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BRIEF REPORT

Healthcare Costs of *Clostridioides difficile* Infection in Commercially Insured Younger Adults

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In a US adult population aged <65 years, attributable costs due to *Clostridioides difficile* infection (CDI) were highest in persons with hospital onset and lowest in those with community-associated CDI treated outside a hospital. The economic burden of CDI in younger adults underscores the need for additional CDI-preventive strategies.

Keywords. attributable costs; claims data; *Clostridioides difficile* infection.

Clostridioides difficile causes both healthcare-associated and community-associated (CA) infections, with typically highest incidence in older adults. *C. difficile* infection (CDI) is well known to be associated with morbidity, death, and increased healthcare costs in older adults [1], but less is known about its economic consequences in younger adults. We recently calculated healthcare costs attributable to CDI in adults older than 65 years insured by fee-for-service Medicare plans and found that costs at 1 year varied depending on CDI surveillance definition, ranging from $14 257 (2017 USD) after hospital onset (HO) CDI to $1013 after CA CDI, with intermediate values for costs due to healthcare facility–associated (HCFA) and other healthcare facility–onset CDI [2]. In a study of Medicare Advantage enrollees Yu et al [3] calculated 1-year costs attributable to CDI of $15 724 (2019 USD). In a study of younger adults in 2010–2014 using MarketScan claims data, Zhang et al [4] calculated attributable healthcare costs of $26 663 (2014 USD) for primary CDI by propensity score matching to uninfected individuals. To our knowledge, the study by Zhang et al is the only one in the literature reporting CDI-attributable healthcare costs in younger adults.

To provide more information on economic costs we calculated attributable healthcare costs in persons aged 25–64 years coded for CDI, compared with control persons without CDI, stratified by onset and healthcare facility association. We also calculated attributable costs in persons with HCFA and CA CDI hospitalized versus not hospitalized for CDI treatment, to determine the magnitude of costs depending on the site of CDI treatment.

METHODS

Data for this study were obtained from the 2010–2017 Merative MarketScan Commercial Database, including medical claims for persons in the United States covered primarily by employer-sponsored private health. The population was restricted to adults aged 25–64 years.

Patient Consent Statement

No patient consent was obtained for this study. The Washington University Office of Human Research Protections considered the MarketScan analyses to be exempt from human studies research requirements owing to the limited data set structure of MarketScan.

Codes from the *International Classification of Diseases, Ninth Revision* (*ICD-9*)/*International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) were used to identify incident cases of CDI, with the first episode coded for CDI used for analysis. Patients with CDI were initially frequency matched 1:4 to uninfected individuals by age group, year of CDI, and CDI surveillance definition, as described elsewhere [2]. Control patients without CDI were assigned index dates to match the distribution of CDI case onset dates and were classified into standard surveillance definitions based on their location on the index date and recent treatment in a healthcare facility. After restriction to CDI case patients and controls with available data at least 1 year before and 1 year after the CDI index date, excess individuals were randomly excluded to maintain the approximately 4:1 ratio of controls to CDI case patients. Costs were also analyzed for HCFA and CA groups based on hospitalization status (hospitalized vs not hospitalized) during the CDI episode [2], with frequency matching to controls, as described above.

Medical claims in the year prior and up to the index date were used to define healthcare exposures, comorbid conditions [5], and recent infections, as described elsewhere [2, 6]. All medical claims within 1 year after the index date were used to compute healthcare costs, calculated as the sum of patient

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payments and allowable health plan expenditures. Costs were adjusted to 2017 USD using the medical care component of the consumer price index.

Inverse weighting by the propensity score was used to balance covariates between CDI case patients and controls within surveillance category. Variables with an absolute standardized mean difference (SMD) of ≥0.1 between case patients and controls were chosen for inclusion in the propensity score model, with CDI case as the outcome (including age group, sex, and year, regardless of degree of imbalance). If residual imbalance remained after weighting, trimming was applied, and the propensity score modeling and weighting was repeated until balance was achieved or the maximum amount of trimming (to the 10th and 90th percentiles) was applied [7].

Two-part models were used for calculation of attributable costs (schematic of the methods shown in Supplementary Figure 1) [8]. The first part involved logistic regression to estimate the probability of any healthcare costs during the 1-year follow-up period, and the second consisted of a generalized linear model with gamma distribution and log link to model total costs among patients with nonzero costs. In addition to the CDI case/control indicator, age group, sex, and year were included as covariates in all models to control for any residual imbalance. The expected cost for each patient was the product of the fitted values from the 2 models. Expected costs were averaged separately among CDI case patients and controls, and the costs attributable to CDI were calculated as follows: (average expected costs among case patients) − (average expected costs among controls). Confidence intervals were obtained by resampling the population and repeating the 2-part models, using the original propensity score weights [9, 10]. The same process was used for the analysis of costs in hospitalized and not hospitalized groups.

RESULTS

The demographic characteristics of the populations by HO, HCFA, and CA surveillance definitions are shown in Table 1 and in more detail in Supplementary Table 1. The HO and HCFA populations included progressively fewer persons by increasing study year, in part owing to the changing epidemiology of CDI, with more CA case patients in later years of the study [11]. For all case patients and controls, female patients predominated, and CA case patients and controls were the least likely to have been hospitalized in the prior year.

After propensity score weighting, the case patients and controls were well balanced, except for 2 variables in the HO population (Supplementary Table 2). The crude and attributable costs of CDI by surveillance category were highest in those with HO CDI, lower after HCFA CDI, and lowest after CA CDI, with attributable costs of $48 225, $43 127, and $13 105, respectively (Table 1).

The demographic characteristics and costs of the HCFA and CA populations stratified by CDI treatment location (hospital vs outside a hospital) are shown in Table 2 and

Table 1. Characteristics and Costs of Commercially Insured Adults Aged 25–64 Years With or Without *Clostridioides difficile* Infection (CDI) by CDI Surveillance Definition

Characteristic	Patients or Controls, No. (%)[a]					
	HO CDI		Community Onset–HCFA CDI		CA CDI	
	Case Patients (n= 5135)	Controls (n = 20 484)	Case Patients (n = 6880)	Controls (n = 27 520)	Case Patients (n = 17 773)	Controls (n = 71 093)
Age, median (IQR), y	55 (47–60)	55 (48–60)	53 (45–59)	54 (45–59)	51 (42–58)	52 (43–58)
Female sex	2593 (50.5)	11 672 (57.0)	4268 (62.0)	16 285 (59.2)	11 933 (67.1)	40 328 (56.7)
Nonelective hospitalization in prior year[b]	2464 (48.0)	3991 (19.5)	4776 (69.4)	14 191 (51.6)	1661 (9.4)	3261 (4.6)
Elective hospitalization in prior year[c]	4627 (90.1)	19 652 (95.9)	4242 (61.7)	15 668 (56.9)	2001 (11.3)	3523 (5.0)
2011	1112 (21.7)	4265 (20.8)	1312 (19.1)	5484 (19.9)	2847 (16.0)	11 483 (16.2)
2012	954 (18.6)	3961 (19.3)	1312 (19.1)	5152 (18.7)	2988 (16.8)	10 195 (14.3)
2013	904 (17.6)	3581 (17.5)	1189 (17.3)	4812 (17.5)	3087 (17.4)	13 380 (18.8)
2014	771 (15.0)	3081 (15.0)	1072 (15.6)	4068 (14.8)	2785 (15.7)	9080 (12.8)
2015	709 (13.8)	2947 (14.4)	1025 (14.9)	4095 (14.9)	3160 (17.8)	14 104 (19.8)
2016	685 (13.3)	2649 (12.9)	970 (14.1)	3909 (14.2)	2906 (16.4)	12 851 (18.1)
Costs, median (IQR), $						
Crude 1-y costs	95 876 (89 856–101 836)	47 651 (42 382–53 399)	74 426 (70 952–77 884)	31 299 (29 502–33 818)	25 977 (25 007–27 014)	12 872 (12 380–13 510)
Attributable 1-y costs	48 225 (40 221–55 993)	…	43 127 (38 450–47 002)	…	13 105 (12 030–14 204)	…

Abbreviations: CA, community-associated; CDI, *Clostridioides difficile* infection; HCFA, healthcare facility–associated; HO, hospital onset; IQR, interquartile range.

[a]Data represent no. (%) of patients or controls unless otherwise specified.

[b]Nonelective hospitalization defined as hospital admission through the emergency department, based on revenue codes.

[c]Elective hospitalization defined as no evidence of hospital admission through the emergency department.

Table 2. Characteristics and Costs of Commercially Insured Adults Aged 25–64 Years With or Without Healthcare Facility–Associated or Community-Associated *Clostridioides difficile* Infection by Hospitalization Status

	Patients or Controls, No. (%)[a]			
	Treated During Hospitalization		Treated In the Community	
Characteristic	CDI Case Patients	Controls	CDI Case Patients	Controls
HCFA CDI	(n = 3806)	(n = 15 224)	(n = 3074)	(n = 12 106)
Age, median (IQR)	53 (45–59)	54 (45–59)	53 (44–59)	54 (45–59)
Female sex	2380 (62.5)	8924 (58.6)	1888 (61.4)	7189 (59.4)
2011	770 (20.2)	3034 (19.9)	542 (17.6)	2391 (19.8)
2012	772 (20.3)	2860 (18.8)	540 (17.6)	2254 (18.6)
2013	656 (17.2)	2648 (17.4)	533 (17.3)	2136 (17.6)
2014	571 (15.0)	2282 (15.0)	501 (16.3)	1780 (14.7)
2015	532 (14.0)	2236 (14.7)	493 (16.0)	1847 (15.3)
2016	505 (13.3)	2164 (14.2)	465 (15.1)	1698 (14.0)
Costs, median (IQR), $				
Crude 1-y costs	102 411 (96 505–108 833)	31 209 (28 778–34 228)	44 632 (41 301–48 013)	28 741 (26 349–31 225)
Attributable 1-y costs	71 202 (64 596–77 906)	…	15 891 (11 155 –19 651)	…
CA CDI	(n = 6260)	(n = 25 040)	(n = 11 513)	(n = 46 053)
Age, median (IQR)	52 (44–58)	52 (43–58)	51 (41–57)	52 (43–58)
Female sex	4183 (66.8)	14 158 (56.5)	7743 (67.3)	26.170 (56.8)
2011	1138 (18.2)	3959 (15.8)	1733 (15.1)	7524 (16.3)
2012	1172 (18.7)	3553 (14.2)	1849 (16.1)	6642 (14.4)
2013	1142 (18.2)	4858 (19.4)	1966 (17.1)	8522 (18.5)
2014	969 (15.5)	3282 (13.1)	1817 (15.8)	5798 (12.6)
2015	1016 (16.2)	4887 (19.5)	2156 (18.7)	9217 (20.0)
2016	823 (13.2)	4501 (18.0)	1992 (17.3)	8350 (18.1)
Costs, median (IQR), $				
Crude 1-y costs	52 184 (49 119–55 273)	16 094 (14 501–17 946)	15 230 (14 303–16 094)	12 166 (11 807–12 805)
Attributable 1-y costs	36 090 (32 778–39 311)	…	3063 (1999–3885)	…

Abbreviations: CA, community-associated; CDI, *Clostridioides difficile* infection; HCFA, healthcare facility–associated; IQR, interquartile range.

[a]Data represent no. (%) of patients or controls unless otherwise specified.

Supplementary Tables 3 and 4, with the SMDs before and after propensity score weighting shown in Supplementary Tables 5 and 6. The CA case patients and controls and the HCFA nonhospitalized case patients and controls were well balanced after weighting. Some residual imbalance remained in the HCFA hospitalized case patients versus controls (4 variables with SMDs >0.1 after weighting) and the CA hospitalized case patients versus controls (2 variables). The attributable costs due to CDI were highest in the hospitalized HCFA group ($71 202), lower in the CA hospitalized group ($36 090), and much lower in the HCFA and CA nonhospitalized groups ($15 891 and $3063, respectively; Table 2).

DISCUSSION

In this analysis of healthcare costs attributable to CDI from the commercial plan perspective, we found that costs were highest for those with HO CDI, intermediate for those with HCFA CDI, and lowest for those with CA CDI. Not surprisingly, we also found that costs were higher in the HCFA and CA groups that were coded for CDI during a hospitalization and much lower for those treated outside a hospital.

We calculated much higher healthcare costs in younger adults than in older adults insured by traditional Medicare [2] or Medicare Advantage plans [3] and in another study of adults in Ontario with CDI in which 74% of patients were ≥65 years old [12]. In a review of 19 studies based on 2010–2017 data, the Kaiser Family Foundation found that private insurers reimbursed hospitals and physicians at much higher rates than Medicare, ranging from 143% more for physician services to 199% more for inpatient hospital services and 264% more for outpatient hospital services [13]. Thus, our finding of higher attributable CDI healthcare costs in a privately insured younger population compared with the estimates from the literature primarily from older persons insured by Medicare is not surprising. An additional reason for the higher costs calculated in the younger adult population may reflect the overall better health of the comparison control persons in the younger versus older populations, despite selecting controls

who met the same surveillance definition as the CDI case patients (eg, HO CDI case patients compared with controls hospitalized for ≥3 days).

The limitations of our study include the identification of CDI using *ICD-9*/*ICD-10-CM* diagnosis codes, resulting in the potential for misclassification owing to imperfect sensitivity and specificity of administrative coding. We were unable to calculate attributable costs of CDI with onset in other healthcare facilities (eg, skilled nursing facilities), owing to the smaller number of persons meeting the surveillance definition, resulting in an inability to obtain an acceptable balance of covariates between case patients and controls. The attributable costs may be overestimated because of residual confounding and/or remaining imbalance for a small number of measured covariates after propensity score weighting. The strengths of our study are the calculation of attributable costs by both surveillance definition and coding for CDI during a hospitalization. The variation in costs is important to consider, since the incidence of CA CDI has increased, while the incidence of HO CDI decreased in recent years. Because of the changing epidemiology of CDI, it is important to distinguish healthcare costs compared with controls meeting the same surveillance definition as the CDI case patients, to determine the economic burden of this infection most accurately. Given the morbidity and excess healthcare costs associated with CDI, novel strategies are needed to prevent these infections in younger as well as older adults.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. M. A. O. reports personal fees from Pfizer for consulting work. H. Y. is an employee of Pfizer. E. R. D. reports receipt of grant funding from Pfizer, Synthetic Biologics, and Ferring in the past 36 months and personal fees from Ferring, Rebiotix, Summit, Merck, Pfizer, and Seres. All other authors report no potential conflicts.

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