (pharyngoamigdalitis, sinusitis and otitis). The local leader (principal investigator) of the AMS programme in each centre will be responsible for encouraging GPs to use it during their regular meetings.

- ▶ Promotion of *Streptococcus pyogenes* antigen test (*Streptotest*). Local leaders at each centre will be responsible for encouraging GPs to use it if bacterial tonsillitis is suspected.
- ▶ Daily microbial reports. All urinary culture tests are performed by the Microbiology Department of HUB. Isolates with a multiresistant profile will be sent to each primary care centre via e-mail. This e-mail will be checked daily by a health assistant who will accordingly inform the GP responsible for the patient.
- ▶ Quarterly reports. Anonymous data sets on quarterly reports will be provided to each primary care centre. This includes data on the main and secondary outcomes, for feedback and benchmarking.

Centres with advanced AMS will receive additional support and continuous training in clinical decisions of infective processes through telephone access on working days and biweekly meetings with ID experts. The choice to consult the ID expert will be at the GP's discretion. Experts are ID physicians or pharmacists with ID experience, from the referral hospital (table 1).

Randomisation and blinding

The main characteristics of the referral population of each participant primary care centres were assessed, and no significant differences between population features were observed. A priori, randomisation will help to keep the groups comparable. However, two centres had a larger referral population, and to ensure this point, a restriction would be introduced to the randomisation process to guarantee that the two centres with the highest referral populations will not fall into the same groups. Randomisation will be performed using a centralised electronic computer system.

Due to the nature of the intervention, GPs will not be blind to their allocation group. However, the two secondary endpoints (unnecessary antibiotic therapy and adequacy of therapy) will be evaluated by two independent investigators (CE and AP). These investigators will be blinded to centre allocation. Disagreements between them will be discussed with a third blinded physician (AL)

Table 1 Components of the antimicrobial stewardship (AMS) programme

Standard AMS programme	Educational materials.
	Updated local antibiotic guidelines.
	Promotion of delayed antibiotic prescription.
	Promotion of <i>Streptococcus pyogenes</i> antigen test (<i>Streptotest</i>) if bacterial tonsillitis is suspected.
	Daily report to GP of multiresistant bacteria isolates in urinary samples.
Advanced AMS programme	Quarterly reports to prescribers of AMS outcomes at the centre-level.
	Antimicrobial stewardship
	Biweekly meetings among GP and ID experts.

The advanced AMS programme also includes the standard AMS programme.
AMS, antimicrobial stewardship; GP, general practitioner; ID, infectious disease.

to achieve consensus. The degree of agreement among investigators will also be assessed using the kappa statistic.

Outcomes

Primary endpoint

- ▶ Overall antibiotic consumption.

Secondary endpoints

- ▶ Related to guideline accomplishments:
 - Unnecessary antibiotic prescriptions in diagnosed upper respiratory tract infections.
 - Unnecessary antibiotic prescriptions in diagnosed urinary tract infections.
 - Adequacy of antibiotic prescriptions.
- ▶ Related to safety:
 - Reattendance to the GP within 30 days after the first GP visit.
 - Attendance to the emergency room for any cause within 30 days of the first GP visit.
 - Hospital admissions for any cause within 30 days after the first GP visit.

Definitions

- ▶ An unnecessary prescription will be considered as follows:
An antibiotic prescribed for upper respiratory infections, which is in disagreement with the local antibiotic guidelines, or an antibiotic prescribed for asymptomatic bacteriuria, which is defined as having a positive urine culture with $\geq 10^5$ CFU/mL of a uropathogen in patients without signs or symptoms of urinary tract infection (dysuria, urinary frequency or urgency, suprapubic pain, fever or flank pain). Pregnant women and patients undergoing urological intervention will be excluded.²³
- ▶ The adequacy of antibiotic therapy will be considered when the prescription fulfils the local guidelines: type of antibiotic +dose+ length of therapy.

Data collection

Monthly DHD²⁴ will be obtained from the dispensing data of the electronic prescribing system of the Catalan Institute of Health.

Information regarding the secondary outcomes will be obtained from patients who had the predefined ICD-10 CM codes in the electronic medical records, and visited on the last working day of every month in each participating centre during the study period. The following variables will be collected: demographics, the Charlson score, type of infection, antibiotics prescribed, doses and length of antibiotic therapy, reattendance to GP, attendance to the emergency room and hospital admission. All included patients will be followed up for 30 days after the GP visit. To ensure data completeness, a telephone call will be allowed if any crucial data are missing from the electronic medical record.

The number of telephone calls received by the ID expert per month and centre, and the number of participants to

biweekly meetings with the expert per centre will also be collected.

All data will be recorded by a study investigator (MR) on a standardised data abstraction form using RedCap (*Research Electronic Data Capture*) hosted at IDIBELL, a secure web application for building and managing online databases.²⁵

Sample size

The study will be conducted in six centres of the health-care area, three in each study arm, implying a coverage of 147 644 inhabitants (37% of the referral population, 402 657 inhabitants). The consumption of antibiotics in 2017 was 8.94 DHD, and this study is expected to reduce this consumption by 10% in the intervention group. The number of three clusters per arm will allow rejection of the null hypothesis of equal consumption with a power of 80%, assuming a moderate intracluster correlation of 0.2, an intracluster variance of 4 and a mean difference of 1 DHD. Type I error will be set at 5%.

Statistical analysis

A descriptive analysis will be performed on the monthly consumption of antibiotics by the study group (standard and advanced AMS), time and cluster. The monthly consumption of antibiotic evolution will be represented on a graph by months, and a smoothed curve will be estimated using locally weighted smoothing.

Antibiotic consumption will be compared according to the study group using a time series model. The dependent variable will be the monthly consumption of antibiotics expressed in DHD and the independent variable the study arm. In the estimation of the model, the seasonality, trend, and first and second-order lags of the series will be analysed. In addition, the use of hierarchical models owing to cluster design will be considered.

A descriptive analysis of the demographic and clinical profiles of the patients surveyed will be performed by each study arm. A McNemar test will be used to compare the groups: the percentage of patients with an unnecessary prescription in diagnosed upper respiratory tract infections, with an unnecessary prescription in diagnosed urinary tract infections, with an adequate prescription according to local guidelines, who revisited the GP or the emergency room within 30 days after the initial GP visit and with hospital admission for any reason within 30 days after the initial GP visit. Additionally, log-binomial regression models will be performed to estimate the effect of the intervention in terms of risk on the aforementioned outcomes adjusted by patients' clinical profiles. To estimate models, patients nested in primary care centres will be accounted; therefore, a correction of the standard errors will be conducted using the variance-covariance matrix.

Data management and statistical analysis will be performed using the statistical package R V.4.0.1 or higher.

Patient and public involvement

To define the main strategies that have been included in the AMS, a survey was sent to the principal investigators of primary care centres (centre leaders). They also participated in the elaboration of the educational materials. Patients were not involved in this protocol.

ETHICS AND DISSEMINATION

This research will be conducted under the standards of good clinical practices following the principles of the Declaration of Helsinki, as well as the current Spanish legislation applicable to this type of study. This study was approved by the Ethics Committee of HUB and the Foundation University Institute for Primary Health Care Research Jordi Gol (IDIAPJGol), who waived the need to obtain informed consent since the intervention is aimed for a GP who will be previously informed of the objective and other relevant aspects of the study (REF. PR277/19-REF. 4R20/26).

The management of clinical data of the participants in this research as well as that of associated professionals and GPs will be conducted following the establishment of the Organic Law 3/2018, 5 December and Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on Data Protection. Based on these regulations, the sponsor will guarantee the protection of the confidentiality of both the patients and doctor associated with the programme.

The data collection sheets will be identified using a code. The name of the doctor or patient will not appear in any document, publication or communication of the study results. GPs will not receive any incentives for their participation in the study.

Publication plans

The sponsor commits to publishing data within 12 months of the completion of the study. The results will be analysed and reported under the Consolidated Standards of Reporting Trials guidelines. Preliminary results will be communicated in international and national ID, primary care and hospital pharmacy conferences. The results will be made available to the participants, professionals from each centre and funders.

Protocol amendments

Any major protocol modifications will be notified to the clinical research ethics committees, following Spanish legislation. After approval, all the participant centres will be informed.

Expected impact

This trial will explore whether including ID experts within primary care AMS programme teams can help improve the quality and quantity of antibiotic consumption. This strategy has been widely explored at the hospital level; however, has rarely been explored in primary care settings.

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