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Quasiexperimental intervention study protocol to optimise the use of new antibiotics in Spain: the NEW_SAFE project

Zaira R Palacios-Baena ,[1] Lucia Valiente de Santis,[2] Natalia Maldonado,[1] Clara M Rosso-Fernández,[3] Irene Borreguero,[3] Carmen Herrero-Rodríguez,[4] Salvador López-Cárdenas,[5] Franciso J Martínez-Marcos,[6] Andrés Martín-Aspas,[7] Patricia Jiménez-Aguilar,[8] Juan J Castón,[9] Francisco Anguita-Santos,[10] Guillermo Ojeda-Burgos,[11] M Pilar Aznarte-Padial,[12] Julia Praena-Segovia,[13] Juan E Corzo-Delgado,[14] M Ángeles Esteban-Moreno,[15] Jesús Rodríguez-Baño,[1,16] Pilar Retamar[1,16]

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For numbered affiliations see end of article.

Correspondence to
Dr Zaira R Palacios-Baena; zaira.palacios.baena@hotmail.com

ABSTRACT

Introduction Ceftaroline, tedizolid, dalbavancin, ceftazidime-avibactam and ceftolozane-tazobactam are novel antibiotics used to treat infections caused by multidrug-resistant pathogens (MDR). Their use should be supervised and monitored as part of an antimicrobial stewardship programme (ASP). Appropriate use of the new antibiotics will be improved by including consensual indications for their use in local antibiotic guidelines, together with educational interventions providing advice to prescribers to ensure that the recommendations are clearly understood.

Methods and analysis This study will be implemented in two phases. First, a preliminary historical cohort (2017–2019) of patients from 13 Andalusian hospitals treated with novel antibiotics will be analysed. Second, a quasiexperimental intervention study will be developed with an interrupted time-series analysis (2020–2021). The intervention will consist of an educational interview between prescribers and ASP leaders at each hospital to reinforce the proper use of novel antibiotics. The educational intervention will be based on a consensus guideline designed and disseminated by leaders after the retrospective cohort data have been analysed. The outcomes will be acceptance of the intervention and appropriateness of prescription. Incidence of infection and colonisation with MDR organisms as well as incidence of *Clostridioides difficile* infection will also be analysed. Changes in prescription quality between periods and the safety profile of the antibiotics in terms of mortality rate and readmissions will also be measured.

Ethics and dissemination Ethical approval will be obtained from the Andalusian Coordinating Institutional Review Board. The study is being conducted in compliance with the protocol and regulatory requirements consistent with International Council of Harmonisation E6 Good Clinical Practice and the ethical principles of the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and disseminated at national and international conferences.

Strengths and limitations of this study

- This study will implement an educational intervention by using a consensus guideline.
- A Delphi methodology survey will be used for the creation of the consensus guideline.
- This approach is useful for controlling the prescription of antibiotics by exploring the relation between antibiotic consumption and incidence of multidrug-resistant pathogens.

Trial registration number NCT03941951; Pre-results.

INTRODUCTION

In the last decade, the rate of infections caused by multidrug-resistant (MDR) pathogens has increased, together with the morbidity, mortality and costs associated with them. Indeed, antimicrobial resistance is considered today to be one of the most important public health problems worldwide.[1 2] The WHO has developed a list of the priority organisms to guide research, as well as guidelines to encourage surveillance and the development of therapeutic strategies for treatment of MDR infections.[3] Based on these criteria, the following pathogens have been established as of critical priority: carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa; Enterobacterales* resistant to carbapenems and third-generation cephalosporins; vancomycin-resistant *Enterococcus faecium* (VREf); and methicillin-resistant *Staphylococcus aureus* (MRSA). Against this background, the WHO is urging the international community to develop strategies to

Table 1 Target antibiotics for the study

Antibiotic	Activity (multidrug-resistant pathogen)	Indications approved (agency)
Ceftaroline	MRSA, VR *Enterococcus faecalis* (not VR *E. faecium*)	ABSSSI (EMA, FDA) CABP (EMA, FDA)
Tedizolid	MRSA, VRE	ABSSSI (EMA, FDA)
Dalvabancin	MRSA, VRE	ABSSSI (EMA, FDA)
Oritavancin	MRSA, VRE	ABSSSI (EMA, FDA)
Delafloxacin	MRSA	ABSSSI (FDA)
Ceftolozane-tazobactam	ESBL and AmpC-producing Enterobacterales and *P. aeruginosa*	cIAI, cUTI (EMA, FDA)
Ceftazidime-avibactam	ESBL, AmpC, KPC, OXA-48-producing Enterobacterales and *P. aeruginosa*	cIAI, cUTI (EMA; FDA) HAP/VAP (EMA)
Meropenem-vaborbactam	ESBL, AmpC, KPC-producing Enterobacterales and *P. aeruginosa*	cUTI (EMA, FDA) cIAI, HAP/VAP, gram negatives with limited options (EMA)
Imipenem-relebactam	ESBL, AmpC, KPC-producing Enterobacterales and *P. aeruginosa*	cUTI, cIAI with limited options (FDA)
Eravacycline	Enterobacterales*	cIAI (EMA, FDA)
Plazomicin	Enterobacterales, *P. aeruginosa**	cUTI with limited options (FDA)

*Not affected by beta-lactamases.
ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections; EMA, European Medicines Agency; ESBL, extended-spectrum beta-lactamases; FDA, Food and Drug Administration; HAP, hospital-acquired pneumonia; KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia; VRE, vancomycin-resistant Enterococcus spp.

prevent infection and optimise management of infections caused by these organisms by developing programmes to optimise antimicrobial use (antimicrobial stewardship programmes) and promoting the development of new molecules to treat these infections.[4–6]

Treatment of infections caused by *Enterobacterales* resistant to third-generation cephalosporins has been based on carbapenems, and infections caused by carbapenem-resistant gram-negative bacteria on colistin-based regimens, frequently in combination with another active antibiotic such as an aminoglycoside, tigecycline, fosfomycin or carbapenems (if the MIC is low enough to be achieved by optimised dosing schemes).[7 8] With respect to VREf and MRSA, treatment has pivoted around glycopeptides, linezolid and daptomycin.[9] In the last few years, some new antibiotics have been introduced to the market. The novel antibiotics have specific indications approved by regulatory organisations, mostly based on the results of pivotal clinical trials (table 1). However, there is medical necessity in the treatment of other infections caused by MDR organisms and in these cases, novel antibiotics are frequently used 'off-label'. Some examples are the use of ceftaroline for endocarditis,[10 11] tedizolid for osteomyelitis[12] and ceftolozane/tazobactam for pneumonia,[13] intravascular infections[14] or patients with cystic fibrosis.[15] This type of use may lead to improved outcomes in patients when they are really needed, but also to increased rates of unexpected adverse events, faster development of resistance and higher acquisition costs. The risk of fast development of resistance to last-resort antibiotics against extensively-drug resistant (XDR) pathogens such as carbapenem-resistant gram negatives is particularly worrying.[16 17] Off-label use of antibiotics in general is known to be common,[18] and increases when antimicrobial resistance is more prevalent.[19] Consequently, off-label use of the new antibiotics is expected to be particularly high in settings where MDR pathogens are endemic, although to the best of our knowledge, the frequency and reasons for this have not so far been assessed. Antimicrobial stewardship programmes should therefore prioritise actions promoting appropriate use of the new antibiotics, which could lead to decreased antimicrobial resistance as well as improved patient outcomes.[20 21]

With the above considerations in mind, the aims of this study are to characterise the use of the new antibiotics in different Spanish hospitals in order to propose a consensus guideline for their use, and to implement a non-compulsory antimicrobial stewardship (AMS) intervention to facilitate adherence to the recommendations.

STUDY OBJECTIVES

The primary objective of the study will be to assess the impact of an AMS educational intervention on physicians prescribing some of the novel antibiotics available for MDR infections. The corresponding outcomes will be acceptance of the intervention and appropriateness of prescriptions.

Secondary objectives will include: (1) creation of a cohort of patients with complex infections caused by MDR microorganisms[22] treated with any of the novel antimicrobials; (2) to carry out a descriptive analysis

(epidemiological, clinical and prognosis) of the retrospective cohort; (3) to develop an Andalusian consensus document for the correct use of the novel antimicrobials, with particular focus on indications that exceed the officially approved ones; (4) to evaluate variables predicting mortality in a cohort of patients treated with the new antibiotics; (5) to evaluate the impact on the development of resistance of an AMS intervention on prescriptions of novel antibiotics; and (6) to analyse the safety of the use of novel antibiotics in a cohort of patients with bacteraemia caused by MDR and XDR organisms. The outcomes corresponding to these objectives are stated in table 2.

METHODS AND ANALYSIS

The Standard Protocol Items: Recommendations forInterventional Trials statement will be followed in order to standardise the trial[23] (see online supplementary table S1).

Study design, setting and study period

This project is conceived as a multicentre registry for target antibacterial antibiotics that have been commercially available in Spain since 2016, including ceftaroline, tedizolid, dalbavancin, ceftolozane-tazobactam and ceftazidime-avibactam; other antibiotics commercialised during the study period will be added. It is designed as an ambispective cohort study with a retrospective phase, including all prescriptions between January 2016 and December 2019, and a prospective phase, from January 2020 to December 2021. A time series analysis of monthly consumption data, measured as defined daily dose (DDD) per 1000 patient days, will enable exploration of the impact of the AMS intervention aimed at improving antibiotic use (see online supplementary table S2).

A 'safety cohort' of patients diagnosed with bloodstream infection (BSI) caused by MDR organisms (see below) during the study period and not treated with the target antibiotics will also be recruited. This safety cohort will be used as a comparator, in terms of safety and clinical outcomes, for patients in the target antibiotics cohort with BSIs caused by the same organisms (see below).

Thirteen tertiary public hospitals located in the region of Andalucía (Spain) will participate. All hospitals have active AMS programmes.

Patients

Patients will be included in the registry if any of the target antibiotics are prescribed in the corresponding study periods. Participants will be detected through the electronic prescribing systems at each hospital. There are no exclusion criteria.

Patients in the safety cohort will include all patients with BSI caused by carbapenem-resistant Enterobacterales and *P. aeruginosa*, MRSA or vancomycin-resistant *Enterococci* not treated with any of the target antibiotics. For the comparison, these patients will be compared with those in the registry with BSIs caused by the same organisms.

Table 2 Variables to be collected during the whole of the study period

Patient characteristics	Hospital, age, gender
	Chronic underlying conditions*
	Charlson Comorbidity Index
	Immunosuppressant antibiotics (past 3 months)
	Surgery (past month)
	Vascular catheter (past week)
	Urinary catheter (past week)
	Mechanical ventilation (past week)
	Pitt score
	Creatinine clearance, renal replacement therapy
Infection related	Acquisition type (community-acquired, community-onset but healthcare-associated,† nosocomial)
	Site of infection‡
	Presentation with sepsis or septic shock§
	Causative microorganism(s)
	Susceptibility
	Presence of bacteraemia
Prescription and management related	Antibiotic(s), start date, discontinuation date
	Dose, route
	Type of indication: prophylaxis, empirical, definitive
	Reasons for discontinuation: end of treatment, clinical failure, microbiological failure, adverse event, de-escalation, switch to oral, switch to a more convenient antibiotic for outpatient use, death
	Total defined daily doses
	Total antibiotic cost
	Source control
	Fluid resuscitation, amines administration
Secondary outcomes	Clinical and microbiological cure¶
	Development of resistance during treatment
	Recurrence, superinfection (until day 30)
	Length of hospital stay
	Adverse events (including *Clostridioides difficile* infection and acute kidney injury), severity

Continued

Table 2 Continued

Patient characteristics	Hospital, age, gender
	30-day mortality
Prescriber	Medical specialty
	Position
Evaluation/audit	Quality of prescription according to local protocol: fully appropriate, inappropriate (reasons: indication, route, dosing, duration), unnecessary.
	Quality of prescription according to consensus recommendations: fully appropriate, inappropriate (reasons: indication, route, dosing, duration), unnecessary (primary outcome).
	Off-label use (EMA label)
	Audit performed/not performed
	If audit performed, recommendation: none, discontinue, specific duration, change in dosing
	Adherence to recommendation: full/partial/none (primary outcome)
Classification of treatment	Empirical/definitive
Type of infection/indication	Site of infection Presence of bacteraemia
Severity of response syndrome	No sepsis Sepsis Septic shock
Dosing	(Specify if adjusted according to renal function)
Start and discontinuation dates	
Reason(s) for using the antibiotic specified in the chart	Failure of previous treatment Isolation of MDR pathogen

*According to chart.
†Acute or long-term care facility admission, invasive procedure or intravenous ambulatory therapy in the last 3 months.
‡According to standard clinical and microbiological criteria.
§Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).
¶Clinical cure: resolution of all new signs and symptoms related to the infection. Microbiological cure: negative follow-up cultures.
EMA, European Medicines Agency; MDR, multidrug resistant.

The exclusion criteria in this analysis include polymicrobial BSIs, death in <48 hours after initiation of active therapy or lack of treatment with at least one active antibiotic in the first 4 days after the blood cultures were taken. In order to avoid survivor bias, patients in the registry will only be included if the antibiotic of interest was started in the first 3 days after the blood culture was taken.

Variables and data collection

The variables to be collected are shown in table 2. The main endpoints for the registry study will include monthly pooled and hospital-specific DDD of the target antibiotics[18] per 1000 patient days; appropriateness of the prescription according to local protocol and consensus document (see definitions in table 2); rate of clinical and microbiological cure; rate of adverse events (including *Clostridioides difficile* infection); and mortality. The main endpoint for the comparative analysis in patients with bacteraemia will be 30-day mortality. Secondary outcomes will include length of stay and rate of severe adverse events.

The evaluation of the quality of prescriptions and outcomes will be assessed by one local and one external investigator. Discrepancies will be resolved by a third, external investigator. The data will be collected from electronic charts and entered into a secure electronic case report form.

Intervention

The intervention will be performed from January 2020 and will include: (1) development of a consensus document by a panel comprising one investigator per site with recommendations for the use of the target antibiotics. The recommendations will be based on data obtained in the retrospective part of the registry and a review of the literature. Because high-level evidence is expected to be lacking for the purposes of stewardship considerations, consensus will be achieved using the Delphi methodology, with three rounds of responses. The questions to be provided to the panel will be designed taking into account the clinical relevance of the decisions, the ecological impact, the costs of the antibiotics and the results obtained from the historical cohort; (2) the consensus document will be disseminated among participating hospitals using the channels provided by the public healthcare system and the Andalusian Society of Infectious Diseases, as well as the social media; (3) for each prescription, a prescribing audit will be undertaken with advice to prescribers. The audit will be performed in the first 24 hours after a prescription is made and will consist of a brief meeting (around 10 min) between a member of the AMS team (also a study subinvestigator) and the prescriber, and will be based on a semistructured interview aimed at evaluating the prescription according to the consensus document, followed by non-compulsory advice to modify the prescription when needed.

Timeline

Figure 1 shows the timeline of the study. The first 6 months are planned for start-up activities. The first analyses will take place at the beginning of 2020. The consensus guideline will be developed between January and September 2020. The final analysis is planned for October–December 2021. The safety cohort will collect information from 2017 to 2021. Inclusion and exclusion criteria of each cohort are included in box 1.

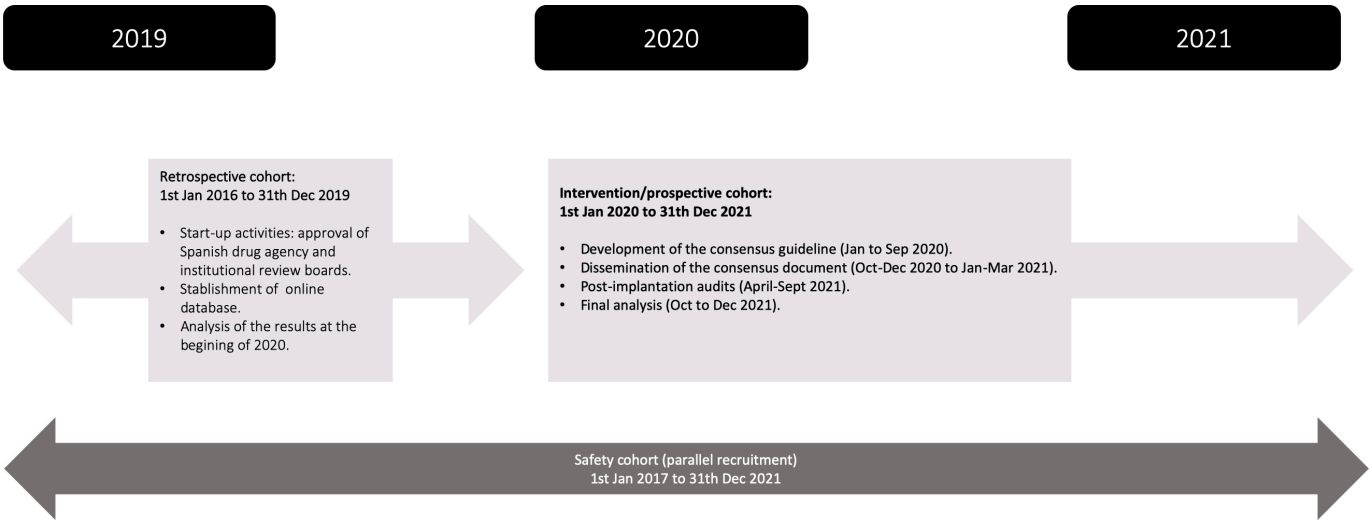

Figure 1 Timeline of NEW_SAFE project.

Box 1 Inclusion and exclusion criteria of the different cohorts

Retrospective cohort

Inclusion criteria

- All patients treated with ceftaroline, tedizolid, dalbavancin, ceftazidime-avibactam and ceftolozano-tazobactam
- Either as an outpatient or hospitalised
- Receiving at least 1 dose of antibiotic, either as empirical or targeted treatment
- ≥18 years old
- From January 2016 to December 2019

Exclusion criteria

- There are not exclusion criteria

Prospective/intervention cohort

Inclusion criteria

- All patients treated with ceftaroline, tedizolid, dalbavancin, ceftazidime-avibactam and ceftolozano-tazobactam
- Either as an outpatient or hospitalised
- Receiving at least 1 dose of antibiotic, either as empirical or targeted treatment
- ≥18 years old
- From January 2020 to December 2021
- Since spread of guideline with recommendations regarding the use of antibiotics

Exclusion criteria

- There are not exclusion criteria

Safety cohort

Inclusion criteria

- All episodes of clinically significant bacteraemia which have received any antibiotic due to: *Acinetobacter baumannii* resistant/intermediate susceptibility to any carbapenem; *Pseudomonas aeruginosa* resistant to ceftazidime and resistant/intermediate susceptibility to any carbapenem; *Enterobacterales* resistant/intermediate susceptibility to any carbapenem, *Enterococcus faecium* resistant to vancomycin and *Staphylococcus aureus* resistant to methicillin
- From January 2017 to December 2021
- ≥18 years old

Exclusion criteria

- There are not exclusion criteria

Sample size calculation

Between 2016 and 2018, a survey of the use of the target antibiotics was conducted in participating hospitals. Overall, 83 prescriptions of ceftazidime/avibactam, 55 of ceftolozane/tazobactam, 5 of ceftaroline, 43 of dalbavancin and 4 of tedizolid were reported. On the basis of these results and the increase in prescriptions from 2019, 400 prescriptions will be included in the registry. In the intervention cohort, we will include 200 patients, which will allow us to plot trends and perform time series analyses. We estimate that 300 episodes of BSIs caused by MDR pathogens will be included in the safety cohort. Estimated mortality is around 35%,[24] allowing 4–5 confounders to be included in the mortality model.

Statistical analysis

Frequencies and percentages of categorical variables will be calculated, with median and IQRs for continuous variables. Trends in bimonthly data of DDDs per 1000 patient days (72 measurements) will be evaluated by time series using autoregressive integrated moving average (ARIMA) models (24 measurements after the start of the intervention). The effect of the intervention and potential confounders will be analysed.

An exploratory comparison of the impact of the intervention on the proportion of appropriate prescriptions before and after the intervention will be performed by logistic regression models, including possible confounders (patient and infection-related characteristics) if potentially associated with the prescription, with different distributions in the before and after periods ($p<0.2$); for comparisons, the Student's t-test or Mann-Whitney U test will be performed for continuous variables with normal and non-normal distributions, and the χ^2 or Fisher's test for categorical variables, respectively.

Clinical outcomes between bacteraemic patients treated with target antibiotics and the control group of patients with MDR bacteraemia will be compared using linear, logistic or Cox regression, as appropriate. A propensity

score for use of target antibiotics will be calculated and used as covariate and matching variable. The final model will be adjusted by centre and comorbidities.

The analyses will be performed using IBM SPSS statistical software.

Patient and public involvement

Neither patients nor public authorities have been involved in the development of this study protocol.

ETHICS AND DISSEMINATION

The study is funded by the Consejería de Salud, Junta de Andalucía (Regional Government of Andalusia). It has been authorised by the Spanish Regulatory Agency (Agencia Española del Medicamento y Productos Sanitarios) and approved by the Andalusian Coordinating Institutional Review Board (CCEIBA), which waived the need to obtain written informed consent as the intervention will be performed as a quality improvement programme. In addition, contracts were signed by the management director of the hospitals. All data will be anonymised. The study will be conducted in compliance with the protocol and regulatory requirements consistent with International Council of Harmonization (ICH) E6 Good Clinical Practice and the ethical principles of the latest version of the Declaration of Helsinki adopted by the World Medical Association. The relevant ethics committee(s) will be notified of each substantial protocol amendment for approval prior to implementation. All data collected will be kept strictly confidential and in accordance with all relevant legislation on the control and protection of personal information. Participants will be identified on documentation by a unique ID number, not by name, in accordance with the European Regulation on data protection (EU 2016/679). All study-related information will be stored securely at the study sites.

Dissemination policy: final results will be publicly disseminated, regardless of the study outcomes. The results of this study will be published in peer-reviewed journals, as well as at national and international conferences. All participating hospitals agree with the dissemination policy.

DISCUSSION

The aims of this study will be to characterise the prescriptions of the newly commercialised antibacterial agents and to evaluate the impact of a non-compulsory intervention on prescribers. It is expected that these antibiotics will be frequently prescribed off-label[10–15] and based on heterogeneous criteria because they first became commercially available when there was medical necessity but very little evidence and experience of the potential benefits and consequences of their use. Our proposal therefore is to develop a guidance document, which will be the basic tool of the intervention, to help prescribers in their decision-making. We will also explore the outcomes of patients treated with these antibiotics in terms of mortality, failure, length of hospital stay, development of resistance and *C. difficile* infection.

New antibiotics are particularly welcome in the present situation because there is a real medical necessity for antibiotics active against some MDR bacteria (and a limited number of antibiotics in the pipeline).[3] However, new antibiotics should always be used prudently, for three reasons: first, some adverse events may have gone undetected in the pivotal trial; second, their efficacy may have been overestimated if higher risk patients were underrepresented in trials; and third, specifically in the case of antibiotics, the development and spread of resistance pose a very real threat. It is very important therefore to develop specific AMS interventions aimed at facilitating appropriate antibiotic use. The task of the stewardship team is to minimise barriers to use in situations where they can be beneficial, while at the same time helping avoid overuse.

Pharmaceutical companies have frequently promoted the development of registries to evaluate the efficacy and safety of their products. However, we think such studies would be better performed by independent academic investigators to avoid the conflicts of interest typical of industry-promoted phase 4 studies. To the best of our knowledge, this will be the first project aiming to characterise the use of all the newer antimicrobials and to evaluate an intervention on their use.

We conceive this project as a registry to provide information about the use of the target antibiotics and as an AMS intervention. In the field of infection control and ASM, quasiexperimental designs have been widely used.[25] Recommendations for designing studies to evaluate AMS interventions have recently been published.[26] A quasiexperimental design can provide an estimation of the impact of specific interventions and is used when randomisation is not feasible for ethical or logistical reasons. However, a quasiexperimental study has limitations. With respect to the methodology of the intervention, peer-to-peer interviews between prescribers and advisors have been shown to be effective for reducing consumption of antimicrobials.[27 28]

The study has some obvious limitations, such as lack of randomisation; we will try to control for the effect of confounders in multivariate analysis. Second, since the epidemiology may differ from site to site, the effect of the site will also be considered. Third, the recommendations provided by the AMS experts may be heterogeneous; to control for that possibility, the consensus document on the use of new antibiotics will be useful to help standardise the recommendations. The strengths of the study include its multicentre design and the inclusion of sites with active AMS programmes.

In conclusion, our study will evaluate the use of new antibiotics and evaluate an AMS intervention to optimise their use. We hope the findings will help improve

antimicrobial prescriptions and save the activity of novel antibiotics for future multiresistant infections.

TRIAL STATUS

Current protocol approved is V.1.1, dated 11 July 2019.

Dates of recruitment for the retrospective cohort: started 1 June 2019 and finished on 31 December 2019; and for the intervention cohort, 1 April to 30 September 2021.

Author affiliations
[1]Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena/ Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain
[2]Unidad Clínica de Enfermedades Infecciosas, Hospital Universitario Regional de Málaga, Málaga, Spain
[3]Unidad de Investigación Clínica y Ensayos Clínicos (CTU), Hospital Universitario Virgen del Rocío-Macarena, Seville, Spain
[4]Unidad Clínica de Enfermedades Infecciosas, Complejo Hospitalario de Jaén, Jaén, Spain
[5]Unidad Clínica de Enfermedades Infecciosas, Hospital de Jerez de la Frontera, Cádiz, Spain
[6]Unidad Clínica de Enfermedades Infecciosas, Hospital Juan Ramón Jiménez, Huelva, Spain
[7]Unidad Clínica de Enfermedades Infecciosas, Hospital Puerta del Mar, Cádiz, Spain
[8]Unidad Clínica de Enfermedades Infecciosas, Hospital Puerto Real, Cádiz, Spain
[9]Unidad Clínica de Enfermedades Infecciosas, Hospital Universitario Reina Sofía, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Córdoba, Spain
[10]Unidad Clínica de Enfermedades Infecciosas, Hospital San Cecilio, Granada, Spain
[11]Unidad Clínica de Enfermedades Infecciosas, Hospital Virgen de la Victoria, Málaga, Spain
[12]Unidad Clínica de Farmacia, Hospital Virgen de las Nieves, Granada, Spain
[13]Unidad de Gestión Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen del Rocío/ Instituto de Biomedicina de Sevilla (IBIS), Seville, Spain
[14]Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen de Valme, Seville, Spain
[15]Unidad de Gestión Clínica de Enfermedades Infecciosas y Microbiología, Hospital de Torrecárdenas, Almería, Spain
[16]Departamento de Medicina, Universidad de Sevilla, Sevilla, Spain

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Contributors JR-B, PR, LVdS, CH-R, SL-C, FJM-M, AM-A, PJ-A, JJC, FFA-S, GO-B, PA-P, JP, MAE-M and JECD conceived the study. ZRP-B, LVdS, JR-B and PR designed the study. ZRP-B obtained funding for the research and wrote the first draft of the manuscript. PR, LVdS and ZRP-B are the study coordinators and ZRP-B is the leader of the coordinating team. NM is also helping with coordination tasks. CMR-F is the coordinator of the Clinical Trials Unit and IBB is the project manager. All authors reviewed, edited and approved the final version of the paper.

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Competing interests ZRPB reports personal fees from Gilead for educational purposes outside the submitted work. PRG and JRB participated in accredited educational activities supported by Merck through unrestricted grants outside the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved on March 2019 by the Andalusian Coordinating Institutional Review Board (CCEIBA). The study has been registered in ClinicalTrials.gov and was approved in May 2019. The CCEIBA also approved an amendment of the protocol in September 2019 (version 1.1, 11 July 2019).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Zaira R Palacios-Baena http://orcid.org/0000-0002-1713-6807

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