Advances in Precision Medicine
2022 Volume 7, Issue 1
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

The Trend of *Clostridioides difficile* Infection in Korean Hospitals with the Analysis of Nationwide Sample Cohort

Kang Ju Son[1,2], Young Ah Kim[3]*, Yoon Soo Park[4]

[1]Department of Research and Analysis, National Health Insurance Service Ilsan Hospital, Goyang, Korea

[2]Department of Biostatistics and Computing, Yonsei University Graduate School, Seoul, Korea

[3]Department of Laboratory Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Korea

[4]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

***Corresponding author:** Young Ah Kim, yakim@nhimc.or.kr

Copyright: © 2022 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract

Background: Clostridioides (*Clostridium*) *difficile* is an important pathogen that causes diarrhea in people who take antibiotics. The recent status of *C. difficile* infection is not well known in Korea. *Methods:* The long-term trend of *C. difficile* infection in Korean hospitals was analyzed using a nationwide sample cohort. The data also included sociodemographic characteristics, disease severity, and healthcare facilities. *C. difficile infection* was defined by the prescription of oral vancomycin or all metronidazole prescriptions under *C. difficile* infectious disease code (A047). *Results:* The rate of *C. difficile* infection has steadily increased from 0.030% in 2006 to 0.317% in 2015. The increased rate correlated to age (0.033% for < 50 years, 0.421% for 70–79 years, and 0.758% for > 80 years of age) and the Charlson comorbidity index score (0.048% for zero versus 0.378% for three or more points). It differed by the type of medical institution (0.270% at referral hospitals versus 0.056 % at general hospitals and mental hospitals). *Conclusion:* The rate of *C. difficile* infection in Korea is significant in patients with advanced age and disease severity. The results show that *C. difficile* infection trend has been increasing steadily in Korea.

Keywords

Clostridioides difficile
Cohort studies
Infections
Rate
Trend

1. Introduction

Clostridioides difficile is a spore-forming, anaerobic, gram-positive bacillus that causes diarrheal illness in patients who have taken antimicrobials for treatment and is the most common cause of hospital-acquired diarrheal disease [1]. Infection with toxin-producing *C. difficile* produces clinical symptoms ranging from mild diarrhea to death in severe cases, and most often produces toxins A and B [1]. However, the incidence and mortality of *C. difficile* infection (CDI) have increased dramatically worldwide since 2003, when outbreaks caused by ribotype 027, which produces an additional binary toxin and has a more severe clinical presentation, were reported in North America and Europe [2,3].

Looking at domestic reports, an analysis of data from 17 tertiary hospitals nationwide from 2004 to 2008 showed that the incidence of CDI increased significantly from 1.7 cases per 1,000 adult inpatients in 2004 to 2.7 cases in 2008 (P = 0.028) [4]. In an analysis of data from the Korea Health Insurance Review and Assessment Service, the number of patients with CDI steadily increased to 700 in 2008, 1,177 in 2009, 1,714 in 2010, and 2,521 in 2011 [5]. However, data on the status and trends of CDI in Korea are limited to tertiary medical institutions, and there are data on long-term changes, including data from general hospitals and hospitals.

The purpose of this study was to investigate the current status of CDI at the national level and long-term changes over the 10 years from 2006 to 2015, and to generate data by demographics, severity, and institutional characteristics to generate evidence for prioritizing CDI management in Korea. For this purpose, the National Health Insurance Service-National Sample Cohort was used [6], which includes a sample of 1,025,340 people (513,258 men and 512,082 women), about 2.2% of the Korean population, and includes socioeconomic variables (area of residence, income class, disability, etc.), deaths, healthcare utilization (billing statements of nursing institutions, medical treatment history, injury history, prescription history, etc.), and medical examination data. In general, sampling does not have a clear population, but this data has the advantage of being able to quickly extract reliable data on universal medical practices because the target population to be statistically inferred from the sample and the actual population to be sampled are matched using stratified stratification by gender, age group, member classification, and income class combination.

2. Materials and methods

The data were analyzed at the level of hospitalization episodes rather than patients to avoid errors due to separate billing, and the same patient was considered to be in the same episode if the end date of treatment in the baseline statement and the start date of treatment in the next claim were within one day. The reason for building hospitalization episodes is that if a patient stays in the hospital for more than one month, nursing homes bill separately by month, so a single statement does not capture all the information from the beginning to the end of treatment.

CDI was operationally defined as the diagnosis associated with the prescription of a therapeutic drug, including oral vancomycin use and oral and suspension metronidazole use for patients with a CDI diagnosis code (A047). This is because the only indication for oral vancomycin is CDI, whereas metronidazole is used to treat anaerobic bacterial infections in addition to CDI. To minimize duplication, patients were excluded if they were re-diagnosed within 60 days of the end of treatment for the infection.

To construct the data, outpatient episodes were excluded, and claims from the same patient and the same healthcare provider of 2,305,446 hospitalizations from 2006 to 2015 were combined, resulting in 1,767,696 episodes. Diagnosis statements and antibiotic prescription statements were also combined to extract infectious and non-infectious episodes, from which the repeat patients were removed (**Figure 1**).

Non-infectious episodes excluded those that were included in an infectious episode and those that used metronidazole.

For each episode, gender, year of birth, insurance quintile, and year of hospitalization were completed from the eligibility database. The income quintile was classified into 10 quintiles through the insurance premium information charged by the health insurance on a household basis, and the medical benefit recipient was taken as the 0th quintile, i.e., the 9th–10th quintile categorized as the top 20% of the income level. To identify the severity of the patients, the principal diagnosis of the first hospitalization statement was selected and identified as the principal diagnosis (first digit), and the Charlson comorbidity index (CCI) was obtained by referring to existing research methods using health insurance claims data [7,8]. For institutional characteristics, the institutional database was used to add the type of nursing home and location (province and city size) to exclude clinic-level and below, limiting the target institutions to hospital-level and above. The reason for excluding outpatients from CDI infections is that it is not easy to diagnose CDI infections in a non-hospital setting, so it is difficult to verify the accuracy of the diagnosis, and due to the nature of insurance data, one diagnosis may be over-collected as multiple outpatient visits, which may cause statistical errors.

The presence of extreme outliers in the data may introduce bias in comparative tests, so missing episodes were excluded to retain only typical episodes. In this study, missing data for gender and age, as well as missing data from a region (Sejong City) with a very small number of patients with CDI were excluded. In addition, to remove mild disease hospitalization episodes, only those with treatment and surgery expenditures in the hospitalization episode were included, because it was judged that mild disease hospitalization episodes without treatment or surgery are difficult to be considered as actual hospitalizations. Although hospitalization costs and days are not the subjects of this study, episodes that deviated from each mean value by three standard deviations were excluded to remove outlier episodes in hospitalization costs and days, leaving only typical episodes. This is because hospitalization costs and length of stay are indicators of the overall volume of hospitalization. In the end, 1,485 episodes of CDI and 822,649 non-infection were extracted (**Figure 1**).

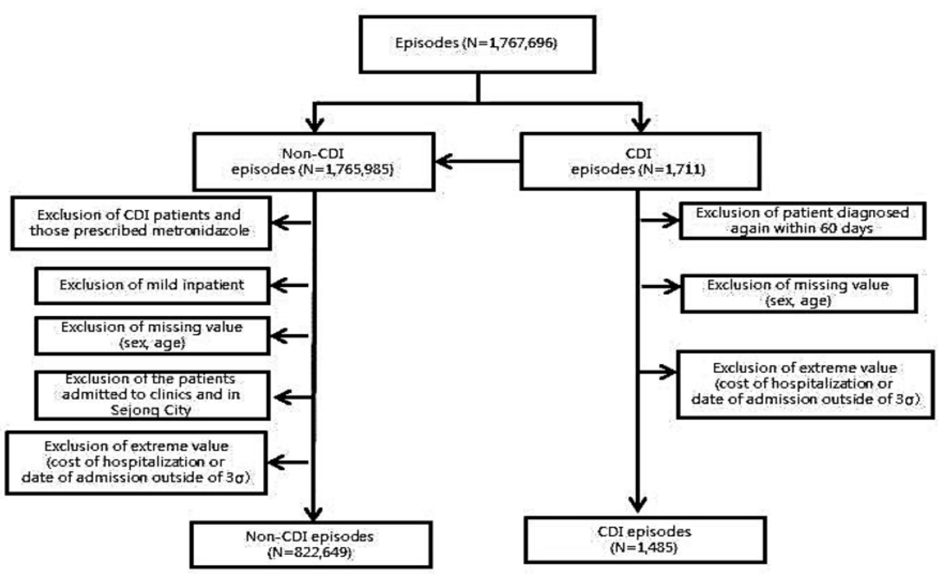

Figure 1. Data construction flow diagram. Abbreviation: CDI, *C. difficile* infection.

The general status of CDI was examined by year and analyzed by demographic, severity, and institutional characteristics. Differences between years were compared by the trend test. Data were analyzed using SAS Enterprise Guide 7.13 (SAS Inc., Cary, NC, USA) and SAS Enterprise Guide 7.15 (SAS Inc., Cary, NC, USA) on the National Health Insurance Service Sample Cohort Data Analysis Server.

This study was approved by the Institutional Review Board of Ilsan National Health Insurance Hospital (IRB No. 2020-05-010).

3. Results

3.1. Changes in the number of *C. difficile* infections and infection rates by year

The number of infections increased approximately 19-fold, from 17 in 2006 to 315 in 2015, and the annual CDI rate increased steadily, from 0.030% in 2006 to 0.317% in 2015 (**Figure 2**). Here, the infection rate was calculated using the 824,134 episodes in the infected and uninfected groups combined as the denominator.

3.2. *C. difficile* infection rates by characteristics

The prevalence of CDI by sociodemographic characteristics was 0.178% in men and 0.182% in women. The infection rate was higher in the elderly: 0.033% in the under-50s, 0.133% in the 50–59s, 0.219% in the 60–69s, 0.412% in the 70–79s, and 0.758% in the 80+s. There were no significant differences by insurance quintile, reflecting differences by income level: 0.289% in the medical benefit group, 0.162% in quintile 1, 0.148% in quintile 2, 0.134% in quintile 3, 0.164% in quintile 4, and 0.210% in quintile 5 (**Table 1**). Looking at infection rates according to the comorbidity index, infection rates were higher for those with higher severity: 0.048% for 0, 0.096% for 1, 0.191% for 2, and 0.378% for 3 or more (**Table 2**).

By region, the infection rate was higher in Jeju 0.405%, Jeonbuk 0.292%, Daejeon 0.273%, Daegu 0.248%, Chungcheongnam-do 0.211%, and Gyeongsangbuk-do 0.209%. According to the size of the city, rural areas were slightly higher than other regions, but the difference was not significant. By type of medical institution, the infection rate was 0.270% in senior general hospitals, 0.231% in general hospitals, 0.185% in nursing homes, and 0.056% in general hospitals (including psychiatric hospitals) (Table 3).

4. Discussion

The increase in healthcare-associated infections is inevitable due to the increase in the elderly population, chronic degenerative diseases, immunocompromised

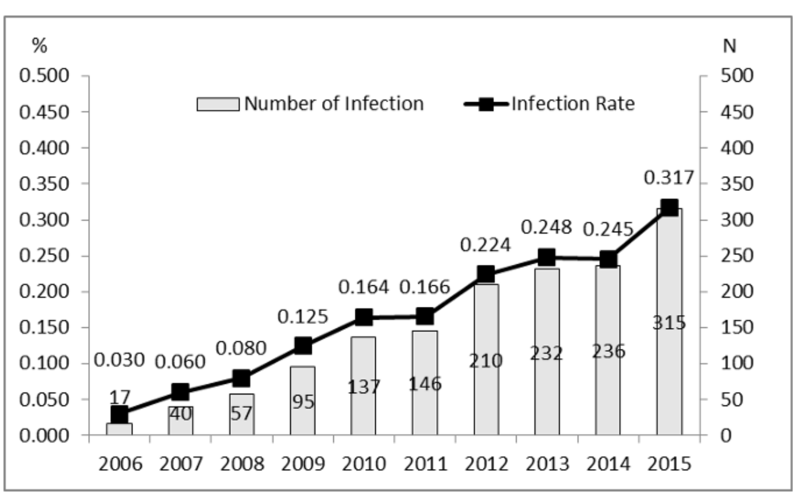

Figure 2. The trend of *C. difficile* infection from 2006 to 2015. Abbreviation: N, number.

Table 1. The number and rates of *C. difficile* infections by demographic characteristics

Characteristic	Cases No. (Infection rate, %)											
Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	*P*-value*
Sex												
Male	9 (0.034)	22 (0.070)	27 (0.080)	42 (0.116)	55 (0.140)	63 (0.150)	118 (0.267)	100 (0.226)	117 (0.255)	143 (0.301)	696 (0.178)	<.0001
Female	8 (0.027)	18 (0.052)	30 (0.080)	53 (0.133)	82 (0.186)	83 (0.179)	92 (0.186)	132 (0.267)	119 (0.236)	172 (0.331)	789 (0.182)	<.0001
Age (yr)												
0-49	1 (0.003)	4 (0.012)	7 (0.020)	11 (0.030)	13 (0.032)	16 (0.039)	21 (0.050)	14 (0.034)	13 (0.031)	25 (0.059)	125 (0.033)	0.0015
50-59	2 (0.025)	4 (0.043)	10 (0.093)	9 (0.075)	11 (0.079)	10 (0.063)	35 (0.204)	20 (0.114)	28 (0.156)	30 (0.165)	159 (0.113)	0.0049
60-69	4 (0.049)	10 (0.099)	14 (0.131)	12 (0.106)	35 (0.287)	36 (0.283)	35 (0.252)	36 (0.257)	42 (0.287)	46 (0.296)	270 (0.219)	0.0009
70-79	7 (0.102)	9 (0.097)	19 (0.191)	32 (0.299)	40 (0.345)	44 (0.352)	76 (0.550)	77 (0.552)	76 (0.533)	104 (0.708)	484 (0.412)	<.0001
> 80	3 (0.113)	13 (0.300)	7 (0.149)	31 (0.615)	38 (0.673)	40 (0.663)	43 (0.612)	85 (1.185)	77 (0.993)	110 (1.272)	447 (0.758)	<.0001
Insurance ranking												
Medical benefits	3 (0.045)	6 (0.075)	10 (0.124)	20 (0.236)	20 (0.242)	20 (0.241)	36 (0.425)	38 (0.477)	28 (0.340)	52 (0.647)	233 (0.289)	0.0001
1, 2	1 (0.014)	4 (0.050)	7 (0.085)	12 (0.13)	17 (0.167)	18 (0.160)	26 (0.215)	29 (0.225)	30 (0.228)	28 (0.195)	172 (0.162)	0.0001
3, 4	3 (0.038)	1 (0.013)	7 (0.076)	7 (0.070)	23 (0.204)	12 (0.103)	23 (0.179)	27 (0.221)	24 (0.193)	32 (0.262)	159 (0.148)	0.0004
5, 6	2 (0.022)	11 (0.095)	5 (0.041)	13 (0.100)	19 (0.133)	18 (0.119)	27 (0.169)	18 (0.112)	31 (0.186)	45 (0.264)	189 (0.134)	0.0008
7, 8	4 (0.033)	8 (0.056)	10 (0.065)	17 (0.103)	20 (0.108)	31 (0.161)	44 (0.216)	60 (0.291)	53 (0.247)	49 (0.222)	296 (0.164)	<.0001
9, 10	4 (0.030)	10 (0.061)	18 (0.101)	26 (0.137)	38 (0.182)	47 (0.208)	54 (0.225)	60 (0.251)	70 (0.288)	109 (0.423)	436 (0.210)	<.0001

**P*-value of the difference over 10 years (2006–2015).

Table 2. The number and rates of *C. difficile* infections by the disease severity

Variable	Cases No. (Infection rate, %)											
Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	*P*-value*
CCI												
0	3 (0.014)	7 (0.030)	6 (0.024)	9 (0.034)	16 (0.058)	17 (0.059)	18 (0.061)	19 (0.066)	19 (0.065)	16 (0.055)	130 (0.048)	0.0011
1	2 (0.015)	8 (0.054)	8 (0.051)	11 (0.064)	16 (0.082)	14 (0.067)	34 (0.152)	27 (0.121)	30 (0.130)	35 (0.150)	185 (0.096)	0.0002
2	4 (0.061)	2 (0.026)	9 (0.108)	11 (0.120)	17 (0.166)	14 (0.124)	27 (0.218)	39 (0.314)	30 (0.236)	46 (0.349)	199 (0.191)	0.0001
> 3	8 (0.058)	23 (0.116)	34 (0.157)	64 (0.271)	88 (0.341)	101 (0.369)	131 (0.442)	147 (0.491)	157 (0.501)	218 (0.648)	971 (0.378)	<.0001

**P*-value of the difference over 10 years (2006–2015). Abbreviation: CCI, Charlson comorbidity index.

individuals treated with anticancer drugs and immunosuppressive drugs, antimicrobial-resistant bacteria, and the development of invasive medical technology [9,10], and the spread of multidrug-resistant healthcare-associated infections is increasing in Korea [11,12]. *C. difficile* is one of the important healthcare-associated infections, and recent data from the Centers for Disease Control and Prevention (CDC) reported an estimated 223,900 infections in hospitalized patients, of which 12,800 were fatal [13]. *C. difficile* ribotype 027 produces binary toxins and is known to have more severe clinical manifestations, but ribotype 027 is still uncommon in Korea [14,15]. In a recent report, 5.1% (13/257) of the toxin-producing strains were binary toxin-producing, and ribotype 018 was the most common, accounting for 25.1% of the total, from February to May 2017 in six hospitals nationwide [14].

Considering that the entire population is covered by

Table 3. The number and rates of *C. difficile* infections by healthcare facility characteristics

Characteristic	Cases No. (Infection rate, %)											
Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	*P*-value*
Location												
Seoul	4 (0.028)	18 (0.107)	16 (0.090)	25 (0.131)	28 (0.138)	31 (0.143)	56 (0.248)	52 (0.234)	47 (0.215)	62 (0.279)	339 (0.170)	<.0001
Busan	2 (0.043)	0	2 (0.035)	7 (0.114)	11 (0.162)	9 (0.125)	12 (0.153)	12 (0.151)	12 (0.143)	25 (0.286)	92 (0.133)	0.0011
Daegu	0	6 (0.153)	7 (0.169)	11 (0.246)	16 (0.317)	8 (0.150)	14 (0.251)	12 (0.218)	21 (0.377)	26 (0.443)	121 (0.248)	0.0038
Incheon	0	0	1 (0.035)	1 (0.031)	4 (0.110)	5 (0.126)	9 (0.213)	10 (0.216)	12 (0.251)	14 (0.279)	56 (0.150)	<.0001
Gwangju	0	2 (0.071)	3 (0.094)	2 (0.059)	9 (0.234)	9 (0.209)	13 (0.277)	8 (0.172)	8 (0.161)	17 (0.342)	71 (0.181)	0.0044
Daejeon	2 (0.101)	2 (0.088)	4 (0.163)	9 (0.340)	7 (0.244)	11 (0.382)	6 (0.194)	7 (0.228)	8 (0.258)	20 (0.565)	76 (0.273)	0.0267
Ulsan	0	0	2 (0.135)	1 (0.063)	1 (0.060)	1 (0.058)	2 (0.098)	3 (0.152)	5 (0.241)	9 (0.435)	24 (0.139)	0.0046
Gyeonggi-do	4 (0.043)	1 (0.009)	8 (0.064)	14 (0.105)	21 (0.144)	28 (0.181)	27 (0.161)	42 (0.249)	45 (0.252)	48 (0.261)	238 (0.162)	<.0001
Gangwon-do	0	2 (0.105)	1 (0.049)	6 (0.281)	2 (0.088)	1 (0.041)	4 (0.151)	5 (0.191)	6 (0.233)	7 (0.272)	34 (0.149)	0.0368
Chungcheongbuk-do	1 (0.079)	1 (0.069)	1 (0.065)	4 (0.233)	3 (0.150)	4 (0.184)	5 (0.216)	3 (0.132)	7 (0.290)	6 (0.236)	35 (0.178)	0.0106
Chungcheongnam-do	0	0	0	1 (0.050)	3 (0.136)	6 (0.254)	8 (0.319)	12 (0.502)	7 (0.306)	8 (0.329)	45 (0.211)	0.0006
Jeollabuk-do	0	3 (0.104)	4 (0.138)	4 (0.129)	9 (0.257)	6 (0.159)	16 (0.434)	17 (0.455)	20 (0.506)	20 (0.495)	99 (0.292)	<.0001
Jeollanam-do	0	0	0	2 (0.044)	5 (0.103)	7 (0.144)	6 (0.121)	13 (0.267)	8 (0.162)	14 (0.265)	55 (0.121)	0.0001
Gyeonsangbuk-do	2 (0.080)	2 (0.071)	6 (0.197)	4 (0.124)	7 (0.207)	7 (0.197)	6 (0.165)	9 (0.249)	11 (0.289)	16 (0.405)	70 (0.209)	0.0007
Gyeongsangnam-do	2 (0.057)	3 (0.072)	2 (0.044)	2 (0.040)	9 (0.162)	12 (0.207)	20 (0.317)	18 (0.287)	13 (0.196)	17 (0.246)	98 (0.179)	0.0036
Jeju-do	0	0	0	2 (0.306)	2 (0.256)	1 (0.136)	6 (0.659)	9 (0.886)	6 (0.567)	6 (0.619)	32 (0.405)	0.0017
Size of city												
Metropolis	4 (0.028)	18 (0.107)	16 (0.090)	25 (0.131)	28 (0.138)	31 (0.143)	56 (0.248)	52 (0.234)	47 (0.215)	62 (0.279)	339 (0.170)	<.0001
Big city	4 (0.025)	10 (0.053)	19 (0.096)	31 (0.144)	48 (0.201)	43 (0.169)	56 (0.204)	52 (0.187)	66 (0.229)	111 (0.367)	440 (0.184)	0.0001
Small town	9 (0.039)	12 (0.044)	22 (0.074)	37 (0.117)	52 (0.148)	63 (0.170)	85 (0.215)	115 (0.290)	111 (0.268)	123 (0.287)	629 (0.181)	<.0001
Rural area	0	0	0	2 (0.051)	9 (0.221)	9 (0.216)	13 (0.310)	13 (0.322)	12 (0.289)	19 (0.453)	77 (0.199)	<.0001
Healthcare facility type												
Referral hospital	8 (0.050)	27 (0.148)	28 (0.142)	50 (0.227)	57 (0.249)	53 (0.220)	86 (0.339)	98 (0.396)	81 (0.336)	114 (0.448)	602 (0.270)	<.0001
General hospital	8 (0.036)	13 (0.051)	24 (0.087)	31 (0.113)	63 (0.207)	74 (0.235)	105 (0.320)	101 (0.306)	120 (0.347)	155 (0.448)	694 (0.231)	<.0001
Hospital (Mental hospital included)	1 (0.006)	0 (0.000)	5 (0.022)	9 (0.035)	15 (0.052)	15 (0.048)	19 (0.055)	31 (0.090)	26 (0.072)	40 (0.107)	161 (0.056)	<.0001
LTCH	0	0	0	5 (0.437)	2 (0.161)	4 (0.325)	0	2 (0.142)	9 (0.578)	6 (0.285)	28 (0.185)	0.1019

**P*-value of the difference over 10 years (2006–2015). Abbreviation: LTCH, long-term care hospital.

a single insurance system, this study has the advantage of being able to easily identify medical conditions and obtain complete data using big data such as data from the Korea Health Insurance Corporation and the Korea Industrial Complex, thus providing reliable data on CDI. A limitation of this study is that the reimbursement of tests for CDI started in 2017, and the test claims in the sample cohort data were unable to check within the study period, so the test status and results in the definition of *C. difficile* infection were not included. In addition, it was difficult to apply the universal criterion of occurrence 48 hours after hospitalization to distinguish between community- and hospital-acquired infections because the claims data did not include the date of onset of symptoms such as diarrhea and the date of positive *C. difficile* culture or related tests such as toxin A/B enzyme immunoassay and PCR [16]. This may have led to the inclusion of data from patients admitted to the hospital after CDI as well as healthcare-acquired infections.

The sample cohort of the National Health Insurance Service can only be extracted until 2015, hence, the latest data are not available, but it is meaningful that this study includes general hospitals, hospitals, and nursing homes, whereas studies on *C. difficile* in Korea are mainly based on tertiary hospitals. In this study, it was found that *C. difficile* infections in Korea are not small and have been steadily increasing, mainly among elderly and severely ill patients.

Disclosure statement

The authors declare no conflict of interest.

Acknowledgment

This study used NHIS-NSC data (REQ0000039182) made by National Health Insurance Service (NHIS). The authors alone are responsible for the content and writing of the paper.

Funding

This work was supported by the National Health Insurance Ilsan Hospital grant (2019-20-003).

References

[1] Bartlett JG, 1994, *Clostridium difficile*: History of Its Role as an Enteric Pathogen and the Current State of Knowledge About the Organism. Clin Infect Dis, 18: S265–S272.

[2] Pepin J, Valiquette L, Alary ME, et al., 2004, *Clostridium difficile* Associated Diarrhea in a Region of Quebec from 1991 to 2003: A Changing Pattern of Disease Severity. Can Med Assoc J, 171: 466–472.

[3] Loo VG, Poirier L, Miller MA, et al., 2005, A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile* Associated Diarrhea with High Morbidity and Mortality. N Engl J Med 353: 2442–2449.

[4] Kim YS, Han DS, Kim YH, et al., 2013, Incidence and Clinical Features of *Clostridium difficile* Infection in Korea: A Nationwide Study. Epidemiol Infect, 141: 189–194.

[5] Choi HY, Park S, Kim Y, et al., The Epidemiology and Economic Burden of *Clostridium difficile* Infection in Korea. Biomed Res Int, 2015: 510386.

[6] Lee J, Lee JS, Park SH, et al., 2017, Cohort Profile: The National Health Insurance Service National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol, 46: e15.

[7] Kim KH, 2010, Comparative Study on Three Algorithms of the ICD-10 Charlson Comorbidity Index with Myocardial Infarction Patients. J Prev Med Public Health, 43: 42–49.

[8] Quan H, Li B, Couris CM, et al., 2011, Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts using Data from 6 Countries. Am J Epidemiol, 173: 676–682.

[9] Martín-Loeches I, Diaz E, Vallés J, 2014, Risks for Multidrug-Resistant Pathogens in the ICU. Curr Opin Crit Care, 20: 516–524.

[10] Yoon YK, Park GC, An H, et al., 2015, Trends of Antibiotic Consumption in Korea According to National Reimbursement Data (2008–2012): A Population-Based Epidemiologic Study. Medicine, 94: e2100.

[11] Kim D, Ahn JY, Lee CH, et al., 2017, Increasing Resistance to Extended Spectrum Cephalosporins, Fluoroquinolone, and Carbapenem in Gram-Negative Bacilli and the Emergence of Carbapenem Non-Susceptibility in *Klebsiella pneumoniae*: Analysis of Korean Antimicrobial Resistance Monitoring System (KARMS) Data from 2013 to 2015. Ann Lab Med, 37: 231–239.

[12] Lee H, Yoon EJ, Kim D, et al., 2018, Antimicrobial Resistance of Major Clinical Pathogens in South Korea, May 2016 to April 2017: First One-Year Report from Kor-GLASS. Euro Surveill, 23: 1800047.

[13] Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019, viewed 4 December 2020, https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

[14] Byun JH, Kim H, Kim JL, et al., 2019, A Nationwide Study of Molecular Epidemiology and Antimicrobial Susceptibility of *Clostridioides difficile* in South Korea. Anaerobe, 60: 102106.

[15] Nicholas A, Kim YK, Lee WK, et al., 2017, Molecular Epidemiology and Antimicrobial Susceptibility of *Clostridium difficile* Isolates from Two Korean Hospitals. PLoS One, 12: e0174716.

[16] Friedman ND, Kaye KS, Stout JE, et al., 2002, Health Care Associated Bloodstream Infections in Adults: A Reason to Change the Accepted Definition of Community-Acquired Infections. Ann Intern Med, 137: 791–797.

Art & Technology Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.