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Oral vancomycin use and incidence of vancomycin-resistant enterococci: time-series analysis

Seongman Bae[1,2*], Kyungkeun Cho[1,2], Inah Park[1,2], Jiae Kim[3], Hyewon Han[3], Jiwon Jung[1,4], Sung-Han Kim[1,4] and Sang-Oh Lee[1,2]

Summary

Background Vancomycin exposure is a major risk factor for vancomycin-resistant enterococci (VRE) colonisation, but the relationship between oral vancomycin and the risk of VRE colonisation remains poorly understood without ecological evidence. In this study, we investigated the association between oral vancomycin usage and the incidence of hospital-acquired VRE using a time-series analysis.

Methods This retrospective ecological study analysed monthly data on antibiotic usage and VRE incidence from January 2013 to December 2022 at a 2700-bed hospital in South Korea. Antibiotic usage was measured in days of therapy (DOT) per 1000 patient-days. Hospital-acquired VRE incidence was defined as the number of VRE isolates identified more than 48 h after admission per 1000 patient-days. The association between oral vancomycin use and VRE incidence was assessed using a multivariate autoregressive integrated moving average (ARIMA) regression model incorporating lag structures.

Results Over 10 years, 5,763 clinical VRE isolates were identified, with 5,133 (89%) being hospital-acquired. Oral vancomycin usage and VRE incidence showed significant upward trends during the study period. In the final ARIMA model adjusting for various types of antibiotic use and baseline VRE carriage rate, a significant association was observed between oral vancomycin use and VRE incidence (coefficient: 0.0160, 95% CI: 0.0030 to 0.0290, $P=0.0162$), with an R-squared value of 0.76. Sensitivity analyses demonstrated the robustness of the association between oral vancomycin use and VRE acquisition across various time lags between antibiotic use and VRE incidence.

Conclusions There was a significant association between institutional oral vancomycin use and hospital-acquired VRE incidence, highlighting the need for antibiotic stewardship for oral vancomycin use to contain the nosocomial spread of VRE in addition to infection control measures.

Keywords Vancomycin-resistant enterococci, Oral vancomycin, Antimicrobial stewardship, Healthcare associated infections

*Correspondence:
Seongman Bae
songman.b@gmail.com
[1]Department of Infectious Disease, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea
[2]Antibiotic Support Team, Asan Medical Center, Seoul, South Korea
[3]Department of Pharmacy, Asan Medical Center, Seoul, South Korea
[4]Office for Infection Control, Asan Medical Center, Seoul, South Korea

Introduction

Oral vancomycin remains a cornerstone in the treatment of *Clostridioides difficile* infection (CDI), particularly when fidaxomicin is not available [1, 2]. Vancomycin exposure is a major risk factor for the colonisation and infection of vancomycin-resistant enterococci (VRE), leading to concerns about the heightened VRE risk associated with oral vancomycin usage [3–6]. To date, however, the relationship between oral vancomycin and the risk of VRE colonisation remains poorly understood. Patient-level data showed inconsistent results on the association between oral vancomycin use and VRE; one study indicated that oral vancomycin increases the risk of VRE colonisation, whereas another found no significant difference [7, 8]. Although ecological studies examining the temporal variations in hospital-wide antibiotic usage and their impact on VRE incidence have identified institution-level glycopeptide use as a significant variable for VRE, the impact of oral formulations of vancomycin has not been separately analysed [9, 10]. In this ecological study, we investigated the association between oral vancomycin usage and hospital-acquired VRE incidence using monthly time-series data collected over a decade from a tertiary hospital in South Korea.

Methods

Hospital settings and data collection

This retrospective analysis utilised monthly time-series data on antibiotic usage and VRE incidence collected from January 2013 to December 2022 at a 2700-bed hospital in South Korea. The collected monthly data included the number of patient-days for all hospitalised patients during the study period, the usage levels of antibiotics, and the number of VRE isolates identified from clinical specimens. In cases where VRE was isolated, contact precautions were implemented, requiring healthcare personnel to wear gowns and gloves during patient care. Additionally, environmental cleaning of the patient's room was performed once daily. We examined whether the monthly usage of oral vancomycin was significantly associated with the incidence of VRE within the hospital. Ethical approval for this study was granted by the Institutional Review Board at Asan Medical Center (IRB No. 2024−0835).

Definitions

Antibiotic usage was measured in days of therapy (DOT), defined as the number of days a patient received a specific antibiotic regardless of the dosage. DOT for each antibiotic was aggregated monthly and standardised per 1000 patient-days. In addition to oral vancomycin, monthly DOT data were collected for intravenous (IV) vancomycin, teicoplanin, metronidazole, fluoroquinolones (ciprofloxacin and levofloxacin), first-generation cephalosporin (cefazolin), second-generation cephalosporins (cefuroxime and cefoxitin), broad-spectrum cephalosporins (ceftriaxone, cefotaxime, ceftazidime, ceftizoxime, and cefepime), carbapenems (meropenem, imipenem, and ertapenem), ampicillin-sulbactam, piperacillin-tazobactam, tigecycline, linezolid, aminoglycosides (amikacin, gentamicin, and tobramycin), co-trimoxazole, and colistin.

VRE cases included either *Enterococcus faecalis* or *Enterococcus faecium* isolates resistant to vancomycin from clinical samples such as blood, respiratory specimens, and urine specimens. Identification and antimicrobial susceptibility testing of *Enterococcus* isolates from clinical specimens were performed using the MicroScan system (Dade Behring, Deerfield, IL, USA). Only the first isolate per patient was counted, and surveillance cultures for infection control purposes were excluded. Isolates identified within 48 h of hospital admission were defined as baseline community-onset carriage, whereas those identified after 48 h were considered hospital-acquired cases. VRE incidence was defined as the number of hospital-acquired VRE isolates per 1,000 patient-days.

Statistical analysis

The trend of monthly antibiotic usage during the study period was estimated using simple linear regression. The association between monthly oral vancomycin DOT and hospital-acquired VRE incidence was assessed using time-series regression with dynamic regression time-series models using an autoregressive integrated moving average (ARIMA) model [11]. The stationarity of the monthly time-series data on hospital-acquired VRE incidence was assessed using an augmented Dickey-Fuller test. Parameters for the ARIMA models for VRE incidence during the study period were selected using the 'auto. arima' function from the 'forecast' package in R software. The ARIMA model was parameterized as ARIMA (p, d, q), where p is the order of autoregressive terms, d is the degree of differencing, and q is the order of moving average terms. These parameters were selected to achieve stationarity and optimize model fit. The ARIMA models included the use of various antibiotics as exogenous variables, along with baseline VRE carriage rate. The time lags between each variable and VRE incidence were determined using the cross-correlation function (CCF). The final ARIMA regression model was fitted with lagged variable data, reflecting the time lags obtained from the CCF. Additionally, the model's fit was evaluated using the Akaike information criterion (AIC) and the coefficient of determination (R^2). The R^2 value represents the proportion of variance in the observed time-series data that is explained by the model. The Ljung-Box test was performed to check for autocorrelations in the residuals of the fitted ARIMA models. Furthermore, the normality

of residuals was assessed using the Jarque-Bera test to ensure that the residuals did not significantly deviate from a normal distribution. We performed several sensitivity analyses to evaluate the robustness of our findings. These analyses included: (i) assuming time lags of three months before or after the lags identified by the CCF to account for various potential delayed effects, (ii) conducting analyses without assuming any time lags, and (iii) performing analysis with the time lag between each antimicrobial use and the VRE incidence estimated using CCF between the residuals of ARIMA models for exogenous variables and VRE incidence. There were no missing values for all independent variables. All statistical analyses were conducted using R Statistical Software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Over the 10-year study period, from January 2013 to December 2022, a total of 9,164,910 patient-days were included, with an average of 76,374 patient-days per month (range: 66,895 to 82,967). During this period, 5,763 clinical VRE isolates were identified, with 630 (11%) identified within 48 h of admission (baseline VRE carriage) and 5,133 (89%) identified after 48 h of hospitalisation (hospital-acquired VRE cases).

Trend of antibiotic use and VRE incidence

Trends of antibiotic usage and hospital-acquired VRE incidence during the study period are summarised in Table 1. Oral vancomycin usage and VRE incidence showed a significant upward trend (coefficient: 0.0013, $P<0.0001$; Fig. 1). Among other types of antibiotics, significant upward trends were observed for teicoplanin (coefficient: 0.0032, $P<0.0001$), cefazolin (coefficient: 0.0165, $P<0.0001$), cefoxitin (coefficient: 0.0087, $P<0.0001$), piperacillin-tazobactam (coefficient: 0.0090, $P<0.0001$), ampicillin-sulbactam (coefficient: 0.0013, $P<0.0001$), and co-trimoxazole (coefficient: 0.0016, $P<0.0001$). Conversely, significant downward trends were observed for intravenous vancomycin (coefficient: -0.0052, $P<0.0001$), metronidazole (coefficient: -0.0061, $P<0.0001$), fluoroquinolones (coefficient: -0.0014, $P=0.0015$), cefuroxime (coefficient: -0.0061, $P<0.0001$), broad-spectrum cephalosporins (coefficient: -0.0029, $P=0.0009$), carbapenems (coefficient: -0.0055, $P<0.0001$), tigecycline (coefficient: -0.0009, $P<0.0001$), and colistin (coefficient: -0.0008, $P<0.0001$). The usage of linezolid (coefficient: -0.0002, $P=0.2066$) and aminoglycosides (coefficient: -0.0003, $P=0.1666$) did not show significant trends. The trends of antibiotic usage other than oral vancomycin are shown in Fig. 2.

Table 1 Trends of monthly antibiotic usage and VRE incidence during 2013 – 2022

	Monthly average	Range	Trend	Coefficient	*P*-value
Type of antibiotic					
Oral vancomycin	4.68	1.45–9.59	Upward	0.0013	< 0.0001
IV vancomycin	35.13	23.10–49.69	Downward	-0.0052	< 0.0001
Teicoplanin	18.24	9.74–27.24	Upward	0.0032	< 0.0001
Metronidazole	52.63	15.74–67.67	Downward	-0.0061	< 0.0001
Fluoroquinolones	59.61	50.46–79.06	Downward	-0.0014	0.0015
Cefazolin	50.89	21.12–96.73	Upward	0.0165	< 0.0001
Cefoxitin	14.41	1.26–33.72	Upward	0.0087	< 0.0001
Cefuroxime	12.17	1.83–28.46	Downward	-0.0061	< 0.0001
Broad-spectrum cephalosporins	153.12	88.76–166.03	Downward	-0.0029	0.0009
Carbapenems	63.69	44.02–89.74	Downward	-0.0055	< 0.0001
Piperacillin-tazobactam	76.85	58.74–102.65	Upward	0.0090	< 0.0001
Ampicillin-sulbactam	25.03	18.67–33.01	Upward	0.0013	< 0.0001
Tigecycline	7.19	3.01–12.58	Downward	-0.0009	< 0.0001
Linezolid	6.25	3.12–10.33	No	-0.0002	0.2066
Aminoglycosides	13.25	8.91–18.96	No	-0.0003	0.1666
Co-trimoxazole	6.78	2.58–12.44	Upward	0.0016	< 0.0001
Colistin	6.53	2.84–11.90	Downward	-0.0008	< 0.0001
VRE incidence					
Hospital-acquired VRE incidence	0.56	0.24–0.99	Upward	0.00003	< 0.0001
Baseline VRE carriage rate	0.01	0.00–0.19	Upward	0.00003	< 0.0001

The antibiotic usage is expressed in days of therapy (DOT) per 1000 patient-days, and VRE incidence is expressed in number of isolates per 1000 patient-days. The coefficients and P-values were estimated from simple linear regression analysis

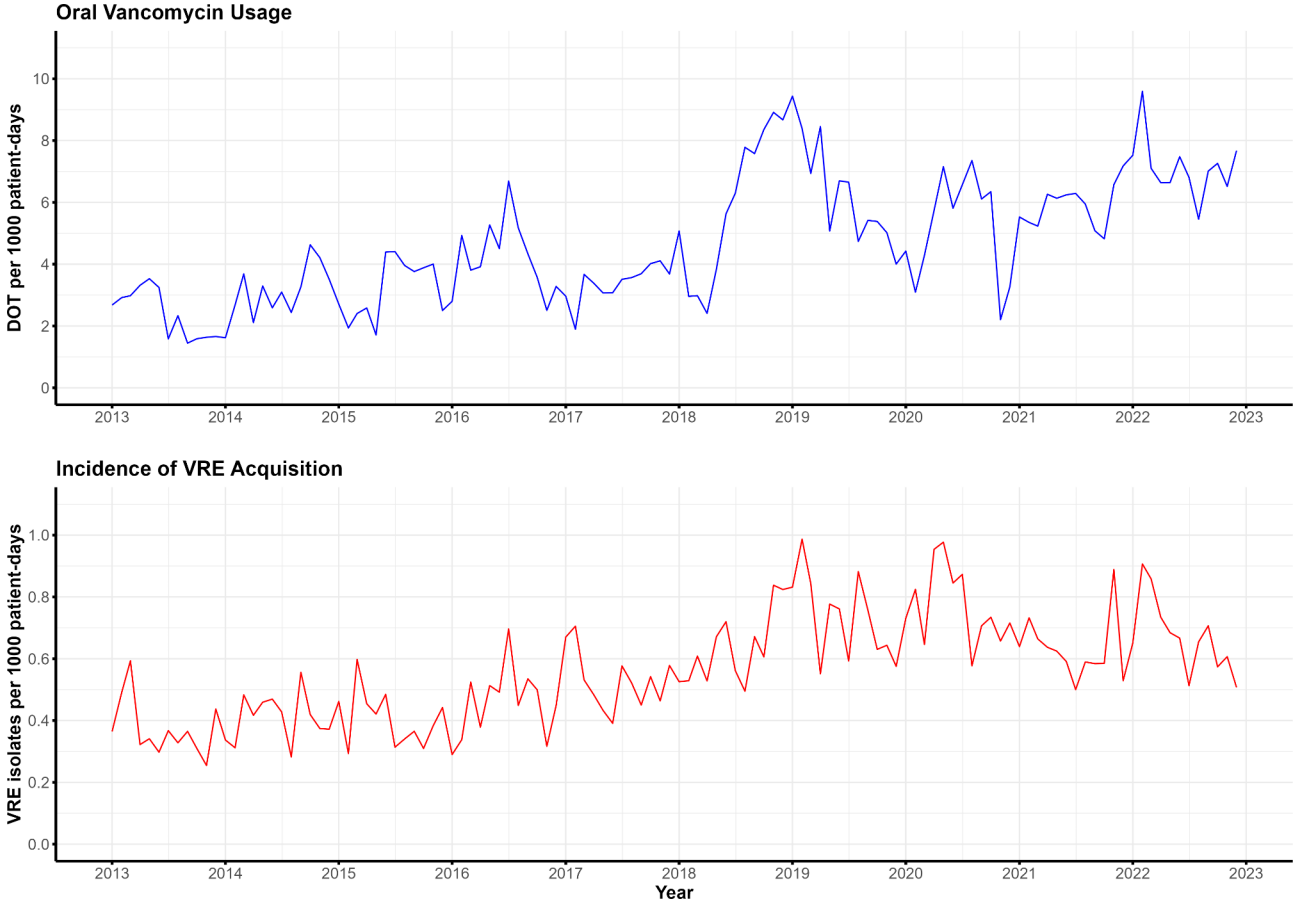

Fig. 1 Monthly Trends of Oral Vancomycin Usage and Incidence of VRE Acquisition (2013–2023)

Association between oral Vancomycin use and hospital-acquired VRE incidence

A simple correlation analysis showed that monthly oral vancomycin use was significantly correlated with VRE incidence (Pearson's $r=0.64$, $P<0.001$; Fig. 3). The 10-year monthly VRE incidence time-series data was analysed using an ARIMA model, with ARIMA ($p=4$, d=1, q=1) being identified as the best-fitting model to describe the VRE incidence trend. The optimal time lag between oral vancomycin use and subsequent VRE incidence determined by CCF was found to be 0 months. In the univariate analysis, the use of oral vancomycin was significantly associated with VRE incidence, with an R-squared value of 0.62 (Table 2). In the multivariate analysis, which adjusted for the usage of different types of antibiotics and the baseline VRE carriage rate as variables, the use of oral vancomycin was significantly associated with VRE incidence, with an R-squared value of 0.76 (Table 2). The model diagnostics for the final ARIMA model are summarized in the Supplementary Fig. 1. In various sensitivity analyses assuming different time lags between antibiotic usage and VRE incidence, a significant association between oral vancomycin use and VRE incidence was consistently observed (Table 3). Detailed results of the sensitivity analyses are summarised in Supplementary Tables S1 to S5.

Discussion

In this time-series study, we found a significant association between oral vancomycin use and the incidence of hospital-acquired VRE. This association remained robust even after adjusting for the usage of different types of antibiotics and the baseline VRE carriage rate in the model, as well as in sensitivity analyses assuming various time lags. These results suggest that increased use of oral vancomycin may be a contributing factor to the rise in VRE colonisation and infection within hospitals.

The acquisition of VRE is attributed to transmission from external sources or other patients, rather than de novo emergence [12]. Therefore, not only individual antibiotic use but also antibiotic use at the surrounding or institutional level contributes to the risk of VRE spread. Indeed, admission to a bed previously occupied by patients with VRE colonisation has been identified as a risk factor for VRE acquisition [13]. Additionally, the presence of neighbouring patients receiving vancomycin

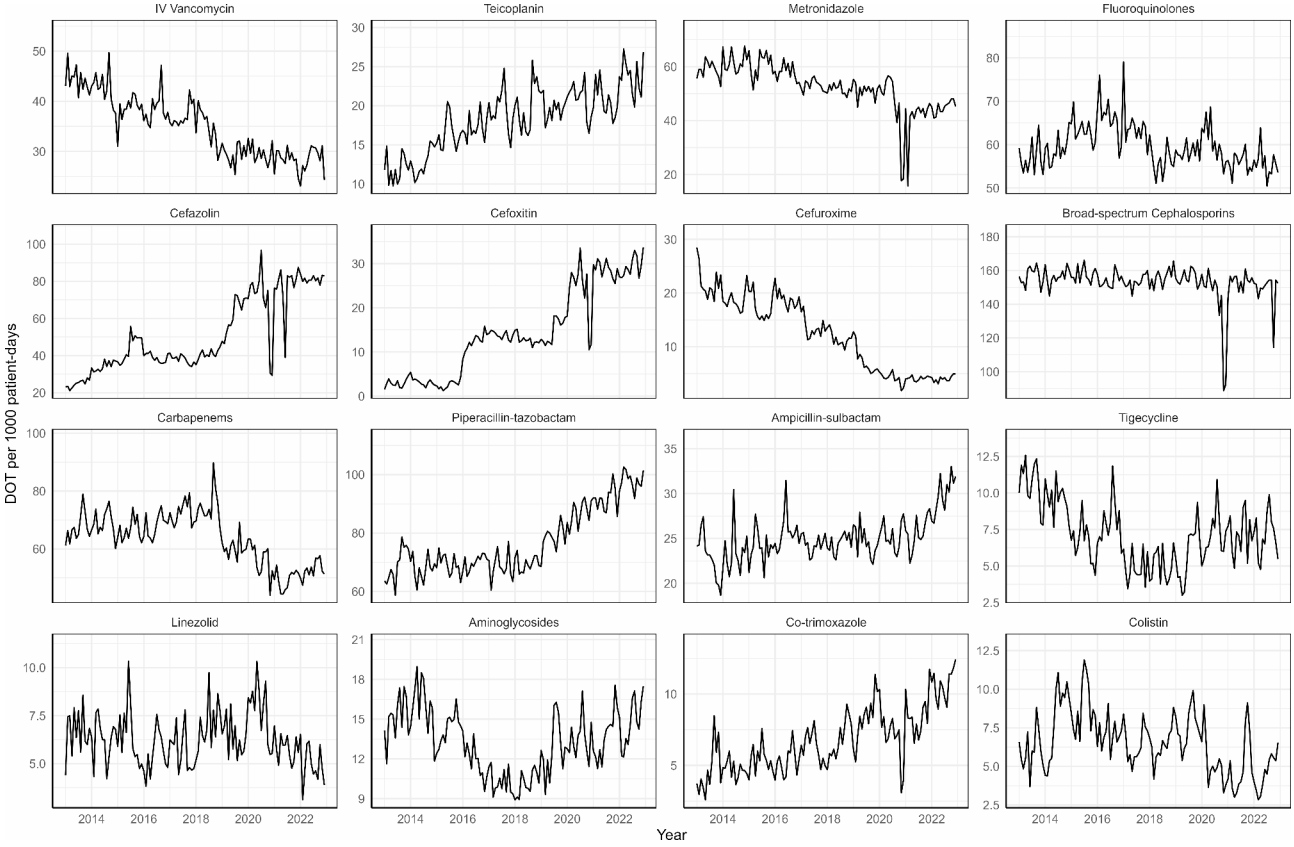

Fig. 2 Monthly Trends of Various Antibiotic Usages

was associated with VRE colonisation, and the duration of VRE colonisation was significantly longer in ICUs with high vancomycin use [14, 15]. This necessitates an analysis of the risk of VRE colonisation based on antibiotic usage, including oral vancomycin, at the institutional level.

In this study, using a dynamic regression time-series model, a significant association between oral vancomycin and the acquisition of VRE was observed. In contrast, the use of IV vancomycin showed no significant association with VRE acquisition. This significant association of oral vancomycin, but not IV vancomycin, with VRE acquisition can be attributed to the fact that the oral form achieves significantly higher concentrations in the gut, the primary milieu for VRE colonisation [16, 17]. Additionally, oral vancomycin interacts with gastrointestinal mucin to form aggregates, which prevents its rapid removal from the gastrointestinal tract [18]. This also leads to prolonged exposure to the antibiotic, thereby contributing more significantly to VRE selection and persistence in the gastrointestinal tract. Indeed, oral vancomycin, compared to metronidazole used in the treatment of CDI, causes greater disruption of normal flora and contributes to VRE persistence in a mouse model [19].

On the other hand, in addition to oral vancomycin, cefuroxime showed a negative association with VRE acquisition, whereas ampicillin-sulbactam showed a significant positive association. Notably, linezolid, an antibiotic used to treat VRE, also showed a positive correlation with VRE acquisition. This counterfactual result may stem from a spurious relationship where increased VRE leads to more linezolid use and decreased VRE leads to less linezolid use [20, 21]. The possibility of spurious relationships between linezolid and VRE is supported by the sensitivity analysis results in this study, that the significant association between linezolid and VRE colonisation at time lag 0 months disappeared at the time lags of 1, 2, and 3 months. In contrast, oral vancomycin was the only antibiotic that consistently showed a robust association with VRE colonisation across all time lags (0, 1, 2, and 3 months), suggesting a true association.

This study has several limitations. First, it was a single-institution observational study. Therefore, further ecological studies from different countries and institutions are needed to confirm the association between oral vancomycin and VRE colonisation. Second, because of the retrospective design of the study, there may have been undetected VRE cases during the study period. Additionally, unmeasured confounders such as changes in

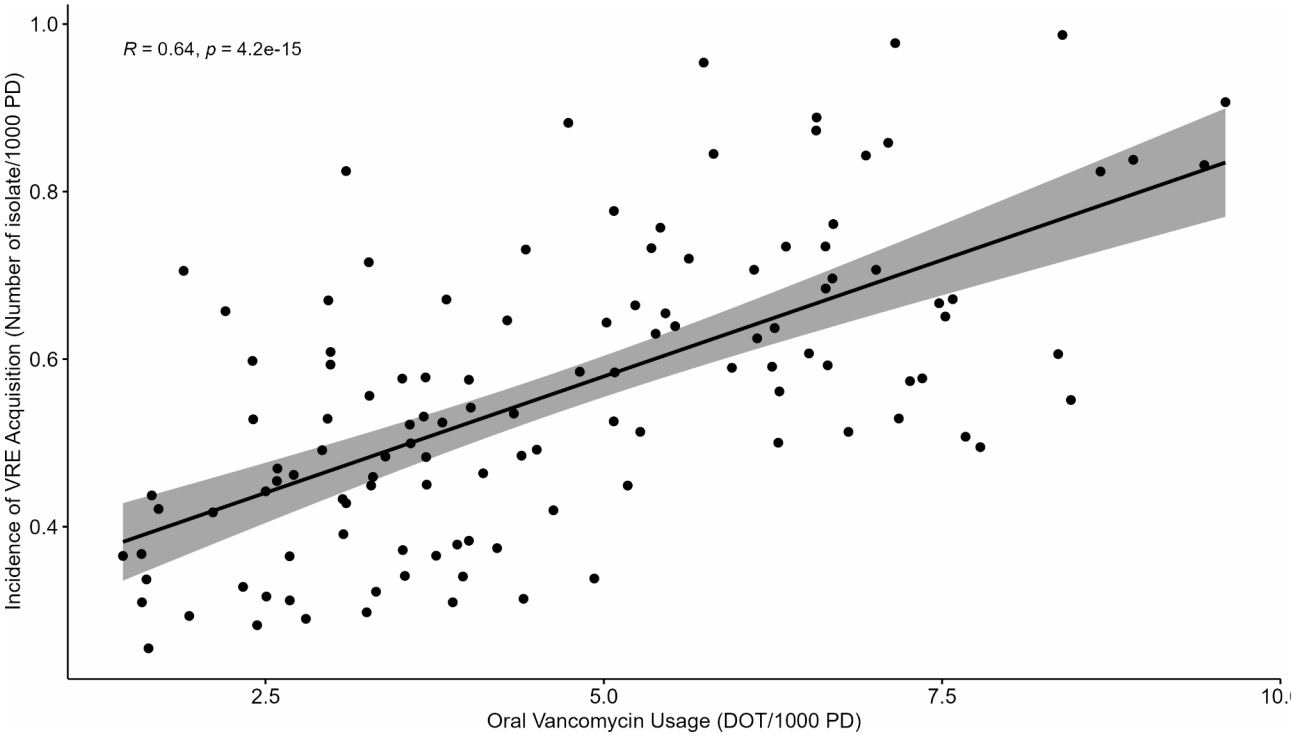

Fig. 3 Correlation Between Oral Vancomycin Usage and Incidence of VRE Acquisition. Scatter plot showing the correlation between oral vancomycin usage (DOT/1000 patient-days) and incidence of VRE acquisition (number of isolates/1000 patient-days). Each point represents the corresponding monthly oral vancomycin use and VRE incidence. The solid line indicates the linear regression line, and the shaded area represents the 95% confidence interval for the regression line

Table 2 Association between antibiotic use and hospital-acquired VRE incidence

		Univariate analysis			Multivariate analysis		
Variable	**Lag**	**Coefficient**	**95% CI**	***P*-value**	**Coefficient**	**95% CI**	***P*-value**
Oral vancomycin	0	0.0191	0.0017 to 0.0364	**0.0312**	0.0160	0.0030 to 0.0290	**0.0162**
IV vancomycin	6	-00.004	-0.0120 to 0.0039	0.3164	-0.0048	-0.0107 to 0.0011	0.1120
Teicoplanin	0	-0.0019	-0.0114 to 0.0076	0.6916	0.0048	-0.0030 to 0.0127	0.2269
Metronidazole	4	-0.0009	-0.0048 to 0.0029	0.6292	-0.0015	-0.0048 to 0.0017	0.3549
Fluoroquinolones	5	-0.0028	-0.0075 to 0.0020	0.2496	0.001	-0.0027 to 0.0048	0.5927
Cefazolin	0	0.00003	-0.0023 to 0.0024	0.9808	-0.0001	-0.0021 to 0.0019	0.9374
Cefoxitin	0	0.0002	-0.0066 to 0.0070	0.9535	-0.004	-0.0089 to 0.0009	0.1132
Cefuroxime	6	-0.0136	-0.0261 to -0.0011	**0.0334**	-0.0181	-0.0250 to -0.0112	**< 0.0001**
Broad-spectrum cephalosporins	6	-0.0018	-0.0040 to 0.0004	0.1105	-0.0009	-0.0030 to 0.0011	0.3734
Carbapenems	5	-0.0018	-0.0062 to 0.0026	0.4190	0.0029	-0.0002 to 0.0061	0.0663
Piperacillin-tazobactam	0	0.0002	-0.0043 to 0.0047	0.9227	-0.0024	-0.0057 to 0.0009	0.1560
Ampicillin-sulbactam	1	0.0171	0.0077 to 0.0265	**< 0.0001**	0.0148	0.0066 to 0.0230	**0.0004**
Tigecycline	6	-0.0031	-0.0165 to 0.0102	0.6449	0.0126	0.0012 to 0.0241	**0.0303**
Linezolid	0	0.0190	0.0047 to 0.0334	**0.0094**	0.0213	0.0089 to 0.0336	**0.0007**
Aminoglycosides	2	-0.0036	-0.0167 to 0.0096	0.5953	-0.0009	-0.0115 to 0.0098	0.8704
Co-trimoxazole	4	0.0101	-0.0054 to 0.0256	0.2010	0.0013	-0.0117 to 0.0143	0.8463
Colistin	5	0.0002	-0.0139 to 0.0142	0.9795	-0.0003	-0.0113 to 0.0107	0.9578
Baseline VRE carriage rate	0	0.0476	-0.5890 to 0.6843	0.8834	0.3640	-0.1986 to 0.9266	0.2048

CI, confidence interval

P-values indicating statistical significance are highlighted in bold

Table 3 Sensitivity analyses for the association between oral Vancomycin use and VRE incidence, assuming various time lag between antibiotic use and VRE incidence

Sensitivity analyses	Coefficient	95% CI	*P*-value
1-month lag between antibiotic use and VRE incidence	0.0193	0.0038 to 0.0349	**0.0145**
2-month lag between antibiotic use and VRE incidence	0.0171	0.0005 to 0.0337	**0.0435**
3-month lag between antibiotic use and VRE incidence	0.0310	0.0141 to 0.0478	**0.0003**
No lag between antibiotic use and VRE incidence	0.0186	0.0022 to 0.0351	**0.0267**
Assuming time lags estimated from residuals of ARIMA models for each variable	0.0192	0.0031 to 0.0353	**0.0194**

CI, confidence interval

P-values indicating statistical significance are highlighted in bold

infection control policies for patients with VRE or the degree of environmental contamination by VRE, which can be measured through environmental cultures, were not accounted for in this study. Third, as this analysis employed models incorporating differencing, there is a potential risk that valuable information regarding cointegration among the variables may have been lost. Fourth, the inclusion of higher-order ARIMA models and additional variables may have reduced the degrees of freedom and increased model complexity. This complexity could compromise the parsimony and interpretability of the results, which should be considered when drawing conclusions. Lastly, although visual inspection of the residuals from the final ARIMA model suggested approximate normality, statistical tests indicated deviations from a normal distribution, which may affect the reliability and robustness of the results.

In conclusion, we found that the institutional level of monthly oral vancomycin use was significantly associated with hospital-acquired VRE incidence. These results emphasise the need for meticulous attention and antibiotic stewardship regarding the use of oral vancomycin.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13756-024-01498-y.

Supplementary Material 1

Author contributions

S.B. was involved in the study design, analysis, and drafting of the manuscript. K.C., I.P., J.K., and H.H. contributed to data collection and curation, as well as the interpretation of the data. J.J., S.K., and S.-O.L. conducted the final analysis, interpreted the statistical results, and supervised the drafting of the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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