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Identification of target risk groups for population-based *Clostridium difficile* infection prevention strategies using a population attributable risk approach

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ABSTRACT

Objectives: We aimed to determine risk factors associated with *Clostridium difficile* infection (CDI) and assess the contributions of these factors on CDI burden.
Methods: We conducted a 1:4 matched case-control study using a national claims dataset. Cases were incident CDI without a history of CDI in the previous 84 days, and were age- and sex-matched with control patients. We ascertained exposure, defined as a history of morbidities and drug use within 90 days. The population attributable risk (PAR) percent for risk factors was estimated using odds ratios (ORs) obtained from the case-control study.
Results: Overall, the strongest CDI-associated risk factors, which have significant contributions to the CDI burden as well, were the experience of gastroenteritis (OR = 5.08, PAR% = 17.09%) and use of antibiotics (OR = 1.69, PAR% = 19.00%), followed by the experiences of female pelvic infection, irritable bowel syndrome, inflammatory bowel disease, and pneumonia, and use of proton-pump inhibitors (OR = 1.52–2.37, PAR% = 1.95–2.90).
Conclusions: The control of risk factors that had strong association with CDI and affected large proportions of total CDI cases would be beneficial for CDI prevention. We suggest performing CDI testing for symptomatic patients with gastroenteritis and implementing antibiotics stewardship.

Introduction

Clostridium difficile is the most common cause of health care-associated infections, and *C. difficile* infection (CDI) is the leading cause of gastroenteritis-associated deaths (Lessa et al., 2015). The incidence and severity of CDI have increased rapidly since 2000, and the risk of recurrent CDI was reported to range from 20% after the successful treatment of an initial CDI episode to more than 60% after several recurrences (Kelly and LaMont, 2008). Severe CDI is associated with increased morbidity, mortality, and financial burdens on healthcare systems (Dubberke et al., 2016).

It is useful to apply both individual and population-based approaches when developing effective strategies to prevent disease within a population (Aral et al., 1996). At an individual level, it is necessary to identify risk factors for the disease. For example, older age, a history of hospitalization, and the use of antibiotics have been identified as major modifiable risk factors for CDI (Surawicz et al., 2013), whereas the use of other drugs, including proton-pump inhibitors (PPIs), has been inconsistently reported as a risk factor for CDI, depending on the geographic study area (Furuya-Kanamori et al., 2015). Furthermore, evidence for the association between morbidities and CDI remains inconclusive (Surawicz et al., 2013).

It is also necessary to identify subpopulations who have risk factors that contribute significantly to the CDI burden when identifying target risk groups for population-based prevention strategies. The population attributable risk (PAR) per cent is a useful epidemiologic tool for identifying specific subpopulations at potential risk for contracting a preventable disease (Poole, 2015; Rockhill et al., 1998b). Currently, the PAR% for CDI among various risk groups have only been reported in the United States (Dubberke et al., 2016). Accordingly, these estimates may not be applicable to other populations or countries with distinct risk group distributions, as the PAR% depends on the prevalence of risk factors in the entire population (Engel et al., 2003).

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Despite the significant increase in CDI in Korea, we lack effective prevention strategies at the levels of both clinical practice and public policy, due to the limited epidemiological evidence regarding CDI in our population (Kim et al., 2013). Therefore, we conducted a population-based epidemiologic study, using nationally representative claims records that encompass the entire Korean population, to identify risk factors that correlate strongly with CDI and the contribution to the CDI burden at a population level.

Methods

Study design

This study was approved by the institutional review board of Yonsei University (IRB No. 7001988-201607-BM-206-01E). The requirement for acquisition of informed consent from the study population was waived by the board. Two-year pooled data from the 2013 and 2014 Health Insurance Review and Assessment Service-National Patient Sample (HIRA-NPS) were used for this study. The HIRA-NPS is an annual 3% random sample (approximately 1400000 individuals with claims records) of the nationwide population, which comprises those enrolled in the National Health Insurance (97%) and Medical Aid (3%) programs. This dataset provides the claims records that include demographic information, as well as diagnostic, procedural, and prescription records for provided all types of health care services (Kim et al., 2014). All diagnoses were coded using the International Classification of Diseases Codes, 10th revision (ICD-10).

The study was conducted using two distinct but complementary approaches: a matched case-control study and a PAR analysis. First, a matched case-control study was conducted to determine the risk factors for CDI at an individual level. Cases were defined as incident CDIs. Patients were identified as incident cases of CDI if they had claim records containing the diagnostic code for CDI (A047) and no history of CDI during the previous 84 days (Dubberke et al., 2016). Control cases had no claim record with a diagnostic code for CDI. Four control patients were randomly matched with each case by sex and age (within 5 years). These matching variables were selected based on the known confounders of CDI (Freedberg et al., 2015). For cases, the index date was defined as the first date with a coded diagnosis of CDI. For controls, index dates were randomly assigned such that the distribution among controls mirrored that among cases.

Second, we estimated the PAR% values of the subpopulations exposed to each risk factor that were identified from the matched case-control study. The PAR%, defined as the proportion of CDI cases that could be attributed to a particular exposure among all exposed individuals, provides an estimate of the proportional reduction in CDI cases in the total population if the exposure or risk factor were eliminated (Dubberke et al., 2016; Rockhill et al., 1998a,b).

Exposures

Based on previous research (Dubberke et al., 2016; Freedberg et al., 2015), we considered the histories of morbidity and drug therapy within 90 days prior to the index date. We determined an exposure period as 90 days, as the majority of exposures related to CDI were reported to occur within 90 days (Dubberke et al., 2016; Jen et al., 2012). In addition, the CDI risk associated with antibiotics was reported to wane after 90 days (Hensgens et al., 2012). Morbidities were classified as non-infectious and infectious diseases. Specific ICD-10 codes for the diagnoses of morbidity are listed in Supplementary Table A1. The following drug classes were evaluated: antibiotics, PPIs, steroids, and antidepressants.

Data analysis

The average annual prevalence of CDI among the population was calculated. We estimated the total number of patients with CDI in Korea during the 2 years as the total number of patients with CDI identified using our data, multiplying it by a sampling weight of 33.33% (i.e., inverse of the sampling probability for the HIRA-NPS data) and then dividing the result by the total population in 2013 and 2014. To identify risk factors for CDI, adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated through a conditional logistic regression analysis. Reduced models including either the history of morbidity or drug use, and a full model including both of these variables were considered. Each reduced model was specified using a forward selection method. The best model was determined based on the multicollinearity diagnosis and goodness-of-fit test outcome. The likelihood ratio test, which compares the reduced model with the full model, was conducted for model selection (Vuong, 1989). The result showed that the null hypothesis (*H0: reduced model is true)* was not rejected at the 0.05 level of significance. That is, this result did not provide evidence against the reduced model in favour of the full model. In addition, a regression model that includes too many independent variables may yield misleadingly high R-squared values, reduced precision, and incorrect explanatory power (Eisenhauer, 2009). Therefore, we finally built two separate regression models based on theoretical and statistical considerations (Dohoo et al., 1997; Freedberg et al., 2015; Miller et al., 2016). Model 1 assessed the association between the history of morbidity and the CDI, and model 2 assessed the association between the history of drug use and CDI. Model 1 was adjusted for the experience of hospitalization, type of national health security program (NHSP) enrolment, and age ($<$65 or $\geq$65 years). Model 2 was adjusted for the experience of hospitalization, type of NHSP enrolment, age ($<$65 or $\geq$65 years), and Charlson comorbidity index (CCI) score used for risk adjustment in claims-based research (D'Hoore et al., 1996). To address the potential confounding by the exposure of antibiotics on the association between the history of infectious diseases and CDI, we analysed the Model 1 for a subgroup of patients with prior antibiotics use within 90 days of the incident CDI. Additionally, to examine whether the association between antibiotics use and CDI varied according to the antibiotic class, a regression model was analysed by breaking down the antibiotics into their respective classes.

To identify the independent contribution of each risk factor to the burden of CDI, the PAR% was calculated for each subpopulation group with the risk factor; these groups were defined by exposure to a non-infectious or infectious disease or a specific drug. The PAR % was calculated using the following formula (Cole and MacMahon, 1971):

$$\mathrm{PAR}\% = (\mathrm{P(E)} \times (\mathrm{RR} - 1)/(\mathrm{P(E)} \times (\mathrm{RR} - 1)) + 1) \times 100\%$$

where P(E) is the proportion of the population exposed to the risk factor, and RR is the relative risk, or the ratio of the risk among the exposed to that among the unexposed. The relative risk was determined in reference to the adjusted OR obtained from the case-control study. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA) at a significance level of 5%.

Results

A total of 2092 patients with CDI were identified from the 2013 and 2014 HIRA-NPS data. The average annual prevalence of CDI was estimated to be 69 per 100,000 population. During a 2-year study period, 1578 CDI cases were identified among the study population and were matched with 6312 controls. Table 1 presents the

Table 1
Characteristics of *Clostridium difficile* infection cases and controls.

	Cases		Matched controls[a]		p-Value[b]
	n	%	n	%	
Number of subjects	1578	100.00	6312	100.00	
Sex					
Male	715	45.31	2860	45.31	1.0000
Female	863	54.69	3452	54.69	
Age (years)					
Median (IQR)	66 (42, 77)		61 (39.5, 73)		0.0007[c]
<65	759	48.10	3480	55.13	<0.0001
≥65	819	51.90	2832	44.87	
National health security program					
National Health Insurance	1427	90.43	6033	95.58	<0.0001
Medical Aid	151	9.57	279	4.42	
Healthcare utilization					
Hospitalization[d]	1293	81.94	433	6.86	<0.0001
CCI scores[e]					
0	393	24.90	3665	58.06	<0.0001
1	302	19.14	1346	21.32	
2	205	12.99	601	9.52	
≥3	678	42.97	700	11.09	

CCI, Charlson comorbidity index; CDI, *Clostridium difficile* Infection; IQR, interquartile range; SD, standard deviation.
[a] Matching variables were sex and age (within 5 years).
[b] The p-value was calculated using the $\chi 2$-test.
[c] The p-value was calculated using the Wilcoxon rank-sum test.
[d] The experience of hospitalization within 90 days of the index date.
[e] The summed CCI scores within 90 days of the index date.

characteristics of CDI cases and controls. The two groups differed significantly in terms of baseline characteristics. The case group included a significantly higher proportion (51.90%) of elderly individuals (age ≥65 years) compared with the control group (44.87%). Furthermore, 81.94% of subjects in the case group experienced hospitalization within 90 days before the index date, compared with only 6.86% in the control group. Consequently, the case group had higher CCI scores within 90 days relative to the control group, which confirmed the more severe health status.

In the Model 1, the risk for CDI associated with the history of morbidity was assessed (Table 2). Five diseases had particularly high ORs: gastroenteritis (OR: 5.08, 95% CI: 3.97–6.50), coagulopathy (OR: 3.07, 95% CI: 1.34–7.06), pneumonia (OR: 2.37, 95% CI: 1.73–3.25), female pelvic infection (FPI) (OR: 2.01, 95% CI: 1.21–3.37), and inflammatory bowel disease (IBD) (OR: 1.96, 95% CI: 1.36–2.81). Other conditions identified as risk factors for CDI included irritable bowel syndrome (IBS) (OR: 1.66, 95% CI: 1.23–2.24), iron deficiency anaemia (IDA) (OR: 1.55, 95% CI: 1.02–2.33), viral infections (OR: 1.51, 95% CI: 1.06–2.15), depression (OR: 1.45, 95% CI: 1.06–1.98), and stroke (OR: 1.43, 95% CI: 1.00–2.03). From Model 1 run for the subgroup of patients with prior antibiotics use, significant association with the infectious diseases such as FPI, gastroenteritis, viral infection and pneumonia were also confirmed (Supplementary Table A2).

In the Model 2, the risk for CDI associated with the history of drug use was assessed (Table 2). The use of antibiotics (OR: 1.69,

Table 2
Risk of *Clostridium difficile* infection (CDI) associated with the histories of morbidity and drug use within 90 days of CDI incidence.

Type of exposure	Cases (n = 1578)		Matched controls[a] (n = 6312)		Adjusted odds ratio[b]	95% CI
	n	(%)	n	(%)		
Model 1						
Non-infectious diseases						
Cancer	262	16.60	201	3.18	1.19	0.88–1.62
Chronic pulmonary disease	530	33.59	832	13.18	1.16	0.93–1.46
Coagulopathy	79	5.01	15	0.24	3.07	1.34–7.06*
Congestive heart failure	116	7.35	123	1.95	0.84	0.55–1.29
Depression	243	15.40	296	4.69	1.45	1.06–1.98*
Diabetes mellitus	488	30.93	966	15.30	0.86	0.68–1.09
Fluid-electrolyte disorders	246	15.59	104	1.65	1.25	0.86–1.82
Hypertension	729	46.20	2131	33.76	0.86	0.68–1.07
Inflammatory bowel disease	158	10.01	176	2.79	1.96	1.36–2.81*
Iron deficiency anaemia	199	12.61	110	1.74	1.55	1.02–2.33*
Irritable bowel syndrome	242	15.34	324	5.13	1.66	1.23–2.24*
Liver diseases	372	23.57	439	6.96	1.03	0.79–1.33
Malnutrition	83	5.26	14	0.22	2.09	0.99–4.42
Paralysis	140	8.87	47	0.74	1.36	0.84–2.20
Peripheral vascular disease	172	10.90	462	7.32	1.05	0.76–1.44
Renal failure	136	8.62	74	1.17	1.30	0.81–2.10
Stroke	233	14.77	250	3.96	1.43	1.00–2.03*
Infectious diseases						
Female pelvic infection	57	3.61	114	1.81	2.01	1.21–3.37*
Gastroenteritis	491	31.12	380	6.02	5.08	3.97–6.50*
Otitis	141	8.94	353	5.59	1.08	0.78–1.50
Pneumonia	350	22.18	150	2.38	2.37	1.73–3.25*
Septicaemia	56	3.55	15	0.24	1.11	0.51–2.40
Upper respiratory tract infection	749	47.47	2336	37.01	1.16	0.96–1.41
Urinary tract infection	206	13.05	65	1.03	1.48	0.98–2.25
Viral infection	156	9.89	229	3.63	1.51	1.06–2.15*
Model 2						
Drug used						
Antibiotics	1078	68.31	2271	35.98	1.69	1.42–2.01*
Antidepressants	832	52.72	1707	27.04	1.01	0.83–1.22
Proton-pump inhibitors	358	22.69	460	7.29	1.52	1.18–1.94*
Steroids	570	36.12	1260	19.96	1.06	0.88–1.29

[a] Matching variables were sex and age (within 5 years).
[b] Model 1 was adjusted for the experience of hospitalization, type of national health security program (NHSP) enrolment, and age (<65 or ≥65 years). Model 2 was adjusted for the experience of hospitalization, type of NHSP enrolment, age (<65 or ≥65 years), and Charlson comorbidity index score.
* $p < 0.05$; CI, confidence interval.

Table 3
Population attributable risk (PAR) per cents of the histories of comorbidities and drug use for the incidence of *Clostridium difficile* infection.

Exposure	Prevalence of exposure (%)	RR[a]	PAR%[b]
Non-infectious diseases			
Coagulopathy	0.16	3.07	0.32%
Depression	2.32	1.45	1.03%
Inflammatory bowel disease	2.36	1.96	2.20%
Iron deficiency anaemia	1.21	1.55	0.66%
Irritable bowel syndrome	3.61	1.66	2.33%
Stroke	1.39	1.43	0.59%
Infectious diseases			
Female pelvic infection	2.95	2.01	2.90%
Gastroenteritis	5.06	5.08	17.09%
Pneumonia	1.45	2.37	1.95%
Viral infection	3.06	1.51	1.53%
Drug use			
Antibiotics	34.05	1.69	19.00%
Proton-pump inhibitors	4.60	1.52	2.31%

CDI: *Clostridium difficile* infection, PAR%: population attributable risk proportion.
[a] RR, the relative risk, was replaced by OR
[b] PAR% = $(P(E) \times (RR - 1))/((P(E) \times (RR - 1)) + 1) \times 100\%$, where P(E) is the proportion of the population exposed (i.e., exposure prevalence) and RR represents the ratio of risk among the exposed to that among the unexposed. The relative risk was determined in reference to the OR obtained from the case-control study.

95% CI: 1.42–2.01) and PPIs (OR: 1.52, 95% CI: 1.18–1.94) within 90 days before CDI were significant risk factors for CDI. Among the classes of antibiotics, the use of penicillins (OR: 1.71, 95% CI: 1.40–2.10), third-generation cephalosporins (OR: 2.99, 95% CI: 2.34–3.82) and ciprofloxacin (OR: 2.30, 95% CI: 1.06–5.00) were shown to increase the risk of CDI, whereas the use of first-generation cephalosporins significantly decreased the risk of CDI (OR: 0.63, 95% CI: 0.46–0.85) (Supplementary Table A3).

The PAR% for each significant risk factor identified from models 1 and 2 are presented in Table 3. The highest PAR% among non-infectious diseases were observed for IBS (2.33%), IBD (2.20%) and depression (1.03%). The highest PAR% among infectious diseases were observed for gastroenteritis (17.09%), FPI (2.90%), and pneumonia (1.95%). Overall, exposures to drugs yielded higher PAR% compared to exposures to disease. In particular, the PAR% for antibiotics and PPI were 19.00% and 2.31%, respectively. The prevalence of these exposures was very high, with rates of 34.05% for antibiotics and 4.60% for PPI.

Figure 1 presents a two-dimensional graph in which the adjusted ORs are plotted on the Y-axis and PAR% for exposures identified from models 1 and 2 as significant risk factors for CDI are plotted on the X-axis. The graph areas are designated first through fourth, in order of the strengths of the associations between risk factors and CDI, which were based on both the magnitude of the association and the contribution of the CDI burden. We assumed a strong association if a risk factor associated with CDI had both a high OR and high PAR%. For example, antibiotics use and gastroenteritis experience are located in the first area, as both factors had the highest adjusted ORs, indicating their strong association on CDI at the individual level, and the highest PAR%, suggesting that the control of these factors would yield the greatest proportional reductions in CDI at a population level. The next strongest risk factors for CDI, which were located in the second area, included the experiences of infectious diseases such as FPI and pneumonia, non-infectious diseases such as IBD and IBS, and PPI use. The third area included the experiences of viral infection and depression. The fourth area included the experiences

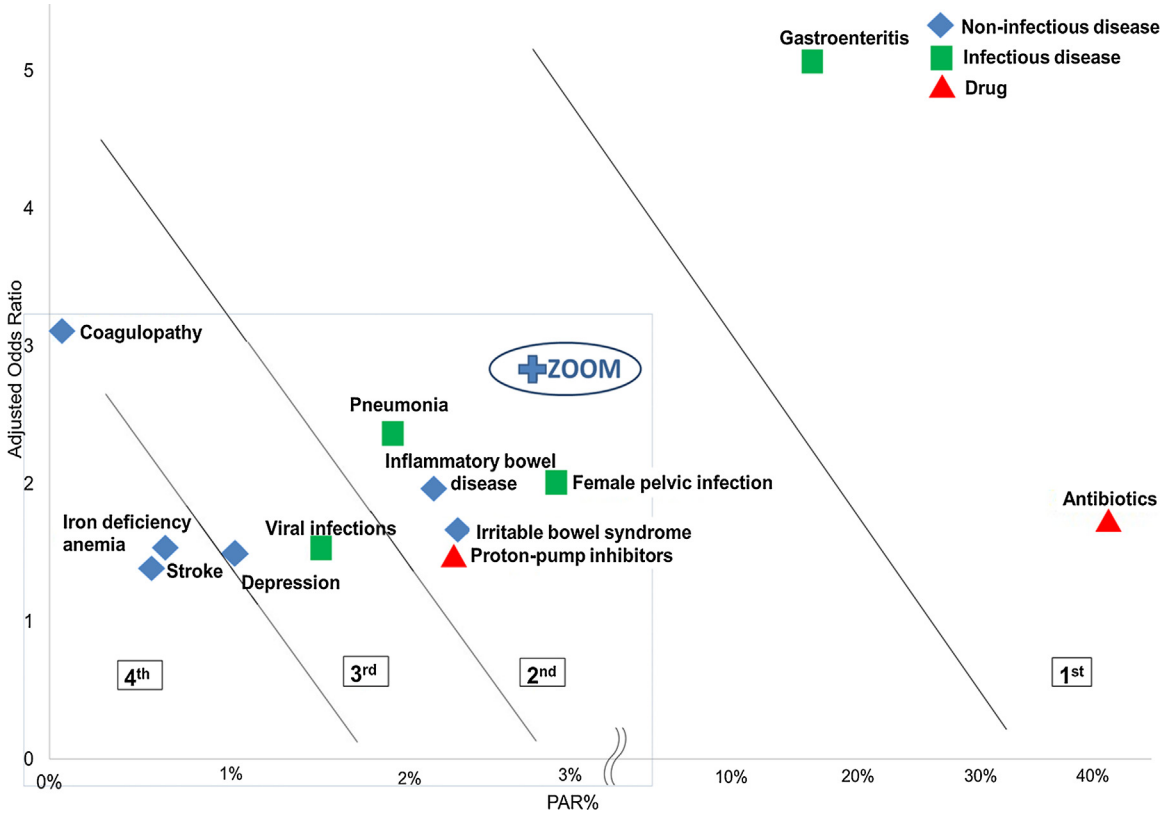

Figure 1. Classification of the identified risk factors for *Clostridium difficile* infection (CDI) according to the strength of the association with CDI and the estimated reduction of CDI in population. Graph areas are labelled as first through fourth, in order of the strength of the association with CDI and the reduction of CDI in population. The risk factors located in the first area had both the highest adjusted odds ratios, which reflecting the strongest associations with CDI, and the highest PAR% values, which reflecting the highest proportional reductions in CDI if these factors were controlled. PAR%, Population attributable risk percent.

of IDA, stroke, and coagulopathy; although these were statistically significant risk factors for CDI, all had relatively low PAR% for CDI (<1%).

Discussion

This is the first complementary study conducted to determine the risk factors for CDI at an individual level while estimating the PAR% of risk factors attributed to the CDI burden at a population level. We applied an approach similar to that used in the INTERSTROKE study (O'Donnell et al., 2010), which assessed the associations of risk factors with stroke and the contributions of these risk factors to the burden of stroke in a population, based on the PAR%. The study concluded that targeted interventions, such as the reductions in blood pressure and smoking, could reduce the burden of stroke in the population. In order to prevent a disease, interventions for the subpopulations that contribute the most to the disease burden at the population level need to be implemented, and the risk factors having strong associations with CDI must be controlled at an individual level (Aral et al., 1996; Dubberke et al., 2016; Rockhill et al., 1998b). This is an important approach when aiming to select the optimum targets for prevention programs, and is useful for determining public health priorities (Northridge, 1995). Therefore, we expect that our findings would be useful in the identification of target risk groups, with the aim of preventing CDI in the Korean population.

Among the risk factors identified through a matched case-control study, the use of antibiotics (19.0%) and the experience of gastroenteritis (17.1%) yielded the highest PAR%. In other words, they contribute most strongly to CDI in the Korean population. By investigating risk factors with high ORs and high PAR%, we identified exposure groups to antibiotics and gastroenteritis (i.e., the risk factors located in the first region of Figure 1) as the most important targets for achieving the greatest CDI prevention outcomes. Therefore, CDI prevention would benefit from implementing CDI testing for symptomatic patients with gastroenteritis, as well as an antibiotics stewardship program. In addition to the stewardship of antibiotics, agents with relatively lower risk of CDI and equal effectiveness may be prescribed if antibiotic therapy is necessary, because the risk of CDI differs depending on the classes of antibiotics (Deshpande et al., 2013). Furthermore, the second-priority exposure groups for prevention included those who experienced IBD, IBS, FPI, and pneumonia and used PPI. This finding suggests that PPI stewardship could be an effective prevention strategy. Moreover, we may consider the feasibility of prevention interventions for IBS, IBD, pneumonia, and FPI.

Consistent with previous studies (Evans and Safdar, 2015; Surawicz et al., 2013), we found that the use of antibiotics was an important risk factor for CDI. The mechanism underlying this association is well known. Antibiotics disrupt human gut microbiota, and, thus, allow *C. difficile* to grow and produce toxins and increase the risk of CDI (Bagdasarian et al., 2015; Bassis et al., 2014; Yoon et al., 2016). Our study also revealed that PPI use increased the risk of CDI. A previous meta-analysis reported that this association between PPI use and CDI was location-dependent. For instance, the use of PPI was a significant risk factor in Europe but not in the United States (Furuya-Kanamori et al., 2015). Although recent studies showed that PPI users may have less healthy gut microbiomes, the mechanism by which PPI therapy contributes to an increased risk of CDI remains unclear (Tleyjeh et al., 2012). Meanwhile, PPIs are frequently overprescribed in many countries, and more than half of CDI patients receive these drugs without evidence-based indications (McDonald et al., 2015). In Korea, the use of PPI has also increased rapidly (Kim et al., 2012). Therefore, the evidence-based use of PPI in patients at high risk of CDI and the cessation of unnecessary PPI use could be considered.

Among the morbidities examined in the present study, gastroenteritis and IBD were identified as risk factors for CDI. Earlier studies also reported significant associations of gastrointestinal disorders and IBD with CDI (Kurti et al., 2015; Lihua et al., 2015). In addition, one report recommended that all patients hospitalized with an IBD flare-up should undergo testing for CDI (Surawicz et al., 2013). Our study also identified depression as a significant risk factor for CDI with an OR of 1.45, consistent with a previous study (Rogers et al., 2013).

Our study provides new information about the associations between the history of morbidities and CDI. We demonstrated that experiencing infectious diseases such as pneumonia, FPI, and viral infection were associated with CDI. Pneumonia was the leading indication for antibiotic prescription in hospitals (Becerra et al., 2015; Chalmers et al., 2016). A study performed in the USA reported that acute infectious diseases were associated with a high incidence of CDI (Dubberke et al., 2016), and this association could be explained by the use of antibiotics, the greatest risk factor for CDI, to treat infections. Our additional analysis for Model 1 restricted to the subgroup of patients with prior antibiotics use supports such a speculation. Although the results of Model 1 for the subgroup still revealed a significant association between the history of infectious diseases, such as pneumonia, and FPI, and the CDI, the magnitude of the association for the subgroup became smaller than that for the entire study population (i.e., smaller regression coefficients). In other words, after controlling for the history of antibiotic use, the association between the history of infectious diseases that often required antibiotic therapy and CDI became mitigated, confirming that the association was partly explained by the use of antibiotics to treat infections.

We found only one previous study that assessed the PAR% for CDI in an elderly US population (Dubberke et al., 2016). This US study examined unadjusted PAR% for all subpopulations of interest, whereas we estimated the adjusted PAR% using adjusted ORs obtained from a regression model. Therefore, comparisons with previous estimates are limited by differences in analytical methods. Furthermore, the US estimates are not applicable to other regions because PAR% depends on the prevalence of exposure in the local population. For example, we demonstrated that the PAR% for CDI was considerably higher among patients with the experience of gastroenteritis in Korea (17.1%) than in the USA (3.6%), which we attributed mainly to the higher prevalence of gastroenteritis in Korea (5.1%) than in the USA (0.2%).

Our study had several limitations. First, CDI cases were only identified based on ICD-10 codes, which potentially allowed misclassification or miscoding. Since the HIRA-NPS data do not provide information on laboratory test results such as the enzyme immunoassay for toxin A/B, we were not able to identify CDI cases based on the diagnostic test results. However, a previous meta-analysis indicated that ICD codes are both sensitive (76%) and specific (99.9%) for the diagnosis of CDI, meaning that the administrative code data for CDI provide moderate-to-strong diagnostic evidence (Goto et al., 2014). Therefore, we consider that the ICD-10 code for CDI can be used as a reasonable alternative to microbiological data (Jen et al., 2012). Second, to constitute a sufficient sample size for the data analysis, we used pooled data from 2-year patient samples. Therefore, each annual dataset might have included identical patients, which cannot be confirmed because the individual patients had been de-identified. However, the 3% sampling rate of patients in the data set each year is sufficiently low, and we consider it unlikely that same patient would have been selected in both years of the study period. Third, the association of gastroenteritis with CDI might be overestimated. Although gastroenteritis has been reported as a risk factor for CDI (Lihua et al., 2015), we cannot exclude the possibility that some patients with gastroenteritis actually had CDI at the time but were

not tested until a subsequent visit. We analysed the time interval between the diagnosis of gastroenteritis and that of CDI. Of 491 patients who experienced gastroenteritis, 94 (19%) patients were diagnosed with gastroenteritis within 1 week of the index date of CDI, which suggests the possibility of co-existence of gastroenteritis and CDI. Therefore, this result should be interpreted with caution. Despite the above limitations, few studies have assessed PAR% to estimate the contributions of risk factors to the CDI burden in a population. We believe CDI prevention strategies would benefit from the control of risk factors that had strong association with CDI and contributed significantly to the total CDI burden. Based on the high ORs and PAR% estimates, we suggest that the implementation of antibiotics stewardship, and CDI testing of symptomatic patients with gastroenteritis should be prioritized in Korea.

Conflicts of interest

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2017.11.021.

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