Clinical Microbiology and Infection 31 (2025) 2025–2032

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.org

Original article

Impact of enhanced infection control and antimicrobial stewardship on infections by *Clostridioides difficile*, vancomycin-resistant *enterococci*, and third-generation cephalosporin-resistant *Enterobacterales:* a stepped-wedge cluster intervention study

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ARTICLE INFO

Article history:
Received 2 April 2025
Received in revised form
13 August 2025
Accepted 14 August 2025
Available online 23 August 2025

Editor: Jesus Rodriguez-Baño

Keywords:
Antimicrobial stewardship
Clostridioides difficile
Haematology-oncology
Infection prevention and control

ABSTRACT

Objectives: Infection prevention and control (IPC) and antimicrobial stewardship (AMS) measures are critical to reducing transmission and infection by *Clostridioides difficile* (CDI) and other enteric pathogens. This study evaluated the impact of enhanced IPC and AMS on CDI and bloodstream infections (BSIs) caused by vancomycin-resistant enterococci (VRE) and third-generation cephalosporin-resistant *Enterobacterales* (3GCREB).
Methods: The study was conducted in five German university hospitals from January 2016 to July 2019. IPC and AMS interventions were sequentially enhanced in three departments with high-incidence CDI at baseline using a stepped-wedge cluster intervention approach. Main outcome measures were incidence densities of CDI and BSI caused by VRE and 3GCREB. An interrupted time series analysis was performed to assess the intervention effects during a normalized study period.
Results: Across 15 departments, >384,000 patient days were included. Incidence density of target infections was low (CDI, 0.77; VRE BSI, 0.07; and 3GCREB BSI, 0.09 per 1000 patient days). Pooled interrupted time series analysis results showed a significant reduction in CDI incidence density following the enhancement of AMS measures (AMS period regression slopes difference, −0.089; F

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https://doi.org/10.1016/j.cmi.2025.08.013

Multiresistant gram-negative bacteria
Vancomycin-resistant enterococci

[p] = 5.400 [0.037]). Regarding the incidence density of VRE/3GCREB BSI, no relevant changes could be observed (regression slopes difference, −0.19; F[p] = 0.667 [0.429]). A subgroup analysis focusing on haematological and oncological departments showed that AMS influenced prescription behaviour according to implemented AMS strategies, but not clinical outcomes.

Discussion: Combined with IPC enhanced short-term AMS measures led to a significant reduction in the incidence of CDI, whereas the incidence of BSI by VRE and 3GCREB remained unchanged in sites with well-established baseline IPC and AMS programmes and low incidence of hospital-associated infections.

Annika Y. Classen, Clin Microbiol Infect 2025;31:2025

Introduction

The healthcare-associated pathogens *Clostridioides difficile*, vancomycin-resistant *enterococci* (VRE), and third-generation cephalosporin-resistant *Enterobacterales* (3GCREB) are an immediate threat to hospitalized patients worldwide, due to their association with poorer outcomes and extended treatment periods [1]. Infection prevention and control (IPC) and antimicrobial stewardship (AMS) are essential strategies for preventing transmission and reducing infection by *C. difficile* (CDI) and other healthcare-associated pathogens. IPC measures aim to reduce in-hospital pathogen transmission using interventions such as optimization of hand hygiene and environmental cleaning [2]. AMS measures aim at reducing selective pressure by ascertaining the adequacy of antibiotic treatment duration, dosing, and choice of antibiotics. Targeted AMS measures have been shown to effectively improve prescription quality and therapeutic outcomes, especially when combined with IPC measures [3,4].

To date, many published AMS studies do not fulfil high methodological quality criteria as recently evaluated in a systematic review [5]. AMS studies from the hospital setting (n = 620) were mostly conducted at a single site (84%), with more than half of these relying on retrospective data acquisition and analysis only (54%) [5]. Despite antimicrobial resistance being a key target of AMS, only a small proportion of assessed trials reported outcome data on colonization/infection by resistant pathogens (24%) or CDI (10%) [5]. Methodologically, most AMS studies employed non-randomized designs (91%), with the majority being before-after studies that lacked interrupted time series analysis (ITSA) to account for time-dependent bias [5]. Differential impact of (combined) IPC and AMS measures was only assessed in a few studies [4,6]. Additionally, there is only limited evidence for AMS to influence clinical outcomes in high-risk patient cohorts, such as in the haematological and oncological setting, potentially due to specific challenges and prejudices associated with the implementation of AMS measures in this vulnerable patient population [7].

The ABSOLUTE study (antibiotic stewardship and infection control in patients at high risk of developing infection by clostridium difficile, vancomycin-resistant enterococci, or multiresistant gram-negatives) was designed to prospectively evaluate the impact of enhanced IPC and AMS measures on CDI and VRE/3GCREB bloodstream infections (BSIs) using a stepped-wedge cluster intervention approach in a multicentre, tertiary care hospital setting.

Methods

Study sites and interventions

The ABSOLUTE trial (NCT 03250104) was conducted in five German university hospitals between 2016 and 2019. Abbreviations used in this manuscript can be found in Table S1. IPC and AMS interventions were enhanced in three departments per site with high baseline CDI incidence (exceeding the 75th percentile of the overall CDI incidence at the participating site), identified using data from the R-NET study (NCT 04937361). The final decision on department inclusion was made by the study leadership in collaboration with local study teams, considering pathogen epidemiology and factors such as antibiotic consumption, departmental interest, and accessibility for interventions. The participating hospitals were large academic medical centres where departments are independent and geographically distinct. Different staff across specialties reduced the likelihood of transfer of intervention behaviours. To prevent cross-contamination, only complete departments were included. A stepped-wedge design was used: IPC measures were enhanced first (IPC intervention period, IPC-IP) and continued during an antimicrobial stewardship intervention period (AMS-IP; Fig. 1). The 6 months before IPC reinforcement served as the baseline period (BP). A 17-month normalized study period was defined, as the number of months included within IPC- and AMS-IPs varied across departments and study sites: 6 months of BP immediately prior to the intervention periods, 6 months of IPC-IP, and 5 months of AMS-IP.

At baseline, all study sites had an active infectious diseases unit with consultation service plus an interdisciplinary AMS team established, whereas IPC and AMS measures were not routinely performed in the selected departments (Text S1and Table S4). Enhancement of IPC interventions included regular hand hygiene (HH) training with direct feedback for medical staff based on the WHO's “5 moments for hand hygiene” [8], and instructional programmes for cleaning staff. Reinforced AMS measures comprised department-specific treatment guideline development and distribution, along with medical staff training and regular point prevalence surveys (PPS) with direct or indirect feedback to the prescribers. Quarterly interdisciplinary team meetings were performed at each department to discuss the results of the interventions.

Outcome measures

Main outcome measures were the incidence of CDI and BSI caused by VRE and 3GCREB. Data were collected on a patient case basis via the R-NET study for all sites except site 3, which reported independently, as it was not part of the R-NET consortium. Only nosocomial cases were included. CDI diagnosis followed R-NET criteria: three loose stools (Bristol types 5–7) within 24 hours and positive C. *difficile* test [9] (see Text S2 for details on diagnostics). CDI also included cases with toxic megacolon, ileus, or pseudomembranous colitis [9,10]. BSI by VRE and 3GCREB were counted when a pathogen was detected in blood cultures, with repeated isolates within ≤30 days counted as one episode [11]. Additionally, department level data on total patient days (PDs) were collected.

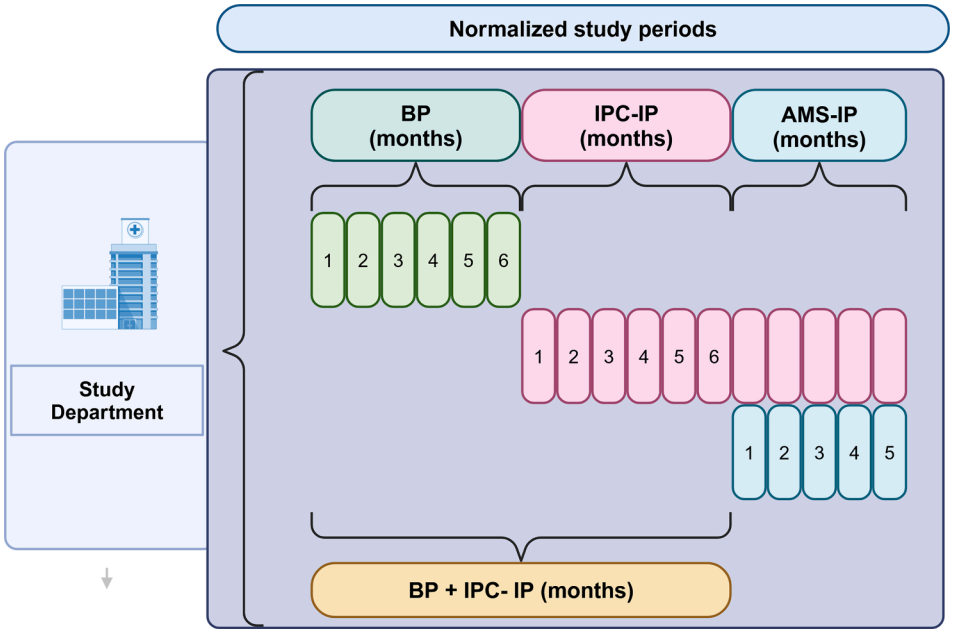

Fig. 1. Illustration of the stepped-wedge design used in the ABSOLUTE trial and the study periods as defined for endpoint analysis. Following an initial baseline period (BP), infection prevention and control and antimicrobial stewardship interventions were implemented (IPC-IP/AMS-IP). Normalized study periods included 6 months of BP, 6 months of IPC-IP, and 5 months of AMS-IP. Additionally, BP and IPC-IP were combined for analysis in comparison to AMS-IP. This design was applied to all the included departments. AMS-IP, antimicrobial stewardship intervention period; BP, baseline period; IPC-IP, infection control intervention period.

IPC process quality was assessed via HH compliance observations (HHC) and cleaning audits (CA) using UV markings of high-touch spots and objects in patient rooms. Results of the regularly performed PPS served for the assessment of the AMS intervention quality. Results were aggregated before submission to the coordinating site.

Statistical analysis

The primary objective was to assess the impact of IPC and AMS interventions on CDI incidence, with secondary analysis assessing the impact on BSI incidence caused by VRE/3GCREB. Infection incidence density was calculated as CDI or BSI cases per 1000 PDs. Data were normalized for pooled analysis across departments and sites (Text S3, Table S2, and Fig. S1). Data for department two at study site 4 were excluded from the endpoint analysis, as implementation of IPC and AMS measures started simultaneously.

Descriptive statistics were calculated, and an ITSA was performed to assess the intervention impact, comparing infection incidence densities from BP to IPC-IP/AMS-IP and BP plus IPC-IP to AMS-IP. The analysis was performed using RStudio (v1.4.1106, Posit, PBC including R-packages "*its.analysis*" (version 1.6.0 [12] and "*car*" version 3.1-3 [13]) and IBM SPSS (v28).

Subgroup analysis in the haematological and oncological setting

Haematology/oncology departments, which were only included at sites 1 to 3, were analysed separately, whereas AMS-IP following study period normalization for this subgroup comprised only 4 months (Text S3; Fig. 2). An ITSA was used to assess the impact of measures on infection incidence density. Additionally, data on monthly antibiotic prescriptions were included on a department level. These data were collected from hospital pharmacies as part of the ADKA-if-DGI project, a cooperation between the German Hospital Pharmacists Association (ADKA), the Division of Infectious Diseases of the university hospital Freiburg (if) and the German Society of Infectious Diseases (DGI), at the university hospital Freiburg using the WHO anatomical therapeutic chemical system code and reported as recommended, hospital-adapted daily doses (RDD) per 100 PDs [14,15]. Prescription density was calculated as RDD per 1000 PDs, and AMS impact on prescription density was analysed via ITSA.

Ethical considerations

The study was approved by the ethics committees of all sites (lead: Cologne, 17-262). Informed consent was waived, as interventions were not patient-specific, and data were anonymized.

Results

Intervention departments and IPC/AMS measures

The ABSOLUTE trial included 15 departments across five German university hospitals, encompassing 30 wards and a total of 707 beds across various medical specialties. Departments differed in size, patient room occupancy, staffing levels, and baseline IPC characteristics. (Tables S3 and S4). Following study period normalization, a total of 85 observation months comprising 384,263 PDs (62.1% of the complete study period) were included in the analysis (Table 1). IPC- and AMS-related measures performed at the departments are shown in Table 1. Detailed data for each site and department during the non-normalized study period can be found in Table S6. The results of HHC, CA, and PPS following IPC and AMS enhancement (Tables S7–S11) varied, with 10 of 15 departments showing improved HHC and PPS results comparing baseline and last assessments within the study period. Improvements were sometimes only slightly pronounced (e.g. at site 4,71% of antibiotic prescription assessments included in the PPS at baseline were considered adequate, and 77% from the last performed PPS). CA showed improved cleaning of selected spots in the

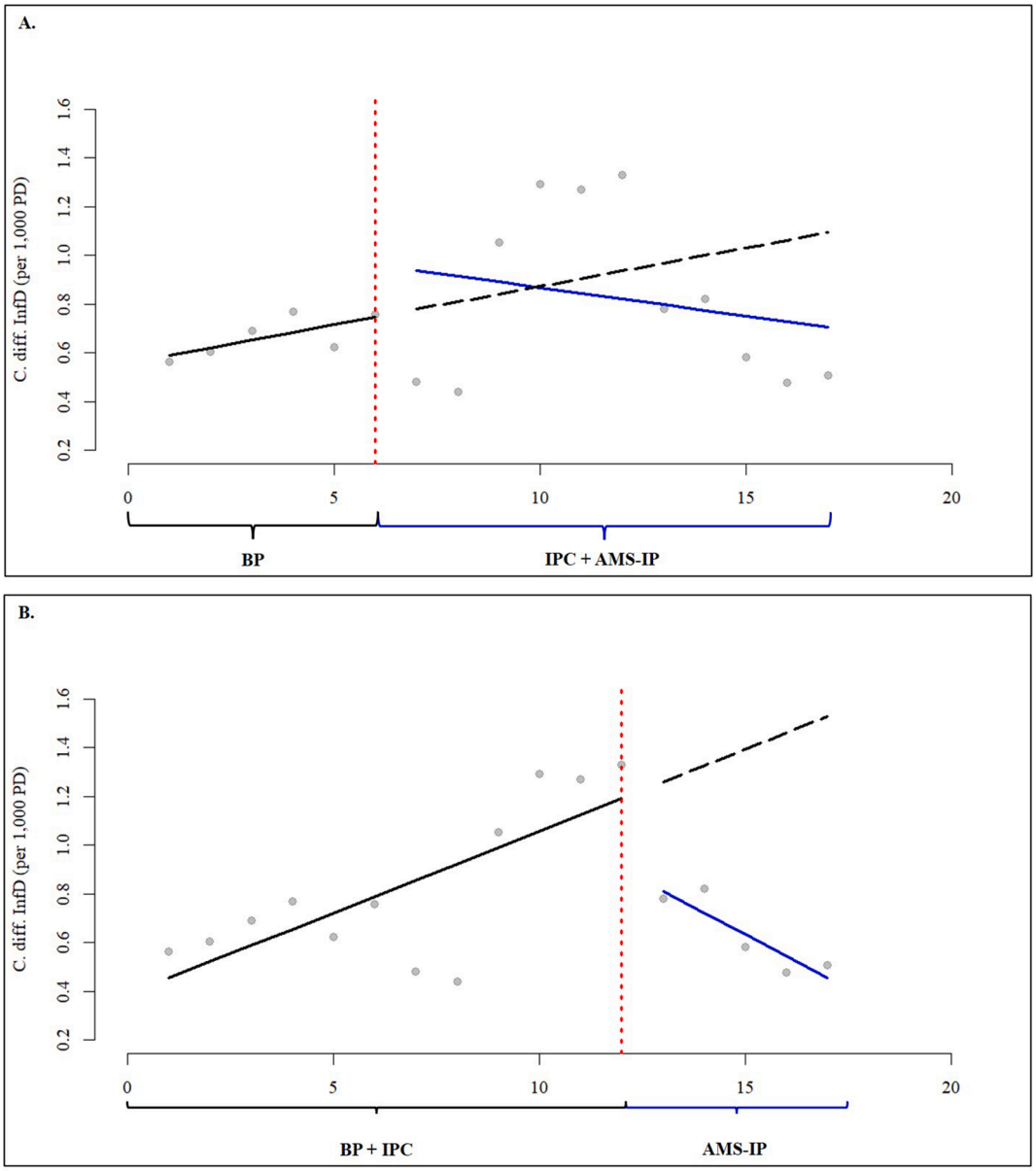

Fig. 2. ITSA analysis plot showing the CDI incidence density before and after implementation of IPC and AMS measures, pooled for all study sites. The y-axis shows the CDI incidence density, and the x-axis shows the study period in months for (A) BP compared with IPC- and AMS-IP and (B) BP plus IPC-IP compared with AMS-IP. The start of the intervention phases is highlighted with a red line at 6 and 12 months, respectively. A total of 17 months was included in the normalized study period. Black (prior to intervention) and blue (postintervention) lines represent the actual incidence density, whereas dotted lines represent the extrapolated trend. AMS-IP, antimicrobial stewardship intervention period; BP, baseline period; IPC-IP, infection prevention and control period.

patient rooms at 9 of 15 departments, but generally, cleaning success was low.

Main outcomes: incidence of CDI and VRE/3GCREB BSIs

During the normalized study period, 294 CDI, 28 VRE, and 36 3GCREB BSIs were recorded (Table 1). Most CDI (n = 84 cases; 28.6%), VRE (n = 9; 32.1%), and 3GCREB BSIs (n = 18; 50%) were detected at site 1. The most prevalent species among 3GCREB BSI was *Escherichia coli* (n = 22, 61.1%; Table S5). The results of the ITSA evaluating the impact of enhanced IPC and AMS measures on incidence density of CDI and VRE/3CGREB BSI for all departments and pooled for all sites are summarized in Table 2 and Fig. 2. The analysis did show a significant impact on CDI incidence density following enhancement of AMS measures (effect during AMS period, regression slopes difference, −.089; F[p] = 5.400 [0.037]). Regarding the VRE/3GCREB incidence density, no relevant changes could be observed (Table 2; Fig. S3).

Subgroup analysis: haematological and oncological departments

Three haematological/oncological departments were recruited, including 76,094 PDs, 78 CDIs, 9 VREs, and 15 3GCREB BSIs (Table S12–S16). The department at site 1 accounted for the highest number of included PDs (48,821, 64.2%) and infections (CDI 50, 64.1%; VRE BSI 6, 66.7%; 3GCREB BSI 14, 93,3%). The most prevalent species among all 3GCREB BSI was *E. coli* (n = 13, 86.7%, Table S13). Notably, no 3GCREB BSIs were recorded at site 2. The implementation quality of IPC and AMS varied (Table S14). Although HHC did improve at site 1, no major improvement could be observed for PPS and CA. In contrast, improvements for PPS,

Table 1
Overviewof recorded data and results of performed intervention period control and antimicrobial stewardship evaluations performed at all study sites within the total and normalized ABSOLUTE (Antibiotic Stewardship and Infection Control in Patients at High Risk of Developing Infection by Clostridium Difficile, Vancomycin-Resistant Enterococci or Multi-Resistant Gram-Negatives) study period

Study site	Months	Patient days	CDI		VRE BSIs		3GCREB BSIs		Team meetings	PPS	HHC	CA
	N (%)	∑ (%)	∑ (%)	InfD (SD)	∑ (%)	InfD (SD)	∑ (%)	InfD (SD)	∑ (%)	∑ (%)	∑ (%)	∑ (%)
All (total SP)	390 (100)	618,523 (100)	447 (100)	-	46 (100)	-	51 (100)	-	97 (100)	7551 (100)	9866 (100)	3422 (100)
All (nSP)	85 (21.8)	384,263 (62.1)	294 (65.8)	0.77 (0.29)	28 (60.9)	0.07 (0.05)	36 (70.6)	0.09 (0.06)	55 (56.7)	5410 (71.6)	6690 (67.8)	2039 (59.6)
1 (nSP)	17 (20)	117,392 (30.5)	84 (28.6)	0.72 (0.42)	9 (32.1)	0.08 (0.09)	18 (50)	0.15 (0.17)	19 (34.5)	355 (6.6)	1691 (25.3)	569 (27.9)
2 (nSP)	17 (20)	53,438 (13.9)	40 (13.6)	0.75 (0.55)	3 (10.7)	0.06 (0.12)	5 (13.9)	0.09 (0.14)	12 (21.8)	633 (11.7)	1270 (18.9)	300 (14.7)
3 (nSP)	17 (20)	91,851 (23.9)	75 (25.1)	0.81 (0.45)	8 (28.6)	0.09 (0.12)	6 (16.7)	0.07 (0.09)	11 (20)	520 (9.6)	2648 (39.6)	655 (32.1)
4[a] (nSP)	17 (20)	42,142 (10.9)	71 (24.2)	2.02 (2.14)	0 (0)	—	2 (5.6)	0.05 (0.13)	4 (7.3)	474 (8.8)	109 (1.6)	147 (7.2)
5 (nSP)	17 (20)	79,440 (20.7)	24 (8.2)	0.3 (0.2)	8 (28.6)	0.1 (0.15)	5 (13.9)	0.06 (0.1)	9 (16.4)	3428 (63.4)	972 (14.5)	368 (18.1)

CA, total number of spots marked during cleaning audits; HHC, total number of hand hygiene compliance indications observed; M, mean absolute patient days/infections per month; *N*, number of observations; nSP, normalized study period; PPS, total number of point prevalence surveys/antibiotic assessments performed on a case level; SP, study period; InfD, mean of infection incidence density per 1000 patient days; ∑, sum of column.

[a] Please note that department 2 (INF) at study site 4 was not included in the endpoint analysis, as IPC and AMS interventions started simultaneously. The results do refer to departments 1 (GAS) and 3 (PUL) only.

Table 2
Results of interrupted time series analysis evaluating the impact of intervention period control and antimicrobial stewardship measures on *Clostridioides difficile* and vancomycin-resistant enterococci/third-generation cephalosporin-resistant Enterobacterales incidence density during the normalized study period

Study site	Effect during IPC and AMS periods (6 mo BP vs. 11 mo IPC- + AMS-IP)				Effect during AMS period (12 mo BP + IPC-IP vs. 5 mo AMS-IP)			
	Reg. slope BP(*p*)	Reg. slope IPC- + AMS-IP(*p*)	Reg. slopes diff.	F(*p*)	Reg. slope BP + IPC-IP(*p*)	Reg. slope AMS-IP(*p*)	Reg. slopes diff.	F(*p*)
CDI incidence density								
1	−0.049 (0.652)	0.057 (0.626)	0.008	.249 (0.626)	0.051 (0.186)	−0.103 (0.487)	−0.052	0.511 (0.487)
2	−0.049 (0.746)	0.074 (0.650)	0.025	0.216 (0.65)	0.029 (0.564)	0.176 (0.370)	0.205	0.861 (0.371)
3	0.142 (0.229)	−0.183 (0.154)	−0.041	2.29 (0.154)	0.052 (0.144)	−0.281 (0.053)	−0.229	4.553 (0.053)
4	0.131 (0.808)	−0.337 (0.562)	−0.206	0.355 (0.562)	0.515 (0.002)	−0.715 (0.195)	−0.2	1.871 (0.195)
5	0.027 (0.617)	−0.039 (0.501)	−0.012	0.479 (0.501)	−0.015 (0.379)	−0.11 (0.106)	−0.125	3.015 (0.106)
All sites pooled	0.031 (0.675)	−0.055 (0.500)	−0.024	0.481 (0.500)	0.067 (0.002)	−0.156 (0.037)	−0.089	5.400 (0.037)
VRE+3GCREB incidence density								
1	0.006 (0.918)	−0.018 (0.767)	−0.012	0.091 (0.767)	0.023 (0.261)	−0.049 (0.531)	−0.026	0.414 (0.531)
2	−0.01 (0.817)	−0.014 (0.751)	−0.024	0.105 (0.751)	0.000 (0.991)	0.031 (0.578)	0.031	0.326 (0.578)
3	0.021 (0.549)	−0.010 (0.788)	0.011	0.076 (0.788)	0.010 (0.415)	−0.037 (0.449)	−0.027	0.611 (0.449)
4[a]	0.036 (0.312)	−0.029 (0.45)	0.007	0.606 (0.450)	−0.005 (0.722)	−0.036 (0.462)	−0.041	0.575 (0.462)
5	−0.096 (0.057)	0.116 (0.036)	0.02	5.482 (0.036)	−0.014 (0.448)	0.000 (0.999)	−0.014	0 (0.999)
All sites pooled	−0.010 (0.664)	0.010 (0.696)	0	0.16 (0.696)	0.007 (0.415)	−0.026 (0.429)	−0.019	0.667 (0.429)

ITSA was performed considering the infection density per 1000 patient days. Associated p values indicate significance of trend in the respective time series ($p < 0.05$). A p value < 0.05 suggests that the intervention had a significant effect on the time series.

AMS-IP, antimicrobial stewardship intervention period; BP, baseline period; CDI, *Clostridioides difficile;* F*(p)*, F-value of the hypothesis test assesses whether there is a significant change in the slope of the regression line during the intervention period, where a high F-value indicates an effect; IPC-IP, infection control intervention period; Sites pooled, sum of the infection density (CDI or VRE+3GCREB) of the respective study sites for the corresponding months; Reg. slopes diff., difference between Reg. slope baseline period/Reg. slope baseline and IPC-IP and Reg. slope IPC- and AMS-IP/Reg. slope AMS-IP; Reg. slope BP, Regression line slopes within the baseline period; Reg. slope BP + IPC-IP, Regression line slopes within the baseline and IPC-IP; Reg. slope IPC + AMS-IP, Regression line slopes within the IPC and AMS periods; Reg. slope AMS-IP, regression line slopes within the AMS period; VRE, vancomycin-resistant enterococci; 3GCREB, third-generation cephalosporin-resistant Enterobacterales.

[a] The results refer to GAS/PUL, INF at study site 4 was not included as IPC and AMS interventions started simultaneously.

HHC, and CA were seen at site 2, and for PPS, but not for HHC and CA, at site 3.

The results of the ITSA analysing the impact of reinforced IPC- and AMS measures on infection incidence densities (Table 3) showed a slight decrease in CDI incidence density during the AMS-IP for all departments pooled (effect AMS-IP: regression slope difference post intervention = −.202, F[*p*] = 0.731 [0.409]), whereas this mostly reflected a reduction at site 1. Simultaneously, a small reduction in VRE/3GCREB BSI incidence density was notable for both, IPC- and AMS-IP as well as AMS-IP only (effect during IPC and AMS period, regression slope difference = −.044; F[*p*] = 0.277 [0.609]; effect during AMS-IP only, regression slope difference = −.097; F[*p*] = 0.713 [0.415]).

The highest antibiotic prescription density was seen for fluoroquinolones (M = 101 RDD/1.000 PD), broad-spectrum penicillins (M = 98 RDD/1000 PD), and carbapenems (M = 80 RDD/1000 PD), whereas site 3 accounted for a high fluoroquinolone usage (M = 256 RDD/1000 PD) (Table S15). The results of the ITSA analysing the impact of AMS measures on prescription density (Table S16) showed a significant reduction in carbapenem usage at site 3 (regression slopes difference = −26.542; F*[p]* = 4.9 [0.046]; Fig. S4). No significant changes could be observed for all sites pooled.

Discussion

This study is the first to evaluate the impact of enhanced IPC and AMS measures on CDI and BSI by VRE and 3GCREB using a stepped-wedge design in a multicentre tertiary care hospital setting. Departments were selected based on a high CDI baseline incidence, assuming that this would reflect a high incidence of VRE and 3GCREB BSI. Our analysis revealed that, combined with IPC, the short-term enhancement of AMS measures led to a significant reduction in the incidence of CDI. For VRE and 3GCREB BSI, no significant reductions were observed, although limited by the relatively low number of recorded infections.

Table 3
Results of interrupted time series analysis evaluating the impact of intervention period and antimicrobial stewardship measures on *Clostridioides difficile* and vancomycin-resistant enterococci/third-generation cephalosporin-resistant Enterobacterales incidence density during the normalized study period at the haematological and oncological departments

Haem/Onc DPs	Effect during IPC and AMS periods (6 mo BP vs. 10 mo IPC- + AMS-IP)				Effect during AMS period (12 mo BP + IPC-IP vs. 4 mo AMS-IP)			
	Reg. slope BP(p)	Reg. slope IPC- + AMS-IP(p)	Reg. slopes diff.	F(p)	Reg. slope BP + IPC-IP(p)	Reg. slope AMS-IP(p)	Reg. slopes diff.	F(p)
CDI incidence density								
1	−0.067 (0.776)	0.056 (0.829)	−0.011	0.049 (0.829)	0.087 (0.288)	−0.448 (0.313)	−0.363	1.109 (0.313)
2	−0.102 (0.696)	0.077 (0.79)	−0.025	0.074 (0.79)	0.009 (0.918)	0.104 (0.830)	0.113	0.048 (0.83)
3	−0.198 (0.532)	0.207 (0.554)	0.009	0.371 (0.554)	−0.206 (0.094)	0.216 (0.732)	0.01	0.123 (0.713)
Haem/Onc DPs pooled	−0.1 (0.491)	0.092 (0.559)	−0.008	0.362 (0.559)	0.018 (0.703)	−0.22 (0.409)	−0.202	0.731 (0.409)
VRE + 3GCREB BSI incidence density								
1	0.000 (0.999)	−0.051 (0.712)	−0.051	0.143 (0.712)	0.054 (0.265)	−0.120 (0.643)	−0.066	0.227 (0.643)
2	0.000 (1)	0.000 (0.392)	0	0.788 (0.392)	0.004 (0.882)	−0.004 (0.978)	0	0.001 (0.978)
3	0.000 (1)	−0.018 (0.89)	−0.018	0.02 (0.89)	0.052 (0.155)	−0.428 (0.041)	−0.406	5.222 (0.041)
Haem/Onc DPs pooled	0.001 (0.995)	−0.045 (0.609)	−0.044	0.277 (0.609)	0.046 (0.163)	−0.143 (0.169)	−0.097	0.713 (0.415)

ITSA was performed considering the infection density per 1000 patient days. Associated p values indicate significance of trend in the respective time series ($p < 0.05$). A p value < 0.05 suggests that the intervention had a significant effect on the time series.
AMS-IP, antimicrobial stewardship intervention period; BP, baseline period; CDI, *Clostridioides difficile;* F(p), F-value of the hypothesis test assessing whether there is a significant change in the slope of the regression line during the intervention period (a high F-value indicates an effect); Haem/Onc DPs, haematological and oncological departments; Haem/Onc pooled: sum of the infection density (CDI or VRE+3GCREB) of the respective study sites for the corresponding months; IPC-IP, infection control intervention period; Reg. slope diff., difference between Reg. slope baseline period/Reg. slope baseline and IPC-IP and Reg. slope IPC- and AMS-IP/Reg. slope AMS-IP; Reg. slope BP, Regression line slopes within the baseline period; Reg. slope BP + IPC-IP, Regression line slopes within the baseline and IPC-IP; Reg. slope IPC + AMS-IP, Regression line slopes within the IPC and AMS periods; Reg. slope AMS-IP, regression line slopes within the AMS period; VRE, vancomycin-resistant enterococci; 3GCREB, third-generation cephalosporin-resistant Enterobacterales.

Our findings align with those of prior research, indicating inconsistent effects of AMS interventions to reduce infections [4,16]. Meta-analyses have shown CDI reductions of up to 32% following AMS, particularly when combined with IPC measures [6]. Same as for the ABSOLUTE sites, most academic medical centres already have robust IPC and AMS measures in place. Additional reinforcement efforts may thus only have a marginal impact on clinical outcomes because most improvements had already been realized [17]. An overall decline in CDI rates in Germany between 2015 and 2021, potentially due to broader hospital hygiene initiatives in general and also at the ABSOLUTE sites, may have contributed to the effect seen in our study [18]. However, the CDI incidence in ABSOLUTE departments was considerably higher than recently published reference data [10].

The subgroup analysis of included haematology and oncology departments revealed a slight decrease in CDI incidence density during AMS-IP. A modest decline in VRE/3GCREB incidence density was observed across IPC and AMS intervention periods. Although not significant, our results highlight the potential of intensified AMS measures to mitigate infections in this setting, and the results might have been more pronounced with no or low AMS baseline levels. Analysis of the antibiotic prescription density in the haematology and oncological setting demonstrated significant reductions in carbapenem usage at site 3, whereas the short AMS-IP (4 months) and outliers in the respective prescription density at the beginning of the AMS-IP led to a larger statistical effect. Notably, recent studies in our university hospital setting have identified carbapenem consumption as the only antibiotic class associated with an increase in CDI incidence in the haematology/oncology [10]. At site 3, where baseline carbapenem and general antibiotic usage were particularly high, no change in CDI incidence density was seen. Antimicrobial prophylaxis with fluoroquinolones was routinely used at site 3, whereas in accordance with national guidelines, it was more restrictively applied at sites 1 and 2 [19]. This explains the notable differences in fluoroquinolone usage among sites and the more pronounced impact on fluoroquinolone prescription density at site 2. Few other studies investigated the impact of AMS measures in this setting. In a tertiary care hospital in France, a multifaceted AMS intervention was implemented to improve febrile neutropenia management [20]. After 6 months, overall antibiotic consumption significantly declined, particularly carbapenem usage. However, this investigation was limited by its single-centre design and did not assess infection-related outcomes. Overall, our findings demonstrate that intensified AMS measures can influence prescribing behaviours in haematological and oncological settings, although their short-term impact on clinical outcomes was limited.

Our study has several limitations. It was conducted in hospitals with pre-existing AMS and IPC programmes, limiting its generalizability to settings with no or low baseline measures. The original recruitment goal (estimated 584,640 PDs) was missed; after normalization of the study period, the data set included 384,263 PDs, potentially underestimating the intervention's impact. The relatively short observation period following interventions, lack of a wash-in phase, and statistical modelling required for data normalization and imputation may have underestimated the impact of interventions. The chosen censoring method may have affected the interpretation of ITSA results. As only positive CDI results were reported, increased testing due to AMS measures and awareness could have increased testing and thereby detection rates. Contact precautions for VRE and 3GCREB varied between the study sites, and the predominance of infections caused by *E. coli*, which is less transmissible than Klebsiella species, may have reduced the impact of IPC measures on 3GCREB infections. No molecular typing or environmental screening was performed, limiting insights into transmission dynamics and potential reservoirs. Multiresistant *Staphylococcus aureus* was not a target pathogen, although an impact of enhanced IPC measures could be assumed. Local differences in intervention implementation, success rates of measures, and staff variability could have affected the results, with a few sites possibly having a disproportionate impact on the overall findings. Additionally, patient-specific risk factors were not considered.

In summary, our study showed that in academic medical centres with well-established baseline IPC and AMS programmes, the combination of IPC with short-term AMS reinforcement led to a significant reduction in the incidence of CDI, whereas no major additional effect on BSI by VRE and 3GCREB was observed. Enhancement of AMS measures in the haematological and oncological setting did influence prescription behaviours according to implemented AMS strategies, whereas our study was not

sufficiently powered to detect the impact on clinical outcomes in this high-risk subpopulation. Future studies and AMS programmes should focus on settings with lower baseline IPC and AMS implementation to achieve a more substantial impact.

CRediT authorship contribution statement

Jörg J. Vehreschild and Annika Y. Classen: Overall project administration and supervision. **Evelina Tacconelli, Winfried V. Kern, Holger Rohde, and Petra Gastmeier**: Site specific project administration. All coauthors participated in the investigation and conduct of the ICP and AMS measures presented in this study. **Jörg J. Vehreschild and Annika Y. Classen, and Thilo Dietz**: Formal analysis and data visualization. **Jörg J. Vehreschild and Annika Y. Classen, and Thilo Dietz**: Wrote the original draft of the manuscript, all authors reviewed and edited the manuscript. All authors were substantially involved in the conceptualization and the design of the methodology of the Antibiotic Stewardship and Infection Control in Patients at High Risk of Developing Infection by Clostridium Difficile, Vancomycin-Resistant Enterococci or Multi-Resistant Gram-Negatives (ABSOLUTE) study.

Transparency declaration

Potential conflict of interest

A.Y.C., T.D., L.D.G., S.E., P.G., S.G., A.H., F.H., N.K., W.V.K., E.K., C.B. C., H.S., A.M., A.M.R., H.R., J.R., E.T., S.V.W., J.Z., and J.J.V. declare that they have no conflict of interest with regard to the presented study. F.P.M. is an employee of Basilea Pharmaceutica International AG Allschwil, Switzerland. The work undertaken by F.P.M. as part of this study was carried out prior to the commencement of this employment.

Financial report

This work was supported by the German Centre for Infection Research (DZIF, grant number TTU 08.810). The founder had no role in the design of the study, performed data collection and analysis, result interpretation and manuscript writing.

Data availability

Upon request to the corresponding author, data supporting the findings of this study can be made available.

Parts of this manuscript have been presented as a poster at the Joint Annual Meeting of the German Society for Infectious Diseases and the German Center for Infection Research in 2019, Bad Nauheim, Germany (abstract number A-213). Moreover, date from study site 1 included in this manuscript have been previously analysed and published as part of an academic master thesis of the coauthor T.D.

Acknowledgements

We would like to thank all members of the ABSOLUTE study group: Hartmut Bertz, Michael Buhl, Lena M. Biehl, Alison Dörnte, Alexander Mischnik, Alessia Savoldi, Silke Peter, Michaela Steib-Bauert, and Maria J. G. T. Vehreschild. Additionally, we would like to thank Stefanie Bastek, Paul Brinkkötter, Antje Deppe, Corinna Grathwohl, Kevin Hartmann, Katharina Ludwig-Stollenwerk, Roman-Ulrich Müller, Dennis Nano, Frank Prison, Holger Schmitt, Heike Spitznagel, Susanna Proske.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.08.013.

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