Evaluation of the effectiveness and safety of oral vancomycin versus placebo in the prevention of recurrence of \textit{Clostridioides difficile} infection in patients under systemic antibiotic therapy: a phase III, randomised, double-blind clinical trial

Rafael San-Juan $^{1,2,3}$, Julia Origuens, $^1$ Karen Campion, $^1$ Mario Fernández-Ruiz, $^{1,2,3}$ Beatriz Díaz-Pollan, $^4$ Alejandro Callejas-Diaz $^5$, Giancarlo Candela, $^6$ Maria Angeles Orellana, $^7$ David Lora $^8$, Irene Llorente Muñoz $^9$, Maria Teresa Garcia, $^9$ Maite Martínez-Uña $^9$, Jose Miguel Ferrari, $^{10}$ Jose M Aguado$^{1,2,3}$

\textbf{ABSTRACT}

\textbf{Introduction} \textit{Clostridioides difficile} infection (CDI) is the most prevalent cause of nosocomial bacterial diarrhoea and it is strongly associated with antibiotic use. The recurrence of CDI is a growing medical problem. Data from real-life studies and one open label randomised clinical trial (RCT) suggest that secondary prophylaxis with oral vancomycin (SPV) during subsequent courses of systemic antibiotics is a promising approach for reducing the risk of CDI recurrence. Our aim is to confirm the role of SPV through a double-blind RCT.

\textbf{Methods and analysis} We will perform a phase III, multicentre, placebo-controlled RCT (PREVAN trial) in a 2:1 ratio in favour of SPV (experimental treatment), in four tertiary care hospitals in Spain. Adult patients (≥18 years) with a previous history of CDI in the previous 180 days and with requirement for hospitalisation and systemic antibiotic therapy will be randomly allocated to receive either 125 mg of oral vancomycin or placebo every 6 hours for 10 days. Patients will be followed for 60 days after the end of treatment to verify a reduction in the rate of CDI recurrence in the experimental group. We assume a recurrence rate of 5\% in the experimental group versus 25\% in the placebo group. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 104 subjects will be required in total (68 assigned to the SPV group and 34 to the placebo group).

\textbf{Ethics and dissemination} Ethical approval has been obtained from the Ethics Committee for Research with medicinal products of the University Hospital “12 de Octubre” (AC069/18) and from the Spanish Medicines and Healthcare Product Regulatory Agency (AEMPS, AC069/18), which is valid for all participating centres under existing Spanish legislation. The results will be presented at international meetings and will be made available to patients and funders.

\textbf{Strengths and limitations of this study}

⇒ A major strength of the study is the design double-blind placebo-controlled randomised clinical trial.
⇒ The target population is a subgroup of patients at a specially high risk of \textit{Clostridioides difficile} infection (CDI) recurrence.
⇒ The selected primary endpoint is CDI recurrence at 60 days which is well established and representative of the efficacy of secondary prophylaxis in these patients.
⇒ A major limitation would be the lack of specific study regarding the impact of secondary prophylaxis with oral vancomycin on the microbiota and the potential emergence of vancomycin-resistant \textit{Enterococcus}.
⇒ Another major limitation is the relatively small sample size was calculated on assumption of potential high rates of risk reduction based on the results of particular retrospective studies.

\textbf{Trial registration number} NCT05320068.

\textbf{INTRODUCTION}

\textit{Clostridioides difficile} infection (CDI) is the most prevalent cause of bacterial diarrhoea in the hospital environment, and it is strongly associated with exposure to antibiotics.\textsuperscript{1} Its incidence and severity has dramatically risen due to the irruption of hypervirulent strains (PCR ribotypes 027 and 078), the widespread use of antibiotics, the ageing of the population and the increase in comorbidity burden, among others.\textsuperscript{2}
The clinical spectrum associated with CDI range from mild, self-limiting diarrhoea to fulminant (pseudomembranous) colitis and toxic megacolon, leading to bowel perforation, sepsis and/or multiple organ failure. Nevertheless, recurrence is considered the major complication due to its high incidence (about 20–25% in different series from the USA and Europe\textsuperscript{4,23} and attributable impact on mortality and health costs.\textsuperscript{5,8–10} Recurrent CDI is most likely related to a persisting dysbiosis of the intestinal microbiota due to the infection itself and the exposure to broad-spectrum antibiotics, which promote a selective advantage for \textit{C. difficile} through additional disruption of the gut microbiome.\textsuperscript{3,11} Although these mechanisms are more evident during the first month after discontinuation of antibiotic therapy, the increased risk of CDI recurrence remains for several months.\textsuperscript{12,13} Several risk factors have been reported, such as advanced age, hospital-acquired CDI, duration of hospitalisation, impaired humoral immunity and the use of proton pump inhibitors.\textsuperscript{4,14} Current approaches for reducing the rate of CDI recurrence among high-risk patients are mostly based on the treatment of the initial CDI episode with fidaxomicin and the co-administration of bezlotoxumab (a monoclonal antibody against toxin B of \textit{C. difficile}).\textsuperscript{15–17} On completion of the standard course of therapy for CDI recurrence, a further preventive measure through restoration of intestinal microbiota by faecal microbiota transplantation has been proven to be safe and effective\textsuperscript{15,16} as are new commercial microbiota-based drugs as the recently approved by U.S. Food and Drug Administration (FDA) REBYOTA\textsuperscript{16} or SER-109 (which is composed of purified \textit{Firmicutes} spores).\textsuperscript{19}

Another proposed measure to prevent CDI recurrence is secondary prophylaxis in patients who need to be treated with broad-spectrum antibiotics. Such high-risk condition seems to be relatively common, since it has been reported that 5–45% of patients with a preceding CDI episode require additional hospital admission and systemic antibiotic therapy in the following 2 months.\textsuperscript{20,21} Fidaxomicin is currently the first agent of choice for the treatment of established CDI\textsuperscript{15,16} and theoretically could be the ideal candidate for secondary prophylaxis in view of its minimal effect on gut microbiota, its efficacy inhibiting sporulation and direct antimicrobial activity on spores in contrast to other available drugs for CDI as vancomycin or metronidazole.\textsuperscript{22} Nevertheless, although development of resistance is very rare, the intensive use of fidaxomicin as prophylaxis potentially increases this risk and could lead to potential treatment difficulties when CDI develops. Indeed, most of the available data supporting the effectiveness and safety of secondary prophylaxis in patients receiving antibiotic treatment is based on real-life observational experiences with oral vancomycin, typically in the context of hospital outbreaks.\textsuperscript{23–25} Recent meta-analyses of such evidence estimates an OR of CDI around 0.3 after secondary prophylaxis with oral vancomycin (SPV)\textsuperscript{26} and particular studies analysing the impact in the high risk profile of hospitalised patients with previous episodes of CDI receiving broad-spectrum antibiotic therapy reported a reduction in the rate of CDI recurrence ranging from 50% to 80%.\textsuperscript{23–25}

Only one randomised controlled trial (RCT) evaluating SPV for primary CDI prevention has been conducted to date.\textsuperscript{24} Of note, low dose vancomycin was used and the design was not blinded. The results confirmed the protective effect of SPV, with no cases of recurrence in the experimental arm over the next 2 months. The main theoretical concern of this strategy is the promotion of vancomycin-resistance in gut microbiota, mostly for enterococci. Although no clear increase in the incidence of infections due to vancomycin-resistant \textit{Enterococcus} (VRE) has been reported in the majority of studies,\textsuperscript{23,24,27–29} the use of low-doses vancomycin have been reported to be associated with VRE colonisation.\textsuperscript{30}

The lack of double-blind RCTs and the potential risk of emergence of VRE have probably led to the reluctance to universally recommend this approach. In view of such scarce evidence, no recommendation regarding SPV strategy is offered in Infectious Diseases Society of America guidelines.\textsuperscript{15} In the same line the 2021 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) panel does not support the routine use of prophylaxis with anti-CDI agents in patients on systemic antibiotic treatment either, although acknowledging that this strategy may be beneficial in selected patients at the highest risk of recurrence.\textsuperscript{16} Only the 2020 the American College of Gastroenterology guidelines consider this preventive approach in spite of admitting low quality of evidence supporting the recommendation.\textsuperscript{31}

**Objective**

To test the hypothesis of whether the use of SPV in patients with a preceding episode of CDI under systemic antibiotic therapy reduces the risk of CDI recurrence through a double-blind placebo-controlled RCT.

**METHODS AND ANALYSIS**

**Patients and public involvement**

Patients will not be involved neither in the enrolment and conduction of the trial, nor in the assessment of the interventions.

**Study design and setting**

We will perform a phase III, multicentre, double-blind, placebo-controlled RCT (PREVAN trial) in proportion 2:1 in favour of oral vancomycin (experimental treatment). Patients will be recruited from four tertiary care hospitals in Spain (a list of study sites is available in the online supplemental material). The trial has been registered in the EudraCT (2019-002677-57) and ClinicalTrials.gov databases. The protocol (PREVAN-1.4_01/08/2022) follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) initiative, and the results will be presented in accordance with...
the CONSORT (Consolidated Standards of Reporting Trials) statement.\textsuperscript{32, 33}

**Study population**

**Inclusion criteria**

- Age \( \geq 18 \) years.
- Previous history of CDI in the 180 days before study enrolment.
- Hospitalisation and need of systemic antibiotic therapy at full doses for \( \geq 24 \) hours due to suspected or confirmed infection.
- Providing informed consent.

**Exclusion criteria**

- Woman with childbearing capacity, pregnant woman or breastfeeding woman.
- Hypersensitivity to vancomycin.
- Inability to comply with study protocol.
- Critically ill condition or life expectancy lower than 30 days.
- Previous diagnosis of inflammatory bowel disease or any conditions that produce chronic diarrhoea.
- Fulfilment of the criteria for diarrhoea or diagnosis of CDI at the time of assessment for eligibility or in the previous 3 days.
- Therapy with oral vancomycin or any other agent with activity against *C. difficile* for \( > 48 \) hours in the previous 3 days.
- Prophylaxis with oral vancomycin or any other agent with activity against *C. difficile* within the 70 days before the assessment for eligibility.
- Systemic antibiotic therapy for \( \geq 72 \) hours before the assessment for eligibility.
- Ongoing enrolment in another RCT evaluating effectiveness of other drugs.
- Estimated duration of systemic antibiotic therapy \( > 4 \) weeks.
- Refusal to give informed consent.

**Intervention**

Hospitalised patients with a history of CDI in the preceding 180 days (index CDI) that require systemic antibiotic therapy will be offered enrolment in the study. Screening of these potential candidates will be performed through a cross-database Structured Query Language (SQL) script specifically built for the present study. This SQL query will be executed on a daily basis by matching the patients admitted to the hospital in the previous 24 hours with those diagnosed with CDI in the previous 180 days. Once written informed consent has been obtained, the participant will be randomly assigned to orally receive every 6 hours a hard capsule containing 125 mg of vancomycin or an identical-appearing capsule containing an inert placebo, for a total duration of 10 days. The study design is shown in figure 1, and the evaluation schedule is summarised in table 1.

**Outcomes**

The effectiveness of the intervention will be analysed in an intention-to-treat (ITT) manner in all randomised patients. All patients who receive at least one dose of treatment in either group will be included in the safety analysis.

![Figure 1](study-design.png)

*Figure 1* Study design. CDI, *Clostridioides difficile* infection.
Primary endpoints
We will assess the effectiveness of SPV to prevent CDI recurrence over the 60-day follow-up period. The main evaluated outcome will be the proportion of patients developing a new episode of CDI within the first 60 days after the end of therapy (EOT). CDI recurrence-free survival will also be measured.

An episode of CDI episode will be considered when both clinical and microbiological criteria are fulfilled:
1. Clinical criteria: An unexplained new episode of three or more loose stools within 24–48 hours (or more than 200 mL of loose stools in patients with colostomy bag).
2. Microbiological criteria: Detection of toxigenic *Clostridiodes difficile* (TCD) and/or its toxins through routine diagnostics methods in microbiology laboratories of participating centres following two-step algorithms recommended by the ESCMID including the following diagnostic tests: enzyme immunoassay for glutamate dehydrogenase (GDH), toxins A and B and detection of TCD by real-time PCR.

Secondary endpoints
In addition to the primary endpoint, we will also test the following outcomes during the duration of the study:
- Effectiveness of SPV to reduce the severity of recurrent CDI. The evaluated outcome will be the proportion of patients developing a new episode of severe CDI within the first 60 days after EOT. Severe CDI recurrence-free time will also be measured.
- Tolerance and safety of SPV. The evaluated outcome will be the proportion of patients with an adverse event (AE) and the proportion of patients voluntarily withdrawing from the RCT within the first 60 days after EOT.

Follow-up and data collection
Patients will be assessed at day 0 (screening visit) and at EOT (+72 hours from the last dose of study drug) by an infectious diseases specialist. Follow-up telephone interviews will be performed to assess new CDI or AEs at days 14 and 42 after EOT. Finally, a structured visit will be arranged at day 60 after EOT to verify the effectiveness and safety of the experimental treatment.

All study data will be collected and managed using MACRO Electronic Data Capture tools hosted at the University Hospital ‘12 de Octubre’ (https://macro.imas12.es/). MACRO is a secure, web-based software platform designed to support data capture for research studies. Authorised staff will be free to examine the records for quality assurance and audit purposes. Scheduled visits are detailed in table 1.

### Statistical analysis plan

#### Sample size
Prior data indicate a recurrence rate in patients with a previous history of CDI requiring systemic antibiotic therapy of about 25%.24 25 35 Assuming a CDI recurrence rate of 5% with SPV and an allocation 2:1 in favour to the experimental arm, and by using a unilateral test (H1: percentage of recurrence with oral vancomycin inferior than placebo) with a type I error probability of 5% and a statistical power of 80%, we estimate a sample size of 102 subjects (68 assigned to SPV and 34 to placebo). The sample size finally will be increased by 6 subjects (108 participants) anticipating a dropout rate of 5%.

#### Allocation
Participants will be assigned a study code linked to a treatment kit based on a random allocation sequence generated by the MACRO Electronic Data Capture tool. Assignment to the experimental or control group will be performed through a minimisation process with an adaptive structure that will take into account the following strata:
- Participating centre.
- Nature of the index CDI episode (first vs recurrent CDI).

The random allocation list with the assignment to vancomycin or placebo according to these strata and the 2:1 ratio criteria in favour of the experimental arm will

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<th>The evaluation schedule of the OREVAN trial</th>
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be previously performed with the SAS V.9.4 statistical software (SAS Institute, Cary, North Carolina, USA) and stored in the Research Institute Hospital ‘12 de Octubre’ (imas12). Only the non-blinded staff will have access to the allocation list.

Masking
The masking process will be carried out by the Department of Pharmacy of the University Hospital ‘12 de Octubre’ to ensure that participants, attending physicians and study staff (including researcher pharmacists) could not be aware of the treatment group to which the patient has been allocated during the randomisation process. Vancomycin and placebo capsules will look exactly the same as each other, in order to avoid the distinction between them. Each package will be exclusively identified by a randomisation code or kit. Neither the Department of Pharmacy at each participating centre nor the research team will have access to this code, except in case of emergency code break (unblinding).

Data analysis
The main analysis will be performed for the ITT population, which will include all randomised patients with a primary endpoint assessment, regardless of the treatment received. All patients who receive at least one dose of treatment will be included in the safety analysis.

Both the primary and secondary endpoints of effectiveness and safety will be assessed by a χ² unilateral test and a type I error probability (α) of 0.05. The adjusted relative risk for success will be calculated with 95% CIs. The absolute risk reduction with 95% CI will also be reported.

The outcomes of CDI-free and severe CDI-free survival will be assessed as time-dependent events and incidence density and HRs between experimental and placebo groups will be quantified. The association between study group and primary and secondary endpoints, adjusted for clinical covariates (including the type of index CDI episode and antibiotic therapy administered) will be evaluated using regression models. In addition, a set of subgroup analyses will be performed.

Monitoring
Monitoring plans
The data monitoring board will ensure the correct progress of the study in terms of safety, as well as the fulfilment of sample size assumptions.

Data Safety and Monitoring Board
An independent Data Safety and Monitoring Board (DSMB) will review safety data and provide advice about the continuation, modification and/or termination of the study, as well as adherence to the protocol, recruitment, outcomes and additional data related to participants’ safety. The DSMB will be composed by specialists in pharmacology, biostatistics and infectious diseases.

Adverse events reporting and quantification
An AE event will be considered if any injury related to medical management occurs during the patient’s participation in the study, even if it is not related to the study medication.

An adverse drug event (ADE) will be considered if any medication-related AE occurs during the patient’s participation in the study.

An adverse drug reaction will be considered if any AE occurs when the medication is used as directed and in the usual dosage.

Serious AE or reaction will be defined as an event or reaction that:
- Results in death.
- Is life-threatening.
- Causes persistent or significant disability.
- Causes a congenital anomaly/birth defect.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (not related to basal diseases), including emerging infections.

ADE of particular interest for the study
Taking into account the negligible systemic absorption of oral vancomycin there are no expected AEs specifically related to the experimental drug. Surveillance of faecal microbiota is not included in the present study. Surveillance of faecal colonisation with vancomycin-resistant enterococci (VRE) in not permitted either, as this event seems unlikely due to the extremely low VRE prevalence in Spain and the use of previously tested high therapeutic doses of vancomycin (125mg every 6 hours). Outbreaks with multidrug resistant organisms defined according to standard criteria in the four participating hospitals will be monitored over the follow-up.

Reporting
Any AE occurring during the patient’s participation in the trial will be recorded by the principal investigator at every scheduled visit. Principal investigator will record its occurrence in the electronic case report form: serious ADEs; any-grade AEs related to the study medication, in the opinion of the investigator; any-grade AEs leading to modification of study drug dosage or its interruption or early discontinuation; and AEs of particular interest for the study. All serious AEs will be notified to the pharmacovigilance unit and to the sponsor within 24 hours.

Trial status
The PREVAN trial opened the first study site on 21 March 2022. The first patient was enrolled on 25 May 2022. Recruitment and follow-up is expected to be completed by March 2024.

ETHICS
The RCT will be conducted in accordance with the principles of the most recent Declaration of Helsinki (agreed...
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by the 64th World Medical Association General Assembly in 2013), the Good Clinical Practice guidelines and the current local legislation.

The study was authorised by the Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS, 18–0905) and by the Ethic Committee for Research with medicinal products (CEIm) of the University Hospital ‘12 de Octubre’ (AC069/18).

The principal investigator or collaborator at each site will provide the participant with the information sheet, and he/she will explain the nature of the study and the objectives and clarify any doubts. Written informed consent will be obtained from all patients or from their legal representatives if they lack capacity before enrolment. Patients (or their representatives) will be free to withdraw from the trial at any time, as explicitly stated on the patient’s information sheet.

Patients’ personal and clinical information will be managed in accordance with European Regulation 2016/679 and Spanish legislation. The trial protocol was approved by the institutional research ethics committee (CEIm) on 28 March 2019 (the informed consent form and information sheet were also approved on the same date) and by the AEMPS on 8 April 2019.

Dissemination

We will communicate the final results of the PREVAN trial to international and national conferences on Infectious Diseases and Clinical Microbiology and publications in peer-reviewed journals. Moreover, the results will be made available to patients, caregivers and funders through press and social media communication. A corporate Twitter account will also be created for direct communication with the general population and other healthcare professionals. Any formal presentation or publication of data collected from this study will be considered as a joint publication by the participating investigators and will follow the recommendations for authorship of the International Committee of Medical Journal Editors.

Protocol amendments

Any protocol modifications will not become effective until approved by relevant authorities and by the institutional CEIm. Exceptions are changes to protect patients from imminent harm and those concerning exclusively logistic or administrative aspects.

Author affiliations

1Department of Infectious Diseases, Hospital Universitario “12 de Octubre”, Madrid, Spain
2CIBERINFEC, ISCIII - CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain
3Instituto de Investigacion Biomédica del Hospital Universitario 12 de Octubre, Madrid, Spain
4Department of Internal Medicine, La Paz University Hospital, Madrid, Spain
5Department of Internal Medicine, Puerta de Hierro University Hospital of Majadahonda, Majadahonda, Spain
6Department of Internal Medicine, Severo Ochoa University Hospital, Leganés, Spain
7Department of Microbiology, Hospital Universitario “12 de Octubre”, Madrid, Spain
8Clinical Research Unit (I+12), Hospital Universitario 12 de Octubre, Madrid, Spain
9SCREN, Fundacion para la Investigacion Biomédica del Hospital Universitario 12 de Octubre, Madrid, Spain
10Department of Pharmacy, Hospital Universitario “12 de Octubre”, Madrid, Spain

Contributors J0 and RS-J are the sponsors and coordinators of the CT. RS-J, J0 and JMA conceived and designed the study protocol. RS-J, J0, MF-R and KC wrote and revised the manuscript. DL and MTG designed and wrote statistical analysis plan including randomisation strategies and electronic database. ILM critically reviewed the protocol, RS-J, MF-R, KC, MAO, BD-P, AC-D and GC contributed to the acquisition of data. MM-U and JMF coordinated the pharmaceutical aspects of the study and the CT protocol. All authors have read and approved the final manuscript.

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Competing interests None declared.

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ORCID iDs

Rafael San-Juan http://orcid.org/0000-0003-3446-1991
Beatriz Diaz-Pollan http://orcid.org/0000-0002-7241-4208
Alejandro Callejas-Diaz http://orcid.org/0000-0002-7516-8348
David Lora http://orcid.org/0000-0002-3317-5689
Irene Llorente Muñoz http://orcid.org/0000-0002-4684-8609
Maite Martinez-Uhia http://orcid.org/0000-0002-3543-5173

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