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A quasi-experimental intervention study protocol to optimize the use of new antibiotics: the NEW_SAFE project.

Running title: quasi-experimental study to optimize the use of new antibiotics.

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Keywords: antimicrobial stewardship, intervention, quasi-experimental study, novel antibiotics.

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ABSTRACT:

Introduction: ceftaroline, tedizolid, dalbavancin, ceftazidime-avibactam and ceftolozane-tazobactam are novel antibiotics used for infections due to multidrug resistance pathogens (MDR). Its use should be supervised and monitored as part of antimicrobial stewardship programme (ASP) in order to avoid their incorrect use. The inclusion in the local antibiotic guidelines of consensual indications for these antibiotics, as well as the educational interventions with advices directed to the prescribers for the assimilation of these recommendations, will favour the adequate use of them.

Methods and analysis: a preliminary historical cohort of patients treated with novel antibiotics will be analysed. Then, a quasi-experimental intervention study will be developed with an interrupted time-series analysis. The study was carried out in 13 hospitals in Andalusia. The intervention consisted in an educational interview between prescribers and leaders on ASP from each hospital to reinforce the proper use of novel antibiotics based in a consensus guideline previously designed and spread by the leaders. The outcomes are the acceptance of the intervention and the appropriateness of prescription. Incidence of infection and colonisation by MDR as well as incidence of *Clostridioides difficile* infection was analysed. Changes in quality of prescription between periods and safety of antibiotics in terms of mortality rate and readmissions were also measured.

Ethics and dissemination: ethical approval has been obtained from the Andalusian Coordinating Institutional Review Board. This study has been registered in clinicaltrials.gov with the number NCT03941951. The results of this study will be published in peer-reviewed journals and disseminated at national and international conferences.

Discussion: this study supports the implementation of a behavioural intervention of ASP into clinical practice in order to maintain and spare the activity of novel antibiotics developed for infections due to multi-resistant microorganisms.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- This study will implement an educational intervention in order to spare the use of novel antibiotics by using a consensus guideline and promoting the correct use of them.
- A Delphi methodology survey will be distributed among infectious diseases physicians and leaders of antimicrobial stewardship programs of different hospitals and used for the creation of the consensus guideline.
- By exploring the relation between antibiotic consumption and incidence of MDR pathogens before and after the educational intervention we will demonstrate that this approach is useful for controlling the prescription of antibiotics.
- Changes in authorized indications of the antibiotics under study, its availability and epidemiology of MDR pathogens across different hospitals could act as confounders and can change the habit of prescription.

INTRODUCTION

In the last decade, the rate of infections caused by multidrug-resistant (MDR) pathogens has increased, and also their associated morbidity and mortality. In fact, antimicrobial resistance is considered nowadays among the most important public health problems worldwide (1). The World Health Organisation (WHO) has established the priority microorganisms for research, as well as the guidelines to favour the surveillance and development of therapeutic strategies for their treatment (2). Based on these criteria, critical priority is established for *Acinetobacter baumannii* and *Pseudomonas aeruginosa* resistant to carbapenems; *Enterobacterales* resistant to carbapenems and third generation cephalosporins; vancomycin-resistant *Enterococcus faecium* (VREf); and methicillin-resistant *Staphylococcus aureus* (MRSA). In this context, WHO urges the international community to develop strategies to prevent and optimize the management of infections caused by these organisms through the development of programs to optimize the use of antimicrobials (antimicrobial stewardship programmes) and promoting the development of new molecules for their treatment (3, 4).

The treatment of infections caused by *Enterobacterales* resistant to third generation cephalosporins have been based on carbapenems, and that of gram-negative bacteria resistant to carbapenems, on colistin-based regimens, frequently in combination with another active drug such as aminoglycosides, tigecycline, fosfomycin or carbapenems (if the MIC was low enough to be reachable by optimized dosing schemes) (5, 6). Regarding VREf and MRSA, treatment pivoted on glycopeptides, linezolid and daptomycin (7). In the last years, some new drugs have been commercialized; these novel antibiotics have specific indications approved by regulatory organisms, mostly based on the results of pivotal clinical trials (Table 1). However, the fact that there is a medical need in the treatment of other infections when caused by MDR microorganisms, they are not infrequently used “off-label”. Some examples are the use of ceftaroline for endocarditis (8, 9), tedizolid for osteomyelitis (10) and ceftolozane/tazobactam for pneumonia (11), intravascular infections (12) or in patients

with cystic fibrosis (13). Such use might lead to improved outcomes of patients when really needed but also to increased rates of adverse events, faster development of resistance and higher healthcare costs. The risk of fast development of resistance to last resorts against extensively-drug resistant (XDR) pathogens such as carbapenem-resistant Gram negatives is particularly worrisome (14, 15). In fact, off-label use of antibiotics in general is known to be frequent (16) and increases when antimicrobial resistance is more prevalent (17). Therefore, off-label use of the new antibiotics is expected to be particularly high in which MDR bacteria are endemic, but to the best of our knowledge, the frequency and reasons for this has not been assessed. Therefore, antimicrobial stewardship programmes should prioritize actions promoting the appropriate use of new drugs.

On the other side, the consumption of broad-spectrum antibiotics is expected to correlate with the rates of the targeted resistant bacteria, as shown in some studies (18), and this would be the case with new antibiotics. However, this is not always the case (19) because of differences in availability of the new drugs, costs issues and antimicrobial stewardship (AMS) activities.

With the above considerations, the aim of this study is to characterise the use of new antibiotics in different Spanish hospitals in order to inform a consensus document for their use, and implement a non-taxative AMS intervention to facilitate adherence to the recommendations.

STUDY OBJECTIVES

The primary objective of the study is to assess the impact of an educational antimicrobial stewardship (AMS) intervention over prescribers who prescribes some of the novel antibiotics available for MDR infections. The corresponding outcome are the acceptance of the intervention and the appropriateness of prescription.

Secondary objectives include: a) to create a cohort of patients with complex infections by MDR microorganisms treated with any of the novel antimicrobials; b) to

carry out a descriptive analysis (epidemiological, clinical and prognosis) of the previous cohort; c) to develop a protocol and an Andalusian consensus document for the correct use of the novel antimicrobials, with particular focus on the indications exceeding those officially approved; d) to evaluate variables predicting mortality in a cohort of patients treated with new antibiotics; e) to evaluate the impact on the development of resistances of a AMS intervention on prescriptions of novel antibiotics; and f) to analyse the safety of the use of novel antibiotics on a cohort of patients with bacteremia by MDR and extremely resistant microorganisms.

METHODS AND ANALYSIS

The SPIRIT statement has been followed in order to standard the trial (20). (Table 3).

Study design, setting and study period

This project is conceived as a multicentre registry for target antibacterial drugs commercialised since 2016 in Spain, including ceftaroline, tedizolid, dalvabancin, ceftolozane-tazobactam and ceftazidime-avibactam; other drugs commercialised during the study period will be added. It is design as an ambispective cohort study, with a retrospective phase including all prescriptions from January 2016 to December 2019, and a prospective phase from January 2020 to December 2021. The monthly consumption data measured as DDD (defined daily dose) per 1,000 patient-days will be analysed as a time-series allowing to explore the impact of an AMS intervention aiming at improving their use.

In addition, a “safety cohort” of patients with bloodstream infection due to MDR organisms (see below) not treated with the target drugs diagnosed during the same time period in the participating hospitals will be used as comparator for patients in the target drugs cohort with bloodstream infections due to the same microorganisms regarding safety and clinical outcomes (see below).

Thirteen tertiary public hospitals located in Andalucía, Spain will participate. All hospitals have active AMS programmes.

Patients

Patients will be included in the registry if prescribed any of the target drugs during the corresponding study periods. The participants will be detected by the electronic prescription systems at each hospital. There are no exclusion criteria.

Patients in the safety cohort will include all patients with bloodstream infections (BSI) due to carbapenem-resistant Enterobacterales and *P. aeruginosa*, MRSA or vancomycin-resistant enterococci not treated with any of the target drugs. For the comparison, these patients will be compared with those from the registry with BSI due to the same microorganisms. Exclusion criteria for this analysis include polymicrobial BSI, death in <48 hours after the initiation of active therapy or lack of treatment with at least one active drug in the first 4 days after the blood cultures were taken. In order to avoid the survivor bias, patients in the registry will only be included if the drug of interest was started in the first 3 days.

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 defined daily doses (DDD) of the target drugs (16) per 1,000 patient-days; appropriateness of the prescription according to local protocol and consensus document and adequacy of the prescription; rate of clinical and microbiological cure; rate of adverse events; and mortality. The main endpoint for the outcome 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 solved by a third, external investigator. The data will be collected from the electronic charts and introduced in a secured electronic case report form.

Intervention

The intervention will be performed from January 2020 and will include: (a) development of a consensus document by a panel formed by one investigator per site, including recommendations for the use of the target antibiotics, based on data obtained in the retrospective part of the registry and a review of the literature. Because of high-level evidence is expected to be lacking for the purpose of stewardship considerations, consensus will be achieved using a Delphi methodology. The questions to be provided to the panel will be designed considering the clinical relevance of the decisions, the ecological impact and the costs of the drugs. Three rounds of responses will be performed. (b) The consensus document will be disseminated among the participating hospitals by the channels provided by the public healthcare system and the Andalusian Society of Infectious Diseases (SAEI), as well as by social media. And (c) audits will be performed for the prescriptions including advice. The audits will be performed in the first 24 hours after a prescription was made and will consist on a brief meeting (around 10 minutes) between a member of the AMS team (also a study sub-investigator) and the prescriber, and will be based on a semi-structured interview aimed at evaluating the prescription according to the consensus document, followed by a non-compulsory advice to modify the prescription if needed.

Timeline

Figure 1 describes the timeline of the study. The first 6 months are planned for start-up activities. First analyses will be hold at the beginning of 2020. The consensus guideline will be developed from January to 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 Table 1.

Sample size calculation

A survey was conducted in the participating hospitals about the use of the target drugs from 2016 to 2018; overall, 83 prescriptions of ceftazidime/avibactam, 55 of ceftolozane/tazobactam, 5 of ceftaroline, 43 of dalbavancin, and 4 of tedizolid were

reported. Based on these results and the increase in prescriptions from 2019, around 600 prescriptions will be included. This would allow to provide the trends and time series analysis. Based on the surveillance system data, we estimate that some 150 episodes of BSI due to the target MDRO organisms will be included, of which at least 50 will be treated with the target drugs, allowing. Expected mortality is around 35%, allowing the inclusion of 4-5 confounders for the mortality model.

STATISTICAL ANALYSIS

Frequencies and percentages of categorical variables, and median and interquartile ranges of continuous variables will be described. Trends in bimonthly data of DDD per 1,000 patient-days (72 measurements) will be evaluated as time-series using ARIMA models (24 measurements after the initiation of the intervention); the influence of the intervention and potential confounders will be analysed.

An exploratory comparison of the impact of the intervention in the proportion of appropriateness of prescriptions before and after the intervention will be performed by logistic regression models, in which potential confounders (patients' and infection features) will be included if potentially associated with the prescriptions and differently distributed in the before and after periods ($p<0.2$); comparisons will be performed using Student's T or Mann-Whitney U test for normally and not-normally distributed continuous variables, and Chi-square or Fisher's test for categorical ones, respectively.

Clinical outcomes will be compared between bacteraemic patients treated with target drugs and the control group of patients with bacteraemia due to MDR organisms using linear, logistic or Cox regression, as appropriate. A propensity score for use of target drugs will be calculated and used as covariate and matching variable.

The analyses will be performed using IBM SPSS Statistics software.

LEGAL AND ETHICAL CONSIDERATIONS

The study is funded by Consejería de Salud, Junta de Andalucía (Andalusian regional government). It was authorised classified by the Spanish Regulatory Agency (Agencia Española del Medicamento y Productos Sanitarios), and approved by the ethical review boards of the participating centres, which waived the need to obtain written informed consent as the intervention is performed as a quality improvement programme. In addition, contracts were signed by the management director of the hospitals. All data will be anonimysed. The study is being conducted in compliance with the protocol, regulatory requirements, International Council of Harmonization (ICH) E6 Good Clinical Practice and the ethical principles of the latest version of the Declaration of Helsinki, as adopted by the World Medical Association. Each substantial protocol amendment will be notified for approval to the relevant ethics committee(s) prior to implementation. The trial is registered with ClinicalTrials.gov as NCT03941951 (May 19, 2019). All data collected will be kept strictly confidential and in accordance with all relevant legislation on control and protection of personal information. The participants will be identified on documentation by a unique ID number, not by name, in agreement with the European Regulation on data protection (EU 2016/679). All study-related information will be stored securely at the study sites.

Patient and public involvement

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

DISCUSSION

The aims of this study are to characterise the prescriptions of the newly commercialised antibacterial agents and to evaluate the impact of a non-taxative intervention on the prescribers. These antibiotics are expected to be frequently prescribed off-label (9-13) and with heterogeneous criteria because their commercialisation starts in a situation in which there is a medical need but scarce

evidence and experience about the potential benefits and consequences of their use. Therefore, we propose to develop a guidance document as the base tool for the intervention in order to help prescribers in their decisions. We will also explore the outcomes of patients treated with these drugs in terms of mortality, failure, length of hospital stay, development of resistance or *C. difficile* infection.

New antibiotics are particularly welcome in the present situation, in which there is a real medical need for drugs active against some multidrug-resistant bacteria. However, the use of new drugs must always be prudent. First, because some adverse events may have been undetected in the pivotal trials; second, because their efficacy may have been overestimated if the higher-risk patients were underrepresented in the trials; and third, specifically in the case of antibiotics, development and spread of resistance is a real threat. Therefore, it is very important to develop specific AMS interventions aimed at facilitating their appropriate use. Stewardship teams are tasked to minimizing barriers for their utilization in situations in which they can be beneficial but at the same time should help avoid their 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, therefore avoiding the typical conflict of interest of the industry-promoted fase 4 studies. To the best of our knowledge, this would be the first project trying to characterize the use of all newer antimicrobials and evaluating an intervention for their use.

We conceived this project as a registry to inform about the use of the target drugs, and an AMS intervention. In the field of infection control and ASM, quasi-experimental designs have been widely used (21). Recently, recommendations for design of studies evaluating AMS interventions have been published (22). Such design may provide estimations about the impact of specific interventions and are used when randomisation is not feasible due to ethical or logistical considerations. However, quasi-experimental studies have limitations. Regarding the planned methodology for the intervention, peer

to peer interviews between prescribers and advisors have shown to be effective in decreasing the consumption of antimicrobials (23, 24).

The study has some obvious limitations, such as lack of randomization; we will try to control the effect of confounders in the multivariate analysis. The site effect will also be considered since their epidemiology may be different. Also, the recommendations provided by the AMS experts might be heterogeneous; to control that, the consensus document for the use of the new drugs will help in homogenizing the recommendations. Strengths include a multicentre design, and inclusion of sites with active AMS programmes.

In conclusion, our study will evaluate the use of new antibiotics and evaluate an AMS intervention to optimize their use. We hope the findings of this study will contribute to improve antimicrobial prescription and to spare the activity of novel antibiotics for future multi-resistant infections.

TRIAL STATUS

Current protocol approved is version 1.1 dated 11th July 2019.

Date recruitment began on 1st June and will finish on 31th December 2019 for retrospective cohort; and 1st April to 30th September 2021 for intervention cohort.

AUTHOR CONTRIBUTIONS

JRB, PRG, LVS, CHR, SLC, FJMM, AMA, PJA, JJCO, FAS, GOB, PAP, JPS and JECD conceived the study. ZRPB, LVS, JRB and PRG, design the study. ZRPB obtained the funding for the research and wrote the first draft of the manuscript. PR, LVS and ZRPB are the Study Coordinators and ZRPB is the leader of the Coordinator Team. NM is also helping with coordination tasks. CRF 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 INTEREST

ZRPB reports personal fees from Gilead for educational purpose outside this work. PRG and JRB participated in accredited educational activities supported by Merck through unrestricted grants, outside the submitted work. The other authors declared that they have no competing interests.

PATIENTS CONSENT FOR PUBLICATION

Not required

ETHICS APPROVAL

The study was approved on March 2019 by the Ethics Coordinating Committee of the Biomedical Research of Andalucía (CCEIBA). The study has been registered in ClinicalTrials.gov and approved in May 2019. CCEIBA also approved an amendment of the protocol at September 2019 (version 1.1, 11st July 2019). 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 national and international conferences. All the participants hospitals agree with the dissemination policy.

ACCESS TO DATA

Data is sustained in an electronic database located at www.lindd.es. Upon request, anonimysed participant data will be made available to researchers whose proposals meet the research criteria. It will be also considered requests for the protocol. Data may be requested until end of 2021 and could be downloaded by an official database administrator (Zaira Palacios, zaira.palacios.baena@hotmail.com). To gain access, data requestors must enter into a data access agreement.

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FIGURE LEGENDS

Figure 1. Timeline of NEW_SAFE project.

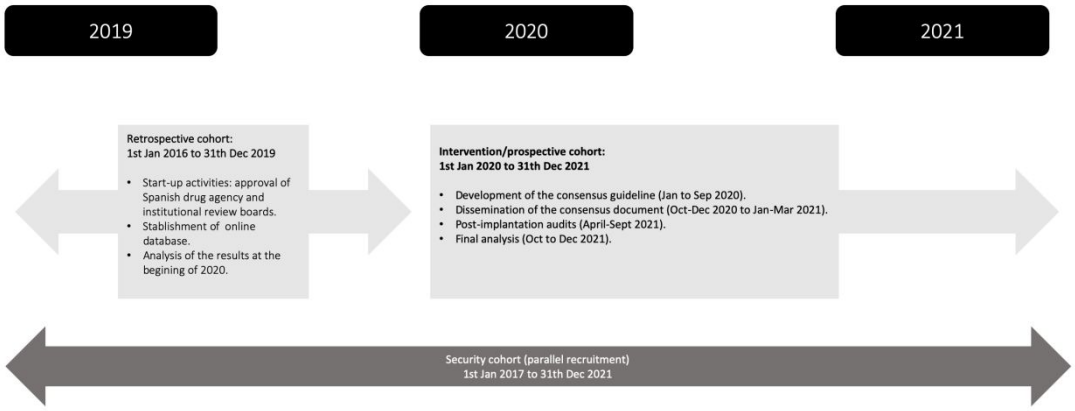

Table 1. Target drugs for the study.

Drug	Activity (multidrug-resistant organisms)	Indications approved (agency)
Ceftaroline	MRSA, VR *E. 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)
Plazomycin	Enterobacterales, P. aeruginosa*	cUTI with limited optins (FDA)

MRSA: methicillin-resistant Staphylococcus aureus. VRE: Vancomycin-resistant Enterococcus spp. ABSSSI: acute bacterial skin and skin structure infections. EMA:

European Medicines Agency. FDA: Food and Drugs Administration. CABP: community-acquired bacterial pneumonia. ESBL: extended-spectrum beta-lactamases. cIAI: complicated intra-abdominal infections. cUTI: complicated urinary tract infections. KPC: *Klebsiella pneumoniae* carbapenemase. HAP: hospital-acquired pneumonia. VAP: ventilator-associated pneumonia.

*Not affected by beta-lactamases.

Table 2. Variables to be collected.

Patients' features	Hospital, age, gender
	Chronic underlying conditions[1]
	Charlson comorbidity index
	Immunosuppresant drugs (last 3 months)
	Surgery (last month)
	Vascular catheter (last week)
	Urinary catheter (last week)
	Mechanical ventilation (last week)
	Pitt score
	Creatinine clearance, renal replacement therapy
Infection-related	Acquisition type (community-acquired, community-onset but healthcare-associated,[2] nosocomial)
	Site of infection[3]
	Presentation with sepsis or septic shock[4]
	Causative microorganism(s)
	Susceptibility
	Presence of bacteraemia
Prescription and management-related	Drug(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 drug for outpatient use, death
	Total defined daily doses

	Total drug cost
	Source control
	Fluid resuscitation, amines administration
Outcomes	Clinical and microbiological cure[5]
	Development of resistance during treatment
	Recurrence, superinfection (until day 30)
	Length of hospital stay
	Adverse events (including *C. difficile* infection and acute kidney injury), severity
	30-day mortality
Prescriptor	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.
	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 / no
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 drug is specified in the chart	Failure of previous treatment Isolation of a MDR

[1]According to chart. [2]Acute or long-term care facility admission, invasive procedure or intravenous ambulatory therapy in the last 3 months. [3]According to clinical and microbiological standard criteria. [4]Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). [5]Clinical cure: resolution of all new signs and symptoms related to the infection. Microbiological cure: negative follow-up cultures.

555 **Table 3. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents**

Section/item	ItemNo	Description	Page in the document
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	12
	2b	All items from the World Health Organization Trial Registration Data Set	--
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	--
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5

	6b	Explanation for choice of comparators	Non-applicable
Objectives	7	Specific objectives or hypotheses	5, 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Non-applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Non-applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Non-applicable

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Non-applicable
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Non-applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Non-applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Non-applicable

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Non-applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	--
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Non-applicable
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	--

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	--
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Non-applicable
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Non-applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7, 12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Non-applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Non-applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	--
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	--
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	30, 31
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Non-applicable

BMJ Open

A quasi-experimental intervention study protocol to optimize the use of new antibiotics in Spain: the NEW_SAFE project.

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Medical management, Infectious diseases
Keywords:	AUDIT, BACTERIOLOGY, Microbiology < BASIC SCIENCES, EDUCATION & TRAINING (see Medical Education & Training), INFECTIOUS DISEASES

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A quasi-experimental intervention study protocol to optimize the use of new antibiotics in Spain: the NEW_SAFE project.

Running title: quasi-experimental study to optimize the use of new antibiotics.

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Keywords: antimicrobial stewardship, intervention, quasi-experimental study, novel antibiotics.

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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 2 phases. First, a preliminary historical cohort (2017 to 2019) of patients from 13 Andalusian hospitals treated with novel antibiotics will be analysed. Second, a quasi-experimental intervention study will be developed with an interrupted time-series analysis (2020 to 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 has 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 (ICH) E6 Good Clinical Practice and the ethical principles of the latest version of the Declaration of Helsinki. This study has been registered on clinicaltrials.gov and assigned the number NCT03941951 (May 8, 2019). The results

will be published in peer-reviewed journals and disseminated at national and international conferences.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- This study will implement an educational intervention to improve the use of novel antibiotics in accordance with a predefined consensus guideline.
- A Delphi survey will be distributed among infectious diseases physicians and leaders of antimicrobial stewardship programs at different hospitals in Andalusia in order to create the consensus guideline.
- By exploring the relationship between antibiotic consumption and incidence of MDR pathogens before and after the educational intervention, we will show that this approach is useful for promoting prudent prescribing of new antibiotics.
- Changes to the authorized indications of the antibiotics under study, their availability and the epidemiology of MDR pathogens across different hospitals could act as confounders in prescribing patterns. These factors will be taken into account in the analysis and interpretation of study 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 World Health Organisation (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 prevent infection and optimize management of infections caused by these organisms by developing programmes to optimize antimicrobial use (antimicrobial stewardship programmes) and promoting the development of new molecules to treat these infections (4) (5), (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 optimized 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 organizations, 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 prioritize 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 AMS intervention to facilitate adherence to the recommendations.

STUDY OBJECTIVES

The primary objective of the study will be to assess the impact of an antimicrobial stewardship (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: a) creation of a cohort of patients with complex infections caused by MDR microorganisms (22) treated with any of the novel antimicrobials; b) to carry out a descriptive analysis (epidemiological, clinical and prognosis) of the retrospective cohort; c) 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; d) to evaluate variables predicting mortality in a cohort of patients treated with the new antibiotics; e) to evaluate the impact on the development of resistance of an AMS intervention on prescriptions of novel antibiotics; and f) to analyse the safety of the use of novel antibiotics in a cohort of patients with bacteremia caused by MDR and extensively drug resistant (XDR) organisms. The outcomes corresponding to these objectives are stated in table 2.

METHODS AND ANALYSIS

The SPIRIT statement will be followed in order to standardise the trial (23) (see supplementary material, 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 DDD (defined daily dose) per 1,000 patient days, will enable exploration of the impact of the AMS intervention aimed at improving antibiotic use (see supplementary material Table S2).

A “safety cohort” of patients diagnosed with bloodstream infection 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 bloodstream infections 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 bloodstream infections (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. 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 defined daily doses (DDD) of the target antibiotics (18) per 1,000 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 *C. 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: (a) 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; (b) 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 (ASID), as well as the social media; (c) 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 minutes) between a member of the AMS team (also a study sub-investigator) and the prescriber, and will be based on a semi-structured 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 Table 3.

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 MDRO BSIs will be included in the safety cohort. Expected mortality is around 35%, 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 interquartile ranges for continuous variables. Trends in bimonthly data of DDDs per 1,000 patient-days (72 measurements) will be evaluated by time series using 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 Chi-square 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.

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 ethical review boards of the participating centres, 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 anonymized. 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. The trial is registered with ClinicalTrials.gov as NCT03941951 (May 8, 2019). 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.

Patient and public involvement

Neither patients nor public authorities will be involved in the development of the study protocol.

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 poses 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 minimize 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 characterize 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, quasi-experimental designs have been widely used (24). Recommendations for designing studies to evaluate AMS interventions have recently been published (25). A quasi-experimental 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 quasi-experimental 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 (26), (27).

The study has some obvious limitations, such as lack of randomization; 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 optimize their use. We hope the findings will help improve antimicrobial prescriptions and save the activity of novel antibiotics for future multi-resistant infections.

TRIAL STATUS

Current protocol approved is version 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 CONTRIBUTIONS

JRB, PRG, LVS, CHR, SLC, FJMM, AMA, PJA, JJCO, FAS, GOB, PAP, JPS, MAEM and JECD conceived the study. ZRPB, LVS, JRB and PRG designed the study. ZRPB obtained funding for the research and wrote the first draft of the manuscript. PR, LVS and ZRPB are the Study Coordinators and ZRPB is the leader of the Coordinating Team. NM is also helping with coordination tasks. CRF 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. The other authors declare that they have no competing interests.

PATIENT CONSENT FOR PUBLICATION

Not required

ETHICS APPROVAL

The study was approved on March 2019 by the Andalusian Biomedical Research Ethics Coordinating Committee (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).

ACCESS TO DATA

Data is held in an electronic database located at www.lindd.es. Anonymised participant data will be made available upon request to researchers whose proposals meet the research criteria. Requests for the protocol will also be considered. Data may be requested until the end of 2021 and can be downloaded by an official database administrator (Zaira Palacios, zaira.palacios.baena@hotmail.com). To gain access, data requestors must agree to the conditions of data access.

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Table 1. Target antibiotics for the study.

Antibiotic	Activity (multidrug-resistant pathogen)	Indications approved (agency)
Ceftaroline	MRSA, VR *E. 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)

MRSA: methicillin-resistant Staphylococcus aureus. VRE: Vancomycin-resistant Enterococcus spp. ABSSSI: acute bacterial skin and skin structure infections. EMA:

European Medicines Agency. FDA: Food and Drug Administration. CABP: community-acquired bacterial pneumonia. ESBL: extended-spectrum beta-lactamases. cIAI: complicated intra-abdominal infections. cUTI: complicated urinary tract infections. KPC: *Klebsiella pneumoniae* carbapenemase. HAP: hospital-acquired pneumonia. VAP: ventilator-associated pneumonia.

*Not affected by beta-lactamases.

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

Patient characteristics	Hospital, age, gender
	Chronic underlying conditions[1]
	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,[2] nosocomial)
	Site of infection[3]
	Presentation with sepsis or septic shock[4]
	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[5]
	Development of resistance during treatment
	Recurrence, superinfection (until day 30)
	Length of hospital stay
	Adverse events (including *C. difficile* infection and acute kidney injury), severity
	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

[1]According to chart. [2]Acute or long-term care facility admission, invasive procedure or intravenous ambulatory therapy in the last 3 months. [3]According to standard clinical and microbiological criteria. [4]Third International Consensus Definitions for Sepsis and

546 Septic Shock (Sepsis-3). [5]Clinical cure: resolution of all new signs and symptoms

547 related to the infection. Microbiological cure: negative follow-up cultures.

548

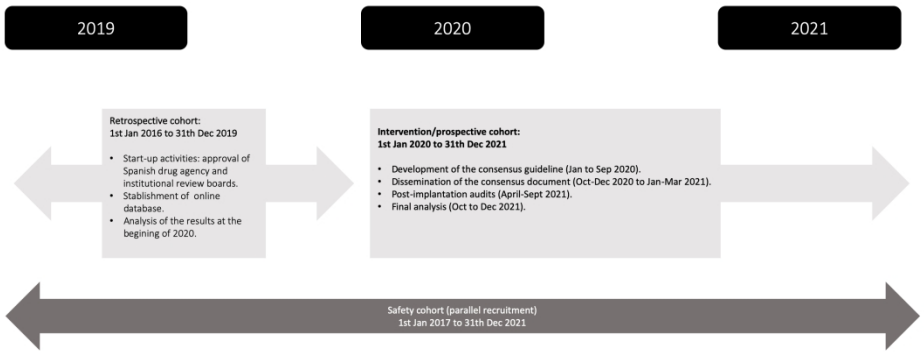
549 **Table 3. Inclusion and exclusion criteria of the different cohorts.**

Retrospective cohort
Inclusion criteria
All patients treated with ceftaroline, tedizolid, dalbavancin, ceftazidime-avibactam and ceftolozano-tazobactam
Either as an outpatient or hospitalized
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 hospitalized
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 bacteremia 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

FIGURE LEGENDS

Figure 1. Timeline of NEW_SAFE project.



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Supplementary material

Table S1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Page in the document
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	11
	2b	All items from the World Health Organization Trial Registration Data Set	--
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	--
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	Not applicable
Objectives	7	Specific objectives or hypotheses	6, 7

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7, 8, table 3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	--
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Not applicable
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	--
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Not applicable
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	--
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	--
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Not applicable
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Not applicable
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4
	31b	Authorship eligibility guidelines and any intended use of professional writers	--
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	--
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

Table S2. Defined daily dose (DDD) for antibiotics under study (1)**.**

Antibiotic	DDD	Unit	Administration
Dalbavancin	1.5	g	Parenteral
Ceftazidime/avibactam	6	g	Parenteral
Ceftolozane/tazobactam	3	g	Parenteral
Tedizolid	0.2	g	Parenteral
	0.2	g	Oral
Ceftaroline fosamil	1.2	g	Parenteral

1. Norwegian Institute of Public Health. WHO collaborating centre for drug statistics methodology [Internet]. Available from: https://www.whocc.no/atc_ddd_index/

BMJ Open

A quasi-experimental intervention study protocol to optimize the use of new antibiotics in Spain: the NEW_SAFE project.

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Medical management, Infectious diseases
Keywords:	AUDIT, BACTERIOLOGY, Microbiology < BASIC SCIENCES, EDUCATION & TRAINING (see Medical Education & Training), INFECTIOUS DISEASES

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A quasi-experimental intervention study protocol to optimize the use of new antibiotics in Spain: the NEW_SAFE project.

Running title: quasi-experimental study to optimize the use of new antibiotics.

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Keywords: antimicrobial stewardship, intervention, quasi-experimental study, novel antibiotics.

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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 2 phases. First, a preliminary historical cohort (2017 to 2019) of patients from 13 Andalusian hospitals treated with novel antibiotics will be analysed. Second, a quasi-experimental intervention study will be developed with an interrupted time-series analysis (2020 to 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 has 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 (ICH) E6 Good Clinical Practice and the ethical principles of the latest version of the Declaration of Helsinki. This study has been registered on clinicaltrials.gov and assigned the number NCT03941951 (May 8, 2019). The results

will be published in peer-reviewed journals and disseminated at national and international conferences.

ARTICLE SUMMARY:

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 MDR pathogens.

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 World Health Organisation (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 prevent infection and optimize management of infections caused by these organisms by developing programmes to optimize antimicrobial use (antimicrobial stewardship programmes) and promoting the development of new molecules to treat these infections (4) (5), (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 optimized 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 organizations, 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 prioritize 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 AMS intervention to facilitate adherence to the recommendations.

STUDY OBJECTIVES

The primary objective of the study will be to assess the impact of an antimicrobial stewardship (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: a) creation of a cohort of patients with complex infections caused by MDR microorganisms (22) treated with any of the novel antimicrobials; b) to carry out a descriptive analysis (epidemiological, clinical and prognosis) of the retrospective cohort; c) 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; d) to evaluate variables predicting mortality in a cohort of patients treated with the new antibiotics; e) to evaluate the impact on the development of resistance of an AMS intervention on prescriptions of novel antibiotics; and f) to analyse the safety of the use of novel antibiotics in a cohort of patients with bacteremia caused by MDR and extensively drug resistant (XDR) organisms. The outcomes corresponding to these objectives are stated in table 2.

METHODS AND ANALYSIS

The SPIRIT statement will be followed in order to standardise the trial (23) (see supplementary material, 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 DDD (defined daily dose) per 1,000 patient days, will enable exploration of the impact of the AMS intervention aimed at improving antibiotic use (see supplementary material Table S2).

A “safety cohort” of patients diagnosed with bloodstream infection 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 bloodstream infections 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 bloodstream infections (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. 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 defined daily doses (DDD) of the target antibiotics (18) per 1,000 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 *C. 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: (a) 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; (b) 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 (ASID), as well as the social media; (c) 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 minutes) between a member of the AMS team (also a study sub-investigator) and the prescriber, and will be based on a semi-structured 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 Table 3.

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 MDRO BSIs 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 interquartile ranges for continuous variables. Trends in bimonthly data of DDDs per 1,000 patient-days (72 measurements) will be evaluated by time series using 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 Chi-square 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 anonymized. 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. The trial is registered with ClinicalTrials.gov as NCT03941951 (May 8, 2019). 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 poses 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 minimize 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 characterize 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, quasi-experimental designs have been widely used (25). Recommendations for designing studies to evaluate AMS interventions have recently been published (26). A quasi-experimental 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 quasi-experimental 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 randomization; 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 optimize their use. We hope the findings will help improve antimicrobial prescriptions and save the activity of novel antibiotics for future multi-resistant infections.

TRIAL STATUS

Current protocol approved is version 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 CONTRIBUTIONS

JRB, PRG, LVS, CHR, SLC, FJMM, AMA, PJA, JJCO, FAS, GOB, PAP, JPS, MAEM and JECD conceived the study. ZRPB, LVS, JRB and PRG designed the study. ZRPB obtained funding for the research and wrote the first draft of the manuscript. PR, LVS and ZRPB are the Study Coordinators and ZRPB is the leader of the Coordinating Team. NM is also helping with coordination tasks. CRF 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.

FUNDING

The study is funded by the Consejería de Salud, Junta de Andalucía, grant PI-0077-2018. The investigators also receive funds for research from the Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Ciencia, Innovación y Universidades, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0001) through the Plan Nacional de I+D+i 2013-2016, co-financed by European Development Regional Fund “A way to achieve Europe”, Operative program Intelligent Growth 2014-2020.

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. The other authors declare that they have no competing interests.

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).

ACCESS TO DATA

Data is held in an electronic database located at www.lindd.es. Anonymised participant data will be made available upon request to researchers whose proposals meet the research criteria. Requests for the protocol will also be considered. Data may be requested until the end of 2021 and can be downloaded by an official database administrator (Zaira Palacios, zaira.palacios.baena@hotmail.com). To gain access, data requestors must agree to the conditions of data access.

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Table 1. Target antibiotics for the study.

Antibiotic	Activity (multidrug-resistant pathogen)	Indications approved (agency)
Ceftaroline	MRSA, VR *E. 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	cUTI, cIAI with limited options

	Enterobacterales and *P. aeruginosa*	(FDA)
Eravacycline	Enterobacterales*	cIAI (EMA, FDA)
Plazomicin	Enterobacterales, P. aeruginosa*	cUTI with limited options (FDA)

MRSA: methicillin-resistant Staphylococcus aureus. VRE: Vancomycin-resistant Enterococcus spp. ABSSSI: acute bacterial skin and skin structure infections. EMA: European Medicines Agency. FDA: Food and Drug Administration. CABP: community-acquired bacterial pneumonia. ESBL: extended-spectrum beta-lactamases. cIAI: complicated intra-abdominal infections. cUTI: complicated urinary tract infections. KPC: *Klebsiella pneumoniae* carbapenemase. HAP: hospital-acquired pneumonia. VAP: ventilator-associated pneumonia.

*Not affected by beta-lactamases.

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

Patient characteristics	Hospital, age, gender
	Chronic underlying conditions[1]
	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,[2] nosocomial)
	Site of infection[3]
	Presentation with sepsis or septic shock[4]
	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[5]
	Development of resistance during treatment
	Recurrence, superinfection (until day 30)
	Length of hospital stay
	Adverse events (including *C. difficile* infection and acute kidney injury), severity

	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

[1]According to chart. [2]Acute or long-term care facility admission, invasive procedure or intravenous ambulatory therapy in the last 3 months. [3]According to standard clinical and microbiological criteria. [4]Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). [5]Clinical cure: resolution of all new signs and symptoms related to the infection. Microbiological cure: negative follow-up cultures.

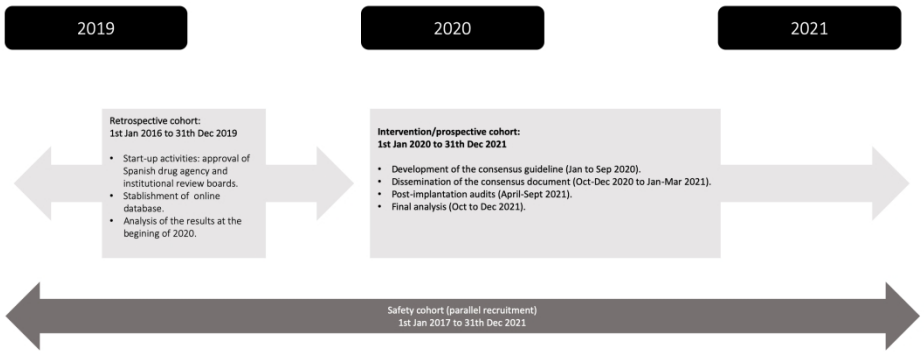
Table 3. Inclusion and exclusion criteria of the different cohorts.

Retrospective cohort
Inclusion criteria
All patients treated with ceftaroline, tedizolid, dalbavancin, ceftazidime-avibactam and ceftolozano-tazobactam
Either as an outpatient or hospitalized
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 hospitalized
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 bacteremia 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

FIGURE LEGENDS

Figure 1. Timeline of NEW_SAFE project.



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Supplementary material

Table S1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Page in the document
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	11
	2b	All items from the World Health Organization Trial Registration Data Set	--
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	--
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	Not applicable
Objectives	7	Specific objectives or hypotheses	6, 7

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7, 8, table 3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	--
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Not applicable
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	--
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Not applicable
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	--
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	--
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Not applicable
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Not applicable
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4
	31b	Authorship eligibility guidelines and any intended use of professional writers	--
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	--
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

Table S2. Defined daily dose (DDD) for antibiotics under study (1)**.**

Antibiotic	DDD	Unit	Administration
Dalbavancin	1.5	g	Parenteral
Ceftazidime/avibactam	6	g	Parenteral
Ceftolozane/tazobactam	3	g	Parenteral
Tedizolid	0.2	g	Parenteral
	0.2	g	Oral
Ceftaroline fosamil	1.2	g	Parenteral

1. Norwegian Institute of Public Health. WHO collaborating centre for drug statistics methodology [Internet]. Available from: https://www.whocc.no/atc_ddd_index/