

Randomized double-blind clinical trial evaluating the effectiveness and safety of secondary prophylaxis with oral vancomycin versus placebo in the prevention of recurrence of *Clostridioides difficile* infection in patients receiving systemic antibiotic therapy (PREVAN trial)

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Background: Recurrence of *Clostridioides difficile* infection (CDI) is frequent, particularly in patients requiring subsequent systemic antibiotics. Observational studies suggest that secondary prophylaxis with oral vancomycin (SPV) may reduce recurrence risk, but randomized evidence remains scarce.

Methods: PREVAN (NCT05320068) was a phase III, double-blind, placebo-controlled randomized clinical trial conducted at a tertiary hospital in Spain. Adults with documented CDI within the previous 180 days who required hospitalization and systemic antibiotics were randomized (2:1) to receive oral vancomycin (125 mg every 6 h) or placebo for 10 days, stratified by type of index CDI episode. Primary endpoints were CDI recurrence within 60 days after end of therapy and CDI recurrence-free survival.

Results: Twenty-one patients were enrolled (14 SPV; 7 placebo). Mean age was 73.5 years and 76.7% had malignancy and/or immunosuppression. CDI recurrence occurred in 5 patients (23.8%): 2 (14.3%) in the SPV group and 3 (42.9%) in the placebo group ($P=0.30$). CDI recurrence-free survival at 60 days was 83% (95% CI 48–95) with SPV versus 42% (95% CI 6–77) with placebo (log-rank $P=0.09$). No treatment-related serious adverse events were observed; one mild diarrhoeal event occurred in a placebo-treated patient.

Conclusions: In high-risk patients with recent CDI requiring systemic antibiotics, SPV appeared safe and was associated with a clinically relevant reduction in recurrence, although the trial was underpowered. These findings support further adequately powered randomized studies to define the role of SPV in preventing CDI recurrence.

Introduction

Clostridioides difficile infection (CDI) is the leading cause of healthcare-associated diarrhea and remains a major contributor to morbidity and mortality worldwide.^{1,2} Its incidence has increased over recent decades, driven by ageing populations, rising comorbidity burdens, and evolving patterns of antimicrobial exposure.^{3–5} Although most patients respond to initial therapy, recurrence remains the dominant clinical challenge, affecting approximately 20%–25% of patients after a first episode and increasing substantially with subsequent recurrences.^{6–8} Current therapeutic strategies—including fidaxomicin, tapered vancomycin, and microbiota-based therapies—can reduce recurrence risk but may be limited by cost, access, or restricted indications.^{9–13}

Among all known triggers, the clinical scenario of patients with a recent CDI episode who require systemic antibiotics is considered one of the strongest drivers of recurrence.^{14–16} Observational studies have suggested that secondary prophylaxis with oral vancomycin (SPV) during systemic antibiotic therapy may substantially reduce recurrence risk.^{17–24} Meta-analyses synthesising these studies have consistently reported protective effects, with pooled odds ratios ranging from 0.14 to 0.34.^{25–27} However, this evidence is largely retrospective, heterogeneous, and subject to confounding. Consequently, guidelines endorsed by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) and the ESCMID acknowledged the potential role of prophylaxis but emphasized the need for robust randomized data before recommending routine use.^{9,10,28} Only the 2020 American College of Gastroenterology (ACG) guidelines support this preventive strategy, while explicitly recognizing the low quality of evidence underpinning the recommendation.²⁸

The PREVAN trial, as described in the published protocol,²⁹ was designed to address this critical evidence gap through a double-blind, placebo-controlled randomized clinical trial (RCT) evaluating SPV in adults with recent CDI who require systemic antibiotics. Here, we report the main results of PREVAN and integrate them within the current evidence base.

Patients and methods

Study design and setting

PREVAN was a phase III, single-centre, double-blind, placebo-controlled RCT with a 2:1 allocation favouring oral vancomycin. Although four tertiary hospitals in Spain were initially selected, only the coordinating centre (Hospital Universitario 12 de Octubre, Madrid) enrolled participants. The protocol and statistical analysis plan are provided in Supplement 1. The trial was approved by the Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS, 18-0905) and the local Ethics Committee (AC069/18), and conducted in accordance with SPIRIT guidelines. All participants provided written informed consent. The study was registered in EudraCT (2019-002677-57) and ClinicalTrials.gov (NCT05320068). Reporting followed CONSORT 2025 standards. All research was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study population

Eligible participants were adults hospitalized with a documented CDI episode within the previous 180 days who were receiving full-dose systemic antibiotic therapy for at least 24 h, initiated within 72 h before screening. Key exclusion criteria included: chronic diarrhoeal conditions; diarrhoea or CDI diagnosis at screening or within the preceding 3 days; and exposure

to oral vancomycin or any agent active against *C. difficile* for more than 48 hours within the previous 3 days. Full inclusion and exclusion criteria are available in the protocol published elsewhere.²⁹

Intervention and procedures

Potential candidates were identified daily through a daily automated Structured Query Language (SQL) cross-database search matching newly admitted patients with those diagnosed with CDI in the previous 180 days (Index CDI). Such SQL-Based Screening tool was specifically built for the present study and was only available at the coordinating Centre. After informed consent, participants were randomly assigned to receive oral vancomycin (125 mg every 6 h) or a matching placebo for 10 days.

Hospitalized patients with a history of CDI in the preceding 180 days (index CDI) that required systemic antibiotic therapy were offered enrolment in the study.

Clinical assessments were performed at baseline (Day 0) and at end of treatment (EOT; ± 72 h) by an Infectious Diseases specialist. Telephone follow-up was conducted at Days 14 and 42 after EOT to identify new CDI episodes or adverse events (AEs). A final in-person evaluation took place at Day 60 after EOT.

All study data were collected and managed using Elsevier MACRO[®], an 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. The study design is shown in Figure 1, and the evaluation schedule is summarized in Table S1 (available as [Supplementary data](#) at JAC-AMR Online).

Randomization and masking

Randomization was performed using a minimization algorithm stratified by type of index CDI episode (first versus recurrent). The random allocation list, based on a 2:1 ratio in favour of SPV and created with SAS 9.4 (SAS Institute), was stored securely at the imas12 Research Institute. Allocation was concealed; only pharmacy staff were unblinded.

The hospital pharmacy prepared indistinguishable vancomycin and placebo capsules and packaged them according to randomization codes. Participants, treating clinicians, investigators, and research pharmacists remained blinded to treatment assignment throughout the study unless emergency unblinding was required.

Outcomes

Primary endpoint

The primary endpoint was CDI recurrence within 60 days after EOT. CDI recurrence-free survival from randomization was also analyzed. Either index or recurrent CDI episodes required *both* (i) clinical criteria (≥ 3 new loose stools in 24 h [or >200 mL in patients with colostomy]) and (ii) microbiological criteria (detection of toxigenic *C. difficile* and/or toxins via standard assays [enzyme immunoassay for toxins A/B, RT-PCR for toxigenic strains]).

Secondary endpoints

Secondary outcomes included (i) severe CDI recurrence (Leukocytosis $>15,000$ cells/mcl and/or serum creatinine >1.5 mg/dL and/or fulminant colitis diagnosis) within 60 days after EOT and severe CDI recurrence-free survival and (ii) safety and tolerability, including incidence of AEs, serious AEs (SAEs), and experimental treatment discontinuations.

Sample size calculation

Previous studies reported a recurrence rate of approximately 25% in patients with recent CDI receiving systemic antibiotics.^{17,19,20} Assuming a CDI recurrence rate of 5% with SPV and a 2:1 allocation ratio, a one-sided

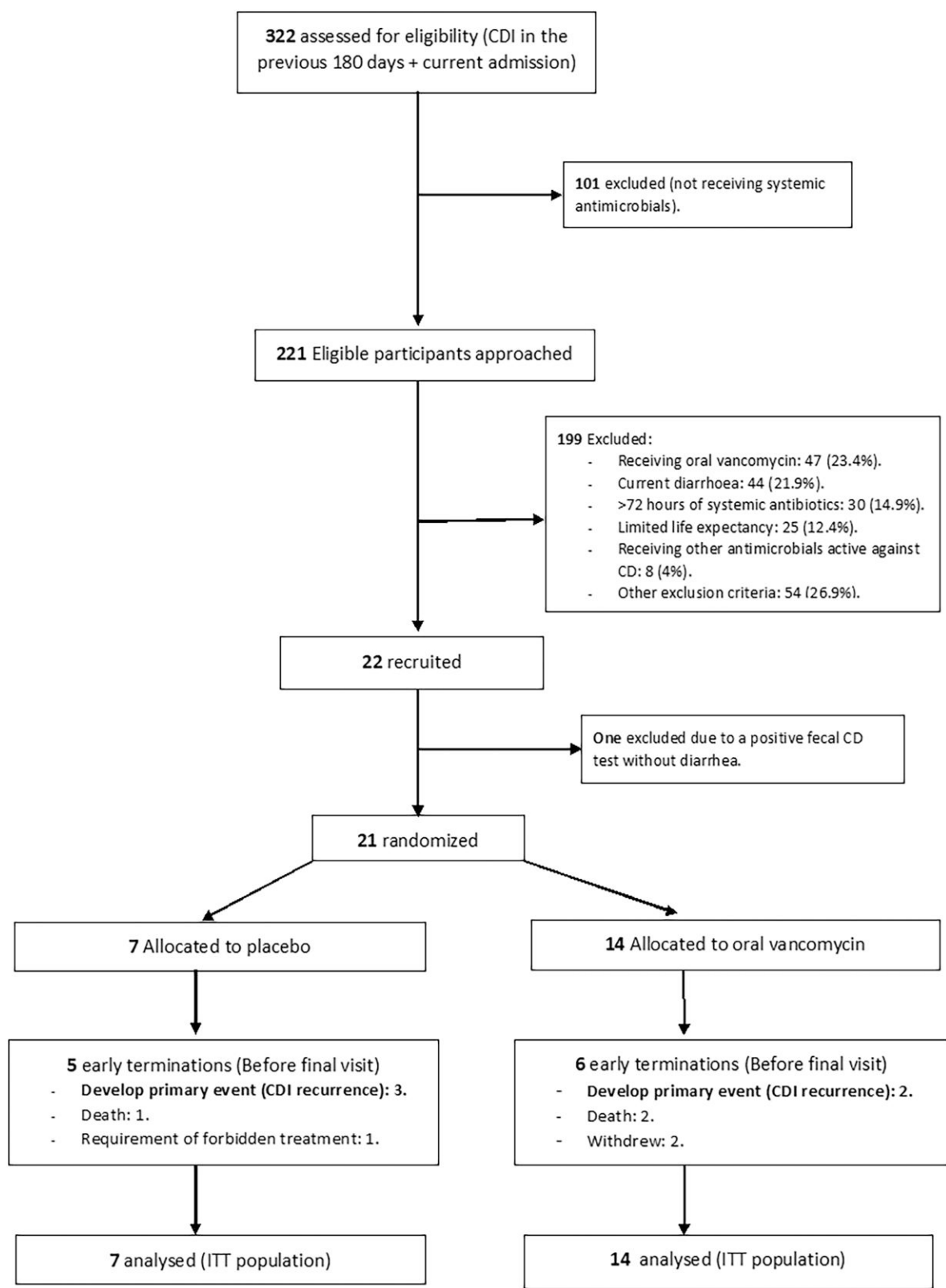


Figure 1. CONSORT flow diagram of the PREVAN randomized controlled trial.

α of 0.05, and a statistical power of 80%, a total sample size of 102 participants (68 SPV; 34 placebo) was calculated as necessary.

Statistical analysis

All analyses followed the ITT principle, including all participants who received at least one dose of study medication. Categorical outcomes were compared using one-sided χ^2 tests ($\alpha = 0.05$), with absolute risk reductions and 95% CIs calculated. CDI recurrence-free and severe recurrence-free survival were estimated using Kaplan–Meier curves and comparisons between groups were performed using the log-rank test. Given the small sample size, statistical significance was interpreted cautiously, and all analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Safety monitoring

An independent Data Safety and Monitoring Board (DSMB) periodically reviewed participant safety, protocol adherence, and trial conduct. AEs, adverse drug events (ADEs), and adverse drug reactions (ADRs) were defined according to regulatory standards. SAEs included events resulting in death, life-threatening conditions, disability, congenital anomalies and/or hospitalization/prolonged hospitalization. Given the minimal systemic absorption of oral vancomycin, no specific drug-related AEs apart from diarrhoea were expected.

Investigators documented all AEs at scheduled visits and assessed potential treatment relatedness. SAEs, treatment-related AEs, AEs leading to study drug modification or discontinuation, and events of special interest were reported in the electronic case report form. All SAEs were reported to the sponsor and pharmacovigilance unit within 24 h.

Results

Participants

From February 2022 to September 2024, 322 hospitalized adults with a CDI episode diagnosed within the previous 180 days were screened. Of these, 221 (68.6%) were receiving systemic antibiotics and met eligibility criteria (Figure 1). A total of 199 were excluded, most commonly due to ongoing oral vancomycin therapy (47; 23.4%), diarrhoea at screening (44; 21.9%), initiation of systemic antibiotics >72 h before assessment (30; 14.6%), or limited life expectancy (25; 12.4%).

Twenty-two participants were enrolled and 21 were randomized (14 to SPV and 7 to placebo) and included in the ITT population. Main characteristics are shown in Table 1. The mean age was 73 years. Most participants had substantial comorbidity as reflected by their mean Charlson index (3.52 [SD 1.4]) and at least one immunosuppression-associated risk factor (16 [76.2%]). The median time of antimicrobial therapy was 8 days (IQR: 6–12.5 days) and carbapenems and third-generation cephalosporins were the most frequently used systemic antibiotics, primarily prescribed for urinary tract (38.1%) and respiratory infections (33.3%). Experimental treatment (either vancomycin or placebo) was administered for a median of 10 days (IQR: 7.5–10).

Primary and secondary efficacy outcomes

Five participants (35.7%) developed CDI recurrence within 60 days after EOT: 2 (14.3%) in the SPV group versus 3 (42.9%) in the placebo group (absolute difference: –28.6%; 95% CI: –69.6 to 12.4; P -value = 0.30; Table 2).

The probability of CDI recurrence-free survival at 60 days in the entire study population was 69% (95% CI: 42–86): 83% in the SPV group versus 42% in the placebo group (log-rank P -value = 0.09; Table 2; Figure 2).

Severe CDI recurrence occurred in two participants (9.5%), one in each treatment group (7.1% with SPV versus 14.3% with placebo; P -value = 0.70).

Secondary safety outcomes

A total of 11 AEs were reported in 9 participants (Table S2): 6 in the SPV group and 3 in the placebo group. Most AEs were deemed unrelated to study treatment. One participant in the placebo group experienced mild, treatment-related diarrhoea leading to early discontinuation.

Six participants experienced SAEs: five in the SPV group and one in the placebo group. SAEs included infectious complications (bacteraemia, respiratory infection, *C. difficile* diarrhoea, septic shock), heart failure, and pneumonia. No cases of colonization and/or infection were detected in either of the study arms. Three deaths occurred during follow-up (14.3%), with none of them considered related to study treatment (two in the SPV group and one in the placebo group).

Discussion

In this double-blind, placebo-controlled RCT, secondary prophylaxis with full-dose oral vancomycin demonstrated a clinically meaningful reduction in recurrent CDI among high-risk adults receiving systemic antibiotics, although the study was underpowered to achieve statistical significance. The direction and magnitude of effect observed in PREVAN are consistent with prior observational studies and meta-analyses supporting a protective role for prophylactic vancomycin in patients at increased risk of CDI recurrence.^{25–27}

These findings must be interpreted alongside the only other double-blind RCT to date, recently conducted by Keating and colleagues.³⁰ Both studies demonstrated a similar protective trend, with fewer CDI recurrences in participants receiving oral vancomycin than in those receiving placebo. However, the magnitude of benefit reported by Keating et al. was more modest, possibly owing to the use of a low-dose regimen (125 mg once daily). Inadequate luminal exposure may also explain their observation of increased vancomycin-resistant *Enterococcus* (VRE) colonization in the prophylaxis arm. PREVAN did not include microbiological surveillance of colonization. However, previous studies using full-dose vancomycin have not demonstrated an increased risk of VRE emergence,^{18,19,22} particularly in settings—such as Spain—where baseline VRE prevalence remains low.

PREVAN and the Keating trial also faced strikingly similar feasibility constraints. Beyond the complexity of timely screening, recruitment was substantially hindered by the growing ‘de facto’ clinical adoption of oral vancomycin prophylaxis in patients perceived to be at highest risk—particularly those with haematological malignancies, solid-organ transplantation, or significant immunosuppression.^{21,22} This resulted in exclusion of many otherwise eligible candidates, contributing to both trials being underpowered. Additionally, PREVAN exemplifies the structural challenges of investigator-initiated, non-commercial clinical research in Spain, where conducting a placebo-controlled RCT

Table 1. Clinical characteristics at randomization

	Total (n = 21)	Placebo (n = 7)	SPV (n = 14)	P-value
Index CDI episode (n [%]):				
First episode	15 (71.4)	4 (57.1)	11 (78.6)	0.35
Recurrence	6 (28.6)	3 (42.9)	3 (21.4)	
Days from Index CDI, Median (IQR)	76 (30.5–96)	46 (19–93)	87 (35.7–163)	0.32
Male sex (n [%])	8 (38.1)	3 (42.9)	5 (35.7)	1
Age mean (SD)	73.48 (14.4)	73.18 (14.91)	73.64 (14.71)	0.94
Risk factors for CDI (n [%]):				
Solid organ transplantation	4 (19.1)	2 (28.6)	2 (14.3)	0.57
Hematopoietic stem-cell transplantation	1 (4.8)	1 (14.3)	0	0.33
Haematological malignancy	6 (28.6)	2 (28.6)	4 (28.6)	1
Solid organ malignancy	5 (23.8)	1 (14.3)	4 (28.6)	0.62
Autoimmune disease	3 (14.3)	0	3 (21.4)	0.52
Active chemotherapy	6 (28.6)	2 (28.6)	4 (28.6)	1
Current immunosuppression	11 (52.4)	4 (57.1)	7 (50.0)	1
Presence of ≥ 1 risk factors [n (%)]	16 (76.2)	4 (57.1)	12 (85.7)	0.36
Charlson comorbidity Index mean (SD)	3.52 (2.1)	3.00 (1.41)	3.79 (2.42)	0.44
Admission ward at randomization [n (%)]				
Internal medicine	7 (33.3)	2 (28.6)	5 (35.7)	0.87
Oncology/haematology	7 (33.3)	2 (28.6)	5 (35.7)	0.87
Nephrology	3 (14.3)	2 (28.6)	1 (7.1)	0.5
Gastroenterology	2 (9.5)	1 (14.3)	1 (7.1)	0.8
General surgery	2 (9.5)	0	2 (14.3)	0.8
Antibiotic agent at randomization [n (%)]				
Imipenem or meropenem	11 (52.4)	2 (28.6)	9 (64.2)	0.28
Third-generation cephalosporins	4 (19)	3 (42.9)	1 (7.1)	0.17
Amoxicillin-clavulanate	3 (14.3)	0	3 (21.4)	0.5
Ertapenem	2 (9.5)	2 (28.6)	0	0.19
Piperacillin-tazobactam	1 (4.8)	0	1 (7.1)	0.71
Indication for antibiotic therapy [n (%)]				
Urinary tract infection	8 (38.1)	3 (42.8)	5 (35.7)	0.87
Respiratory tract infection	7 (33.3)	2 (28.5)	5 (35.7)	0.87
Febrile neutropenia	3 (14.2)	1 (14.3)	2 (14.2)	1
Other	3 (14.2)	1 (14.3)	2 (14.2)	1
Days of antibiotic therapy. Median (IQR)	10.95 (6–12.5)	7 (3–12)	8.5 (6–13)	0.55
Days of experimental treatment Median (IQR)	10 (7.5–10)	10 (3–10)	10 (10–10)	0.23

CDI, *Clostridioides difficile* infection; IQR, interquartile range; SD, standard deviation; SPV, secondary prophylaxis with oral vancomycin.

Table 2. Efficacy endpoints at 60 days after EOT

	Total (n = 21)	Placebo (n = 7)	SPV (n = 14)	Estimated differences (95%CI)	P-value
CDI recurrence [n (%)]	5 (35.7)	3 (42.9)	2 (14.3)	(–12.4 to 69.6)	0.3
Kaplan–Meier probability of CDI recurrence-free survival [% (95% CI)]	69 (42–86)	42 (6–77)	83 (48–95)	(–0.5 to 82.5)	0.09
Severe CDI recurrence [n (%)]	2 (9.5)	1 (14.3)	1 (7.1)	(–22 to 36.4)	0.7

CDI, *Clostridioides difficile* infection; CI, confidence interval; EOT, end of therapy; SPV, secondary prophylaxis with oral vancomycin.

without industry support is uncommon and demanding. Limited funding and the absence of financial incentives for participating centres may have contributed to poor engagement and lack of recruitment outside the coordinating site. Furthermore, the

cross-database SQL screening system, which greatly facilitated real-time identification of eligible patients, could only be implemented at the sponsor center, limiting systematic screening capability elsewhere.

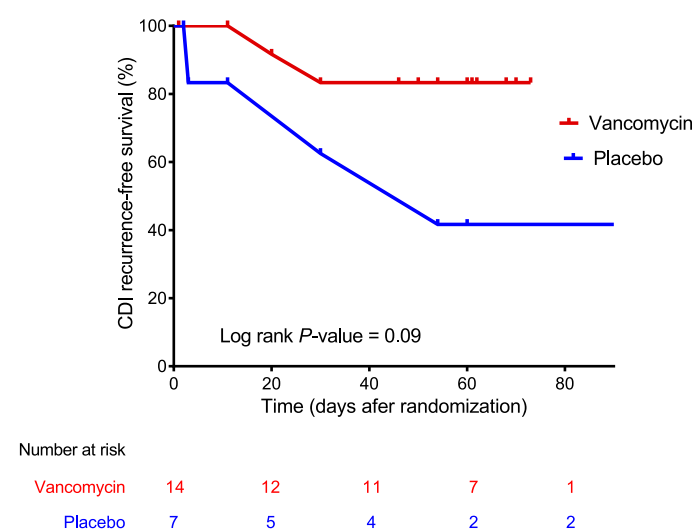


Figure 2. Kaplan-Meier CDI recurrence-free survival curves. CDI: *Clostridioides difficile* infection.

The PREVAN population, characterized by advanced age, substantial comorbidity, and a high prevalence of immunosuppression, reflects the real-world patients at greatest risk of recurrent CDI.^{6,7,15} Participants frequently received high-risk systemic antibiotics, including carbapenems and third-generation cephalosporins.³¹ The protective trend observed in PREVAN is therefore biologically plausible and clinically relevant.

Safety outcomes were favorable, with no treatment-related serious adverse events and only one mild reaction attributable to study medication. Although the absence of microbiological monitoring limits conclusions regarding ecological impact, no clinical evidence of antimicrobial resistance emerged.

This study has several limitations. The foremost is the small sample size, driven largely by exclusion of patients already receiving off-label SPV and by operational constraints inherent to investigator-initiated research. The single-centre recruitment limits generalizability, although the population enrolled is representative of patients at highest risk. Although systematic microbiological surveillance was not included, vancomycin resistance in *Clostridioides difficile* has not been detected at our institution, and no infections caused by vancomycin-resistant enterococci were observed during follow-up in either study arm. Future randomized studies should integrate microbiological monitoring to better define the ecological impact of secondary prophylaxis. Finally, although full-dose vancomycin was used, the optimal dosing schedule and duration for prophylaxis remain uncertain.

PREVAN and the Keating trial together constitute the entire double-blind randomized evidence base evaluating secondary prophylaxis for CDI with oral vancomycin. Despite limited power, the consistency of protective trends across both studies supports a potential clinical benefit in select high-risk patients. Two questions warrant further investigation: (i) whether a meta-analysis combining the two available RCTs could provide more precise effect estimates; and (ii) whether prolonging prophylaxis beyond 10 days could enhance protection, particularly in patients requiring extended systemic antibiotic therapy. Ultimately, larger multicenter pragmatic RCTs, adaptive designs, or pooled

individual-level meta-analyses will be critical to define efficacy, optimize dosing, and clarify ecological impact. Until such data emerge, decisions regarding CDI prophylaxis should be individualized, balancing potential benefit against antimicrobial stewardship considerations.

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Transparency declarations

All the authors declare no potential conflict of interest regarding this study.

Author contributions

J. O. and R. S. J. are the sponsors and coordinators of the C. T. R. S. J., J. O. and J. M. A., conceived and designed the study protocol. R. S. J., J. O. and K. C. wrote the manuscript. C. M. A. designed and wrote statistical analysis plan including randomization strategies an electronic database. R. S. J., K. C., C. M. A. and M. T. U. critically reviewed the protocol. R. S. J., M. F. R., K. C., J. V., B. D. P., A. C., J. T. S., F. L. M., J. B., A. P. J., I. R. G. and G. C. contributed to the acquisition of data. M. T. U. and J. M. F. coordinated the pharmaceutical aspects of the study and the CT protocol. All authors have read, revised and approved the final manuscript.

Supplementary data

Tables S1 and S2 is available as Supplementary data at [JAC-AMR](https://doi.org/10.1093/jac/dkz100) Online.

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