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Original Article

Potential causal effect of contact precautions and isolation on *Clostridioides difficile* infection in the hyperendemic setting: Interrupted time-series analyses before and after implementation

Eun Hwa Lee [a,1], Hye Sun Lee [b,1], Kyoung Hwa Lee [a], Young Goo Song [a], Sang Hoon Han [a,c,*]

[a] *Division of Infectious Disease, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea*
[b] *Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Republic of Korea*
[c] *Institute for Innovation in Digital Healthcare, Yonsei University College of Medicine, Seoul, Republic of Korea*

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KEYWORDS
Clostridioides difficile;
Contact precaution;
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Abstract *Background:* Recent studies disputed the effectiveness of efforts to comply with contact precautions and isolation (CPI) considering relatively low intra-hospital transmission rate of healthcare facility-associated *Clostridioides difficile* infection (HCFA-CDI). We evaluated the potential causal effect of CPI on HCFA-CDI occurrence by comparing the incidence rate (IR) for different time periods with and without CPI implementation.
Methods: Long-term observational time-series data were separated into three periods (pre-CPI: January 2012—March 2016, CPI: April 2016—April 2021, post-CPI: May 2021—December 2022). CPI was suspended owing to the restriction of isolation rooms during the COVID-19 pandemic. We inferred potential causal outcomes by comparing predicted and observed IRs of HCFA-CDI using interrupted time-series analyses, including the Bayesian structural time-series or autoregressive integrated moving average (ARIMA) model in the R-language or SAS software.
Results: The monthly observed IR (44.9/100,000 inpatient-days) during the CPI period was significantly lower than the predicted IR (90.8) (−50.6% relative effect, P = 0.001). However,

* Corresponding author. Division of Infectious Disease, Department of Internal Medicine, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul, 06273, Republic of Korea.
E-mail address: shhan74@yuhs.ac (S.H. Han).
[1] These authors contributed equally to this work.

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the observed IR (52.3) during the post-CPI period was significantly higher than the predicted IR (39.1) (33.6%, P = 0.001). The HCFA-CDI IR decreased during CPI (−14.3, P < 0.001) and increased post-CPI (5.4, P < 0.001) in the multivariable ARIMA model, which controlled for antibiotic usage, handwashing with soap and water, and number of toxin tests.
Conclusions: Various time-series models revealed that CPI implementation had a potential causal effect on the reduction of HCFA-CDI incidence.

Introduction

Clostridioides difficile infection (CDI), a common and important healthcare facility-associated (HCFA) infection worldwide,[1,2] can lead to significant mortality, morbidity, longer hospital stays, and higher costs.[3—5] These adverse outcomes, coupled with the risk of *C. difficile* spore transmission through environmental surfaces provides a rationale and validity for implementing infection prevention and control (IPC) measures to minimise new in-hospital acquisitions.[1,6]

The guidelines strongly recommend hand hygiene practices and wearing gloves and gowns for healthcare workers (HCWs) as well as isolation of confirmed CDI patients in a single room or cohort ward with dedicated toilet facilities from low or moderate quality of evidence.[7,8] However, a large population-wide cohort study by the Ontario Ministry of Health and Long-Term Care did not reveal that the hospital-level IPC processes including early contact precautions and isolation (CPI) substantially reduced HCFA-CDI.[9] The transmission rate of predominantly non-hypervirulent *C. difficile* was as low as only 1.3% among 451 exposures, and no outbreak of HCFA-CDI occurred during the suspension of CPI in a long-term prospective observational study.[10]

Recently, with the exception of disinfection of hands or hospital environment for multidrug-resistant organisms (MDROs) and CDI, the negative impacts and disadvantages of CPI have been suggested,[11—14] and their effectiveness and relevance have been refuted.[9,10,15,16] CPI implementation can impede physicians from promptly examining or frequently visiting patients, potentially delaying further medical management.[13,17] Furthermore, CPI strategies could limit some of the comprehensive rehabilitation and cause discomfort and discrimination by allowing tests, procedures, or surgeries to be performed as the last procedures of the day in clinical practice, potentially leading to suboptimal care.[18,19] Moreover, we should acknowledge dissatisfaction from inadequate information and psychological impacts of depression, anxiety and anger, especially in patients who are in isolation for a long period of time.[18,20—22] Taken together, the implementation of CPI may result in patient unsafety including non-infectious adverse events or drug prescription/administration errors and treatment beyond the best.[11,12,23,24]

The number of asymptomatic MDRO carriers requiring IPC continues to increase, but hospital resources are limited. Therefore, we need to investigate whether CPI with drawbacks and potential problems have a potential causal effect on the prevention of toxigenic *C. difficile* strains. Herein, we evaluated the impact of CPI on the incidence of HCFA-CDI by comparing three different periods: before, during, and after CPI implementation.

Methods

Study design and data collection

This retrospective, longitudinal, observational cohort study was conducted from January 2012 to December 2022 at Gangnam Severance Hospital, a university-affiliated tertiary referral hospital in Seoul. CPI strategies were applied for confirmed HCFA-CDI patients during the 61 month-period from April 2016 to April 2021 (intervention period). Our hospital launched CPI measures because of the hyperendemic situation in which the HCFA-CDI patients had consistently increased, but the CPI was suspended due to the lack of isolation rooms after the coronavirus disease (COVID-19) pandemic (Fig. 1A).

To evaluate the difference in monthly incidence rates (IRs) (cases per 100,000 inpatient-days) of HCFA-CDI before and after CPI, we defined the 51-month period from January 2012 to March 2016 as the pre-intervention period, and the 20-month period from May 2021 to December 2022 as the post-intervention period. During the pre- and post-intervention periods, general standard precautions without wearing gloves and gowns for CDI patients were implemented, but patients were not isolated (Fig. 1A).

To infer the potential causal effect of CPI on HCFA-CDI occurrence through in-hospital acquisition, this study only included patients with HCFA-CDI, including healthcare facility-onset (HO-HCFA) and community-onset (CO-HCFA).[1,8] Community-associated and indeterminate-onset CDI were excluded. HO-HCFA CDI were defined as the onset of symptoms correlated with CDI after 3 days of hospitalisation. CO-HCFA CDI was defined as the onset of symptoms in the community or ≤3 days of admission, having started within ≤4 weeks of the last discharge.[1,8] CDI that occurred within 4—8 weeks of a previous episode in which all symptoms improved after complete treatment was considered reinfection during the same admission and was included as a new case, but patients with CDI reoccurring within 4 weeks were treated as duplicates considering of treatment failure and relapse.[8,25]

To control for confounding factors,[1,26] we collected the following data: (1) the monthly number of *C. difficile* toxin assays, excluding repetition on the same day and follow-up

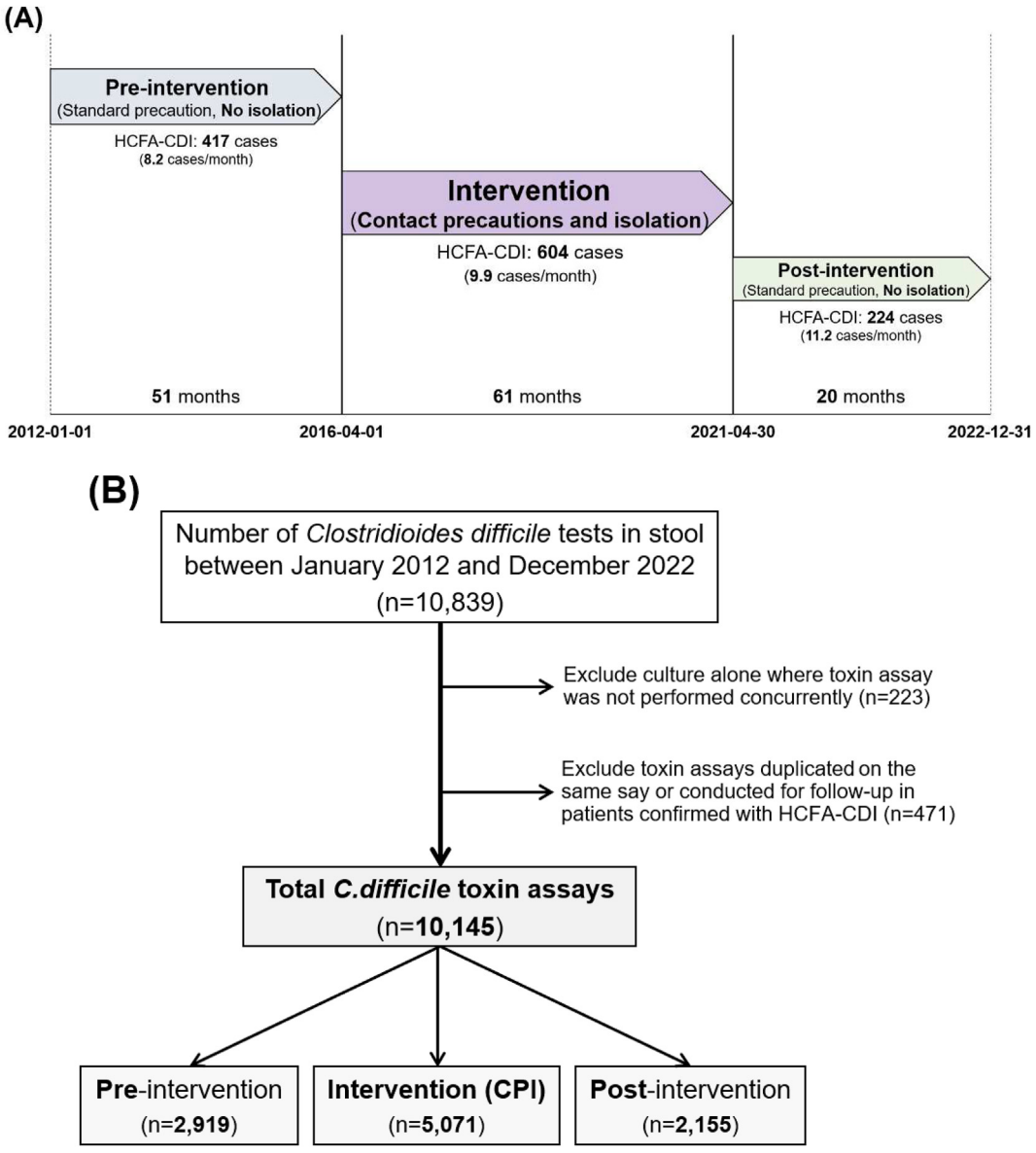

Figure 1. Schematic representation of study periods and selection process of *C. difficile* toxin assays in stool
Aberrations: HCFA-CDI, healthcare facility-associated *C. difficile* infection.; CPI, contact precautions and isolation

tests (Fig. 1B); (2) monthly antibiotic usage; (3) performance rates (%) of handwashing with soap and personal protective equipment (PPE) use of HCWs per quarter of a year, which were investigated prospectively for routine IPC in the hospital-based infection control unit (number of correct executions according to the guidelines divided by number of observations).

The antimicrobial use density (AUD) (defined daily doses [DDD]/1000 patient-days) in all hospitalised patients was examined for antibiotics commonly associated with the occurrence of CDI, which were ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones,[26] and calculated as follows: (amount of antibiotics consumed in one month [mg or g or unit]/DDD)/(inpatient-days in the month) × 1000.[27]

This study was approved by the Institutional Review Board of Gangnam Severance Hospital was exempt from the need to obtain informed consent, because it was a retrospective medical record data analysis and all data were collected and analysed after being anonymized (approval No. 3-2022-0451).

Case definition of *C. difficile* infection

An episode of CDI was defined as described previously.[7,25] We determined the toxigenic *C. difficile* strain from polymerase chain reaction (PCR)-based detection of toxin genes.[25] Loose stool samples from patients with symptoms consistent with CDI were tested for *tcdA* and *tcdB*, which

encode toxin A and B, respectively, using an AdvanSure™ CD multiplex real-time PCR kit (LG Life Sciences, Seoul, South Korea).[28]

Standard IPC and CPI processes for *C. difficile*

Special enteric precautions including handwashing with water and soap for HCWs, patients, and caregivers were implemented according to guidelines.[7,8,29] Isolation for CDI was performed from the date of toxin positivity to 48 h after improvement of diarrhoea.[7,8] A cohort of patients with CDI, without MDROs, was isolated in the shared room only if private rooms were not available.[7,8] A clear and explicit precaution notice including all detailed information about CPI policies including proper hand hygiene methods and procedures was attached in front of the CDI isolation rooms. The trained and dedicated personnel of infection control unit continuously provide education and encouragement on handwashing with water and soap before contact with CDI patients and after removing gloves.[7] In addition, the infection control unit evaluated the execution rates, and conducted on-site inspections and training for improvement of correct hand hygiene and PPE use (see supplementary material for details). Active surveillance or pre-emptive isolation for risky or suspected cases was not conducted during the observational study period.

Statistical analyses

The interrupted time-series (ITS) analyses of our longitudinal data aimed to infer the potential causal effect of CPI implementation on the occurrence of CDI based on a potential outcome framework.[30] To achieve this goal, we applied the following three methodologies.

(1) A Bayesian structural time-series (BSTS) model, which is the combination of a linear Gaussian state-space model containing three components of local linear trend, seasonality, and autoregression, and a Kalman filter (see the supplementary materials) applying Bayesian inference, for estimating causal effects caused by intentional interventions using the CasualImpact package from Google Inc. (Mountain View, CA, USA) in R-language (version 4.1.3).[30,31] This model acquires monthly pointwise and cumulative residuals, which are equal to the difference between the predicted values from the model (counterfactuals, IR of HCFA-CDI that would have occurred if the CPI had never been implemented during the intervention period, and IR that would have occurred if the CPI had been implemented during the post-intervention period) and the actual observed data. It can infer the potential causal effects through relative effects calculated from the average pointwise residuals.
(2) An autoregressive integrated moving average (ARIMA) model to investigate whether CPI intervention leads to an independent change in the HCFA-CDI IR after controlling for confounding variables that may affect the HCFA-CDI IR in R-language, and multivariable models, by applying ITS multiple linear regression analyses to obtain the coefficients (standard error [SE]) in SAS software (version 9.4).[32] Our time-series data, which are stationary with constant statistical properties over time and autocorrelated characteristics, apply a non-seasonal ARIMA model with elements of p (order of the autoregression), d (degree to which the first difference is included), and q (order of the moving average) determined from the autocorrelation function (ACF) and partial ACF.[32,33]
(3) A semi-smooth step linear function algorithm (SSL) using the Prophet package in Python-language (version 3.11.1) to validate the trends of HCFA-CDI IR predicted using the BSTS and ARIMA models.[34] A trend line in SSL algorithm was generated by adjusting the slope of the linear function representing the trend of time-series data at several changing points based on Bayesian inference (Monte Carlo Markov Chain).[33—35] The algorithm was implemented using the Prophet package on Facebook (Meta Platforms, Inc. Menlo Park, CA, USA) based on the Scikit-learn Application Programming Interface (version 1.2.1), a machine learning library, and Python programming language (version 3.11.1).[33—36]

The handwashing and PPE performance rates between two and three periods were compared using independent t-tests and one-way ANOVA with Bonferroni post hoc test, respectively. In all statistical analyses, a two-tailed P value $\leq$ 0.05 was considered statistically significant. Data were visualized using the Matplotlib library (version 3.6.3) in the analysis based on Python.

Results

Performance rates of handwashing and PPE

Except for periods as low as 70—80% in both late 2012 and 2013, handwashing rates with soap and water remained around 90—95% throughout the study. Average handwashing rates were similar between the CPI intervention (91.5%) and discontinuation (91.6%) periods, but pre-implementation of CPI (84.3%) showed the lowest rate (pre-vs. CPI, P = 0.002 and pre-vs. post-, P = 0.028). The rates of wearing PPE, measured from the second quarter of 2016, did not differ between the CPI (81.8%) and post-CPI (87.8%) periods (P = 0.126) (Supplementary Fig. 1).

Determining the parameters of an ARIMA prediction model

To confirm stationarity, additional differencing was performed until the P value in the augmented Dickey-Fuller unit root test was $\leq$0.05.[32,33] We determined pairs of three elements (p, d, q) that minimised the values of Akaike's information criterion through a grid search to obtain the most suitable ARIMA model.[32,37] The ARIMA (0, 1, 1) and (0, 1, 3) models were used to compare the differences in IR of HCFA-CDI before and during CPI implementation, and between intervention and suspension (Supplementary Table 1).

Seasonality and observed or predicted trends of *C. difficile* infection

No outbreaks occurred during the study period. The time-series decomposition of *C. difficile* incidence in the SSL algorithm, which analysed the total study period of 132 months without considering CPI implementation, did not show seasonal change over the course of the year (Supplementary Fig. 2). The pronounced increment before CPI intervention changed to a continuously decreasing slope after intervention but returned to growth after CPI suspension (Figs. 2 and 3). The observed trend during CPI intervention showed much lower CDI IR values than the predicted trend from pre-intervention period, whereas the trend of the actual observed values after CPI discontinuation showed much higher IRs than the predicted trend estimated from the intervention period (Fig. 3).

Comparison of changes according to implementation of contact precautions and isolation

Although the number of *C. difficile* toxin assays during CPI intervention was lower than predicted (relative effect [95% CI]: −18 [−26 to −10]%, P = 0.001), there was a continuous increasing trend both before (57 tests/month) and after implementation of the CPI policy (83 tests/month), as well as after discontinuation (108 tests/month). In particular, after CPI suspension, a significantly higher number of toxin assays was conducted than predicted (92 tests/month, 17 [9−24]%, P = 0.001) (Table 1 and Supplementary Fig. 3A).

The use of the five antibiotics increased during the CPI intervention period (pre-intervention vs. intervention, 422 vs. 471 AUD/month), but the total antibiotics used were much less than predicted (626 AUD/month, −25 [−33 to −16] %,

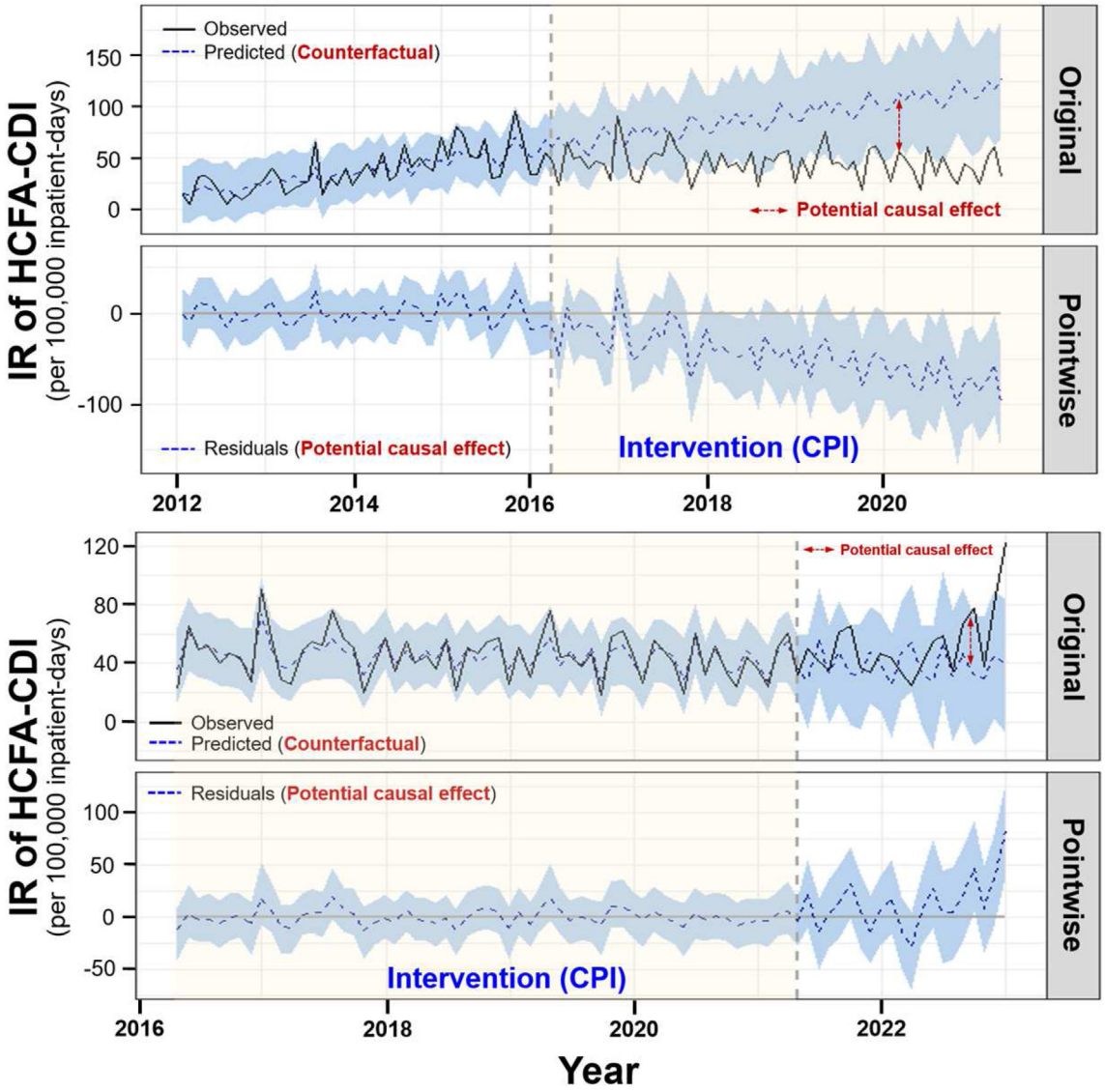

Figure 2. Changing trends of observed and predicted values for healthcare facility-associated *C. difficile* infection according to implementation periods of contact precaution and isolation

Light orange shading indicates the period of CPI implementation. Aberrations: CPI, contact precautions and isolation; HCFA-CDI, healthcare facility-associated *C. difficile* infection; IR, incidence rate.

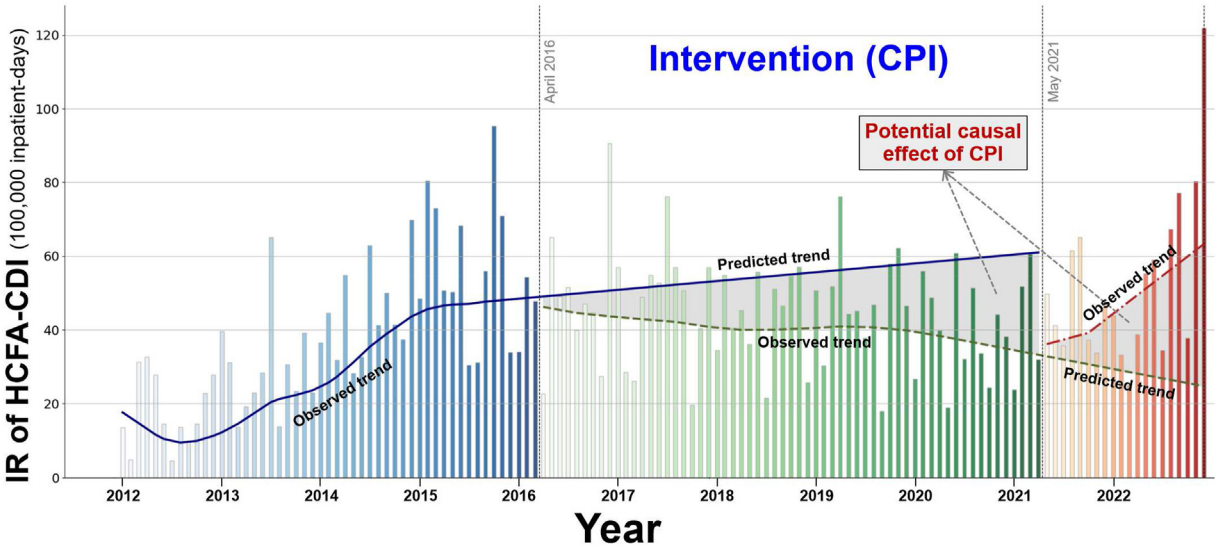

Figure 3. The observed and predicted trends of healthcare facility-associated *C. difficile* infection and prediction of incidence rates of *C. difficile* infection after contact precautions and isolation discontinuation using the observed data during all study periods

Graph was obtained from the Prophet model. Abbreviations: ARIMA, autoregressive integrated moving average; CI, confidence interval; ARIMA, autoregressive integrated moving average; CPI, contact precautions and isolation; HCFA-CDI, healthcare facility-associated *C. difficile* infection; IR, incidence rate.

P = 0.001). During the post-CPI period, antibiotic use decreased to being equal to the predicted value, and the use of all antibiotics decreased compared to the intervention period (Table 1, Supplementary Fig. 3B, and Supplementary Fig. 4).

After the CPI implementation, the HCFA-CDI IR increased slightly (pre-intervention vs. intervention, 38 vs. 44/100,000 inpatient-days) but decreased more than the predicted IR (91/100,000 inpatient-days, relative effect that could be considered a potential causal effect; −51 [−66 to −35] %, P = 0.001). After CPI discontinuation, the actual HCFA-CDI IR (52/100,000 inpatient-days) increased compared to IR during CPI intervention, and showed a significant increase compared to the predicted IR (39/100,000 inpatient-days, 34 [13–54] %, P = 0.001) (Table 1 and Fig. 2).

Alteration in incidence rates of *C. difficile* infection after adjustment for confounding variables

After ARIMA model construction, we performed multiple regression analysis including potential confounding factors, to infer the potential causal effect of CPI implementation on the HCFA-CDI IR. Multivariable model 1 included the number of *C. difficile* tests, performance of handwashing using soap, CDI IR, and the total AUD of all five antibiotics as independent variables; model 2 included the AUD of each of the five antibiotics as confounders. In model 1, the incidence of HCFA-CDI independently decreased during CPI intervention (estimate of coefficients [SE], −16.6 [3.9], P < 0.001) and increased after discontinuation (6.8 [0.5], P < 0.001). This pattern of change was also observed in model 2 (pre-vs. CPI, −14.3 [4.9], P < 0.001, CPI vs. post-CPI, 5.4 [1.0], P < 0.001) (Table 2).

Discussion

CPI, which is important IPC policy for CDI, may not be applied for various reasons, including an unexpected pandemic of a new infectious disease and an increase in MDROs. The problem of limited resources creates situations in which the priority of IPC policy may be focused on controlling more influential pathogens at a point in time, making it impossible to manage HCFA infections with relatively lower urgency. Restrictions on IPC measures in these instances may lead to greater social impact in resource-limited countries or regions. Our research design began from the policy change and we evaluated the quality of evidence for recommending CPI as an effort to prevent intra-hospital CDI transmission.[7]

The results of this study through ITS modelling stably support a temporal association between CPI and CDI IR. Proper CPI implementation in hyperendemic settings reduced the CDI IR by 50% compared to the predicted value, and the suspension of CPI resulted in an increase of ~30% above the predicted value. The potential causal effect of CPI on CDI occurrence did not change, even after controlling for confounding variables. In particular, although the number of *C. difficile* toxin assays increased over time, CPI implementation was independently correlated with the CDI incidence in the multivariable ARIMA models. The substantially higher CDI IR in the last two months of 2022 (80.3 and 121.9 cases per 100,000 inpatient-day in November and December, respectively) may have potentially over-influence the predicted values. Sensitivity analysis after excluding these two data as outliers did not show a significant difference in the BSTS and multivariable ARIMA model, even though the absolute effect of the CDI IR, which

Table 1 Bayesian structural time-series model to evaluate the difference (potential causal effect) between the predicted value (counterfactual) from observations in the previous period and the actual measurements of the following period.

Variables		Bayesian structural time-series model				
	Pre-intervention period	Intervention period				
	Observed	Observed	Predicted	Absolute effect	Relative effect (%)	*P* value
IR[a] of HCFA-CDI	37.72	44.91	90.84	−45.92 (−60.07 ~ −31.91)	−50.6 (−66.1 ~ −35.1)	0.001
C. difficile toxin tests (No.)	57.24	83.13	101.44	−18.31 (−26.60 ~ −10.11)	−18.1 (−26.2 ~ −10.0)	0.001
Handwashing[b] (%)	84.12	90.52	—	—	—	—
Antibiotic usage (AUD)	422.08	471.53	625.72	−154.19 (−208.28 ~ −100.36)	−24.6 (−33.3 ~ −16.0)	0.001
Ampicillin ± BLI	102.89	86.39	210.32	−123.93 (−154.88 ~ −92.95)	−58.9 (−73.6 ~ −44.2)	0.001
Amoxicillin ± BLI	1.47	0.28	0.11	0.17 (−1.08–1.39)	154.5 (−981.8–1263.6)	0.392
Cephalosporines	212.14	271.35	294.03	−22.68 (−46.20 ~ −0.71)	−7.7 (−15.7 ~ −0.2)	0.028
Clindamycin	1.80	1.42	3.83	−2.38 (−3.57 ~ −1.21)	−62.1 (−93.2 ~ −31.6)	0.001
Quinolones	103.79	112.09	117.29	−5.20 (−18.50–7.94)	−4.4 (−15.8–6.8)	0.235
Variables	**Intervention period**	**Post-intervention period**				
	Observed	**Observed**	**Predicted**	**Absolute effect**	**Relative effect (%)**	***p*-value**
IR[a] of HCFA-CDI	44.91	52.27	39.11	13.16 (4.88–20.96)	33.6 (12.5–53.6)	0.001
C. difficile toxin tests (No.)	83.13	107.75	92.34	15.41 (8.30–22.15)	16.7 (9.0–24.0)	0.001
Handwashing[b] (%)	90.52	91.55	—	—	—	—
Antibiotic usage (AUD)	471.53	372.11	346.38	25.73 (−3.97–56.58)	7.4 (−1.1–16.3)	0.052
Ampicillin ± BLI	86.39	24.97	10.19	14.78 (1.20–38.52)	145.0 (11.8–378.0)	0.001
Amoxicillin ± BLI	0.28	0.19	0.21	−0.02 (−0.26–0.21)	−9.5 (−123.8–100.0)	0.416
Cephalosporines	271.35	245.26	288.60	−43.34 (−56.90 ~ −29.64)	−15.0 (−19.7 ~ −10.3)	0.001
Clindamycin	1.42	1.33	0.68	0.65 (0.16–1.06)	95.6 (23.5–155.9)	0.005
Quinolones	112.09	100.39	98.17	2.22 (−9.51–13.92)	2.3 (−9.7–14.2)	0.352

[a] Per 100,000 patient-months.

[b] Performance rate using soap and water. Abbreviations: AUD, antimicrobial use density; BLI, β-lactamase inhibitor; CDI, *Clostridium difficile* infection; HCFA, healthcare facility associated; IR, incidence rate; No., number.

Only the relative effect and handwashing were expressed as percentages, and the rest of the data were expressed as numbers. Except for the quarterly hand hygiene rate, all variables were monthly data. The absolute effect was calculated as the difference between the observed and predicted values, and the relative effect was calculated using the following formula: (observed − predicted)/predicted × 100.

is the most representative evaluation of our study, slightly decreased from 13.2 to 8.0 (P = 0.005) (data not shown).

The randomised control trial is the gold standard to elucidate definite causality of CPI on the CDI IR.[38] However, it is impossible to obtain a comparable control group because practice guidelines strongly recommend CPI implementation.[7] Despite not being able to definitively confirm causality, ITS analyses with long-term observational data before and after CPI intervention would present reasonable alternatives to infer a potential causal relationship.[30,32] To supplement the shortcomings of each ITS model and infer a robust potential causal relationship,[30,31,34] we performed predictions at various time points using various methodologies. The similarity of the results derived from the different methods ensures objectivity in drawing conclusions. In addition, predicted values or trend lines from models or algorithms presented an important perspective for inferring a causal relationship.

Although the incidence of the BI/NAP1/027 hypervirulent strain in South Korea is lower than that in Europe and North America,[39–42] HCFA-CDI can extend hospitalisation and increase complications or medical costs,[1,26] Therefore, we need to contemplate efficient methods to prevent intra-hospital transmission of toxigenic *C. difficile* strains in the context of insufficient private or cohort rooms for isolation. Learning from the COVID-19 pandemic, it will be necessary to propose guidelines on the order of priority for transmissible pathogens requiring special infection control measures in resource-limited settings. Furthermore, these guidelines should be applied individually according to the characteristics of each country, region, and hospital.

Our study has some limitations: (1) given that fidaxomicin and bezlotoxumab are not available, our hospital used oral metronidazole or vancomycin without faecal microbiota transplantation to treat CDI; (2) even though ITS investigation is a strong method for trying to infer

Table 2 Changes in healthcare facility-associated *C. difficile* infection rates before and after contact precaution and isolation policy, and between implementation and discontinuation of the policy with adjustment of time-varying confounding variables.

Periods	Variables	Multivariable model 1[a]		Multivariable model 2[a]	
		Estimate[b] (SE)	*P*-value	Estimate[b] (SE)	*P* value
Pre-vs. intervention	IR of HCFA-CDI	−16.55 (3.92)	<0.001	−14.32 (4.94)	<0.001
	C. difficile toxin tests	0.74 (0.12)	<0.001	0.84 (0.12)	<0.001
	Handwashing[c]	0.28 (0.24)	0.258	0.45 (0.29)	0.121
	Antibiotic usage	0.04 (0.02)	0.033	—	—
	Ampicillin ± BLI	—	—	0.06 (0.04)	0.144
	Amoxicillin ± BLI	—	—	3.05 (1.55)	0.053
	Cephalosporines	—	—	−0.01 (0.07)	0.952
	Clindamycin	—	—	−0.72 (1.34)	0.592
	Quinolones	—	—	0.12 (0.09)	0.202
Intervention vs. post-intervention	IR of HCFA-CDI	6.76 (0.48)	<0.001	5.37 (0.96)	<0.001
	C. difficile toxin tests	0.49 (0.08)	<0.001	0.51 (0.09)	<0.001
	Handwashing[c]	0.41 (0.91)	0.655	0.86 (1.08)	0.427
	Antibiotic usage	0.06 (0.02)	0.009	—	—
	Ampicillin ± BLI	—	—	0.08 (0.04)	0.039
	Amoxicillin ± BLI	—	—	5.65 (5.87)	0.339
	Cephalosporines	—	—	0.05 (0.10)	0.619
	Clindamycin	—	—	0.10 (2.29)	0.964
	Quinolones	—	—	−0.01 (0.10)	0.962

[a] Each multivariable model was obtained by applying interrupted time-series multiple linear regression analysis after ARIMA modelling.
[b] Represents the difference between the coefficients (slopes) of the regression lines in the two disjoint periods.
[c] Performance rate with soap and water. Abbreviations: ARIMA, autoregressive integrated moving average; BLI, β-lactamase inhibitor; CDI, *C. difficile* infection; HCFA, healthcare facility associated; IR, incidence rate; SE, standard error.
Except for the performance rate of handwashing collected quarterly, all variables were monthly data.

causality from long-term observation, ITS model, not true experiment, cannot fully affirm causality; (3) there was no perfectly exchangeable control period or group for which parallel trend estimation could be applied; (4) potential observable confounders highly correlated with the CDI occurrence were controlled in the multivariable ARIMA models, but endogeneity caused by unobservable variables could not be eliminated. We attempted to overcome the limitations by applying the different ITS models with consistent results, suggesting robustness to the varying assumptions within each model. In spite of an observational study, our investigation has the following strengths: (1) ITS analysis is one of the most appropriate and useful methods for longitudinal quasi-experimental studies; (2) our approach can assess effect at CPI intervention initiation and again at discontinuation; (3) multivariable ARIMA model could adjust for the potential confounders including antibiotic use, hand hygiene, and number of toxin tests.

Conclusions

Appropriate implementation of CPI in the hyperendemic setting reduced the increasing CDI IR by half of the predicted value, but the CDI continued to grow after the suspension of isolation due to the COVID-19 pandemic.

Institutional Review Board and informed consent statement

This study was approved by the Institutional Review Board of Gangnam Severance Hospital was exempt from the need to obtain informed consent, because it was a retrospective medical record data analysis and all data were collected and analyzed after being anonymized (approval No. 3-2022-0451).

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None.

Declaration of competing interest

None of the authors declare any conflicts of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.06.003.