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Kelly R Reveles
University of Texas at Austin

Min Yang
Analysis Group

Viviana Garcia-Horton
Analysis Group

Marie Louise Edwards
Analysis Group

Amy Guo
Ferring Pharmaceuticals

See next page for additional authors

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ORIGINAL RESEARCH

Economic Impact of Recurrent *Clostridioides difficile* Infection in the USA: A Systematic Literature Review and Cost Synthesis

Kelly R. Reveles · Min Yang · Viviana Garcia-Horton · Marie Louise Edwards · Amy Guo · Thomas Lodise · Markian Bochan · Glenn Tillotson · Erik R. Dubberke

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ABSTRACT

Introduction: Up to 35% of patients with a first episode of *Clostridioides difficile* infection (CDI) develop recurrent CDI (rCDI), and of those, up to 65% experience multiple recurrences. A systematic literature review (SLR) was conducted to review and summarize the economic impact of rCDI in the United States of America.

Methods: English-language publications reporting real-world healthcare resource utilization (HRU) and/or direct medical costs associated with rCDI in the USA were searched in MEDLINE, MEDLINE In-Process, Embase, and the Cochrane Library databases over the past 10 years (2012–2022), as well as in selected scientific conferences that publish research on rCDI and its economic burden over the past 3 years (2019–2022). HRU and costs identified through the SLR were synthesized to estimate annual rCDI-attributable direct medical costs to inform the economic impact of rCDI from a US third-party payer's perspective.

Results: A total of 661 publications were retrieved, and 31 of them met all selection criteria. Substantial variability was found across these publications in terms of data source, patient population, sample size, definition of rCDI, follow-up period, outcomes reported, analytic approach, and methods to adjudicate rCDI-attributable costs. Only one study reported rCDI-attributable costs over 12 months. Synthesizing across the relevant publications

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K. R. Reveles
College of Pharmacy, The University of Texas at Austin, Austin, TX, USA

M. Yang (✉)
Analysis Group, 111 Huntington Avenue, 14th Floor, Boston, MA 02199, USA
e-mail: min.yang@analysisgroup.com

V. Garcia-Horton · M. L. Edwards
Analysis Group, New York, NY, USA

A. Guo
Medical Affairs, Ferring Pharmaceuticals, Parsippany, NJ, USA

T. Lodise
Albany College of Pharmacy and Health Sciences, Albany, NY, USA

M. Bochan
Outpatient Integrated Strategies, Carmel, IN, USA

G. Tillotson
GST Micro, Henrico, VA, USA

E. R. Dubberke
Division of Infectious Diseases, Washington University School of Medicine in St. Louis, St. Louis, MO, USA

using a component-based cost approach, the per-patient per-year rCDI-attributable direct medical cost was estimated to range from $67,837 to $82,268.

Conclusions: While real-world studies on economic impact of rCDI in the USA suggested a high-cost burden, inconsistency in methodologies and results reporting warranted a component-based cost synthesis approach to estimate the annual medical cost burden of rCDI. Utilizing available literature, we estimated the average annual rCDI-attributable medical costs to allow for consistent economic assessments of rCDI and identify the budget impact on US payers.

Keywords: Cost estimation; Healthcare resource utilization; Medical costs; Recurrent *Clostridioides difficile* infection; Systematic literature review

Key Summary Points

Why carry out this study?

Clostridioides difficile infection (CDI) is a bacterial infection that may cause severe diarrhea and colitis. Recurrence of CDI is common, and older patients (> 65 years old) are especially vulnerable, with infection often leading to hospitalization and, in advanced cases, sepsis, colectomy, or death.

High medical costs associated with rCDI in the USA have been reported in the literature; however, there has often been lack of consistency in the methodologies used or ways in which results are reported. With the emergence of new therapies for rCDI, establishing a benchmark medical cost burden for this condition will set a foundation for effectively evaluating the impact of such therapies in the real world.

We conducted a systematic literature review (SLR) on the economic burden associated with rCDI with currently available therapies to estimate the average annual per-patient rCDI-attributable medical costs from a US third-party payer's perspective.

What was learned from this study?

Our SLR found considerable variability in study design, population definition, and reporting approaches for the medical cost burden of rCDI in the USA with current available treatments. The variability prevented use of meta-analyses to comprehensively assess the annual medical cost per rCDI patient. Maximizing the available data in the literature, we used a component-based cost synthesis approach and provided an estimated range of the annual average per-patient rCDI-attributable medical costs to a third-party payer in the USA.

The cost estimation underscores the need for more effective therapies to prevent rCDI, improve rCDI-associated patient outcomes, and reduce rCDI-associated costs.

INTRODUCTION

Clostridioides difficile infection (CDI) is characterized by severe diarrhea and colitis. *C. difficile* is an anaerobic gram-positive, spore-forming, toxin-producing bacillus transmissible via the fecal-oral route. CDI frequently occurs among patients recently exposed to antibiotics. Its spores are common in healthcare facilities and are also found in the environment and the food supply [1]. Older adults (aged 65 years or older) are especially vulnerable to CDI. With an estimated median age of diagnosis at 71 years, older adult patients have an estimated 5.7-fold higher incidence rate of CDI infection than patients younger than 65 years [2, 3]. Standard treatment typically involves antibiotic therapy such as oral vancomycin or fidaxomicin for an initial episode of CDI [4]. Recurrent CDI (rCDI) remains common with currently available therapies. It is estimated that more than 35% of patients treated for an initial episode of CDI will have a rCDI, and approximately 65% of patients with an initial rCDI will experience subsequent recurrences [5–7].

The economic burden associated with rCDI is substantial due to the frequent need for hospitalizations, including treatment for sepsis, post-acute care, and in some more extreme cases, surgical interventions, including colectomy [8]. Moreover, rCDI-associated mortality is high, especially among older patients [9]. To address this high, unmet medical need, novel therapies are emerging for preventing rCDI [10]. With the expected availability of new treatment options for patients with rCDI, it is critical to establish a benchmark medical cost estimation for this condition, as it will provide an evidence-based foundation for effectively assessing the potential economic impact of these emerging rCDI therapies in the real-world clinical practice setting. We conducted a systematic literature review (SLR) on the economic burden associated with rCDI with currently available therapies to provide an estimate of the average annual per-patient rCDI-attributable medical costs from a US third-party payer's perspective.

METHODS

Literature Search

Real-world studies published in English reporting the healthcare resource utilization (HRU) or direct medical costs of adult patients with rCDI in the USA were identified following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [11]. The search was conducted in April 2022 in MEDLINE, MEDLINE In-Process, Embase, and the Cochrane Library databases, and in selected scientific conferences that publish research on rCDI and its economic burden. Seven scientific conferences were also included: Academy of Managed Care Pharmacy (AMCP), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Digestive Disease Week (DDW), Infectious Disease Week (IDWeek), United European Gastroenterology Week (UEG Week), American College of Gastroenterology (ACG), and Making a Difference in Infectious Diseases Annual Meeting (MAD-ID). The search included studies published over the past 10 years between January 1, 2012–April 13, 2022; conferences were searched for the past 3 years from 2019 through 2022. The search strategy and screening of studies followed the population, interventions, comparisons, outcomes, and study (PICOS) designs approach, as recommended by the Centre for Reviews and Disseminations (CRD) review guidelines (Table 1) [12].

Included studies were required to report at least one type of HRU (e.g., hospitalization, readmissions, intensive care unit (ICU) visits, emergency department (ED) visits, post-acute care, outpatient visits, stool tests, colectomy, ileostomy reversal, or terminal care), or a direct cost component for any of these HRU items, in the intended patient population. The search focused on real-world cohort studies (retrospective) to reflect costs that are relevant to payers. Studies that did not report primary data on HRU or direct medical costs, and those not conducted in real-world settings (e.g., economic models, clinical trials, case reports, case series) were excluded. The full search strategy is detailed in Appendix Table 1. This study is based upon published literature and does not contain any new studies involving human participants or animals.

Publication Screening

All articles identified from the search were screened using a two-stage process. In stage one, all articles were screened based on their title and abstract. In stage two, those meeting the inclusion criteria were screened based on their full text using the same eligibility criteria as in stage one. To ensure accuracy, the screening of both publications and conference proceedings was conducted by two reviewers independently. Discrepancies were resolved through discussion between the two reviewers or by a third reviewer. Publications that satisfied all selection criteria were included for data extraction.

Medical Cost Data Extraction

Extracted data included publication year, study type (e.g., claims database analysis, chart review), data source (e.g., survey, claims,

electronic health record [13], methods, patient population, availability of data on specific rCDI populations (e.g., patients with first rCDI, with second or third rCDI), sample size by subgroup, cost year, duration of follow-up, and year(s) for reported outcomes. Availability of HRU outcomes and costs was summarized, and it was noted whether they were all-cause or attributable to rCDI.

Patient characteristics, prior treatments, and risk factors for rCDI, key comorbidities (e.g., heart failure, renal insufficiency, inflammatory bowel disease, diabetes, cardiovascular disease) were extracted. HRU prior to rCDI, and all-cause and rCDI-attributable per-patient per-year costs and HRU were extracted from all publications meeting the SLR criteria. Costs were adjusted for inflation to 2022 USD using the medical component of the Consumer Price Index (CPI). To describe the available data, minimum and maximum all-cause and rCDI-attributable HRU and cost values were summarized for each given HRU category (i.e., hospitalizations, ICU visits, post-acute care, ED visits, or outpatient visits) with an annual time horizon.

Component-based Cost Synthesis for Annual rCDI-attributable Medical Cost

A meta-analysis of the SLR findings was considered to estimate per-patient per-year rCDI-attributable medical costs. However, substantial heterogeneity in the methods and characteristics of the populations across the publications made a meta-analysis infeasible. We therefore estimated per-patient per-year rCDI-attributable medical costs using a component-based cost synthesis approach. With this approach, available data are maximized for establishing the estimation in a transparent manner. Furthermore, this approach confers the ability to identify cost drivers and conduct sensitivity analyses to assess the impact of a specific HRU or cost component included in the estimation. This methodology is also adaptable to incorporate new evidence, when available, to provide the most up-to-date estimate.

The key components considered in the cost synthesis analysis were rCDI-attributable hospitalizations, ICU visits, post-acute care (receipt of care post-hospital discharge in a non-acute healthcare facility [i.e., rehabilitation center, long-term care facility, skill nursing facility]), ED visits, outpatient visits, stool tests, colectomy, and ileostomy reversal. Given that death events are observed in these patients, rates of negative rCDI-attributable outcomes (i.e., need for terminal care, and mortality rate) and associated costs were also identified. Since the objective of the study was to estimate the average annual per-patient rCDI-attributable medical costs from a US third-party payer's perspective, the components of the cost-based cost synthesis analysis (i.e., annual utilization rates for each HRU category and associated unit costs) were extracted from the publications identified in the SLR with a $\geq$ 6-month duration of follow-up. In instances where data on HRU or costs from a single publication reported results separately for subgroups of patients by number of rCDI recurrences (e.g., patients with one rCDI, patients with two rCDIs) along with the sample sizes of each subgroup, weighted averages based on sample size distribution of the subgroups were calculated. When a range of utilization rates and/or unit costs were available for a given component, all values were considered to best inform the input(s) for the cost synthesis analysis. The minimum and maximum cost estimates for each HRU component were summed, respectively, to provide a range of rCDI-attributable annual per-patient total medical costs. A supplemental targeted search was conducted to provide data when cost elements were not available from the publications identified in the SLR, for example, ICU-day unit cost, cost of terminal care, etc. For such instances, PubMed, Google Scholar, and HCUPnet were searched to inform the value components.

As the objective was to estimate the average annual per-patient rCDI-attributable medical costs from a US third-party payer's perspective, the base case cost calculation utilized data from publications reporting estimates with a 12-month follow-up period. This threshold was selected to ensure proper extrapolation of the annual outcomes, HRU, and costs associated with rCDI. To test the robustness of the

synthesized annual cost estimation for rCDI, sensitivity analyses were performed using additional values for the key cost drivers that were not considered in the base case evaluation. Specifically, the sensitivity analyses used data from publications that met all other requirements except for having a shorter follow-up period than 6 months. As such, publications used in the sensitivity analyses reported relevant HRU or cost results and had a duration of follow-up from 90 days to less than 6 months. Relevant HRU and costs inputs were annualized as appropriate. The sensitivity analysis values were individually tested in the cost component calculation while keeping all other base case inputs constant.

RESULTS

A total of 661 publications were identified for stage one screening (see PRISMA diagram, Fig. 1). Screening of titles and abstracts resulted in a total of 221 relevant articles. From the stage two (full-text) screening, a total of 31 publications were included for data extraction (Table 2).

Study Characteristics of All Included Publications

The 31 publications identified for data extraction have substantial variability in terms of data source, studied populations, sample size, definition of rCDI, follow-up period, outcomes reported, analytic approach, and methods to adjudicate rCDI-attributable (Table 2). Studies include analyses of claims databases (9/31) [14–22], national hospital databases (4/31) [23–26], multi-center EHRs (5/31) [13, 27–30], single-center EHRs (10/31) [31–40], and survey/chart review studies (3/31) [41–43] (Table 2).The reported subgroups by number of recurrences were 18 studies on first rCDI, 9 on second rCDI, and 10 on third or greater rCDI. Sample size for subgroups by number of recurrences ranged from 13 (Sadeghi et al. 2022b, rCDI—fourth recurrence with prior CDI admission) to 354,009 patients (Kruger et al. 2019, rCDI—any recurrence without cirrhosis).

Definitions for rCDI also varied. For example, Rodrigues et al. 2017, a single-center EHR study with a literature review for cost inputs, performed a manual chart review for patients who had at least three International Classification of Diseases, 9th edition (ICD-9) codes for CDI and at least two prescriptions for oral vancomycin to confirm an rCDI diagnosis through physician adjudication; this yielded a cohort of patients with at least two episodes of CDI with the second infection occurring within 56 days after the end of treatment for the index infection [31]. Feuerstadt et al. 2020 was a claims database analysis of the IQVIA PharMetrics Plus database that defined two episodes of CDI as at least one inpatient claim with an ICD-9 code for CDI or one outpatient medical claim with an ICD-9 code for CDI plus a CDI treatment, with the second episode occurring within an 8-week (56 days) window following a 14-day claim-free period after end of treatment for the index CDI episode [20]. Zhang et al. (2018) was a claims database analysis of MarketScan data that defined an episode of CDI as any claim with at least one ICD-9 code for CDI and defined recurrences as any CDI episodes that occurred within 84 days (12 weeks) of the previous episode [19]. Other studies met the inclusion criteria for the study and are included in Table 2 but did not meet the criteria for the cost calculations [28, 36, 41].

In terms of duration of follow-up, eight reported annual cost and/or HRU [14, 18, 20–22, 27, 31, 37]. Among these, six reported for populations with first rCDI, five with second rCDI, and six with third or greater rCDI. Four of them reported both annual cost and HRU. However, only Rodrigues et al. 2017 reported rCDI-attributable costs, while the others reported all-cause costs only. Two studies reported 6-month estimates; one was by Dubberke et al. 2014, which was a single-center EHR study and included patients with any recurrence, and the other was by Zhang et al. 2018, which was a MarketScan analysis and included patients with first rCDI only [19, 33]. The remaining studies reported costs and/or HRU over shorter time periods, including over the course of one hospitalization, 1 month, or 3 months (Table 2).

Table 1 PICOS inclusion and exclusion criteria for studies in the SLR

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients with rCDI in the USA	Study not including the patient population specified
Intervention and comparators	Any [e.g., standard of care antibiotics (e.g., vancomycin taper-pulse, fidaxomicin)]	N/A
Outcomes	Studies reporting at least one of the following HRU OR cost outcomes	Any study not including the outcomes specified
	HRU of patients with rCDI (e.g., rates per year):	
	Hospitalization	
	Readmissions	
	ICU	
	ED visit	
	Post-acute care—including a skilled nursing facility, inpatient rehabilitation facility, or long-term acute care hospital or services provided by a home health agency	
	Outpatient visit	
	Stool test	
	Colectomy	
	Ileostomy reversal	
	Terminal care	
	Direct healthcare costs to US third-party payers (e.g., Medicare, commercial insurers) incurred by patients with rCDI:	
	Direct healthcare costs associated with the above items	
	Studies will be selected for inclusion based on availability of the outcomes listed above	
Study design	Observational studies (e.g., prospective study, case–control study, case series), retrospective studies (e.g., claims analyses, EMR studies, registry studies)	Non-real-world evidence (e.g., clinical trials, editorials, letters, comments, economic models [cost–utility analysis, cost-effectiveness analysis, cost–consequence analysis; cost–benefit analysis; cost minimization analysis; other economic models]); case reports of individual patients; SLRs, meta-analyses, article reviews
Other	Studies published in English USA setting	Studies not published in English; studies not set in the USA

Table 1 continued

Criteria	Inclusion criteria	Exclusion criteria
Time period	Studies published within the last 10 years (2012–2022)	Studies published prior to the time period of interest

ED emergency department, *EMR* electronic medical record, *HRU* healthcare resource utilization, *ICU* intensive care unit, *rCDI* recurrent *Clostridioides difficile* infection, *SLR* systematic literature review

Study Characteristics of Publications Reporting Annual or Semi-annual Estimates

Across the eight publications reporting annual estimates, there were substantial variations in population characteristics (Table 3). The mean age ranged from 47.9 years (Feuerstadt et al. 2020) to 78.3 years (Nelson et al. 2021 and Feuerstadt et al. 2022). Percentage of female patients ranged from 54.3% (Tariq et al. 2021) to 69.1% (Feuerstadt et al. 2022) [14, 20, 22, 37]. Insurance or medical networks included in these patient populations were Kaiser Permanente (Kuntz 2017), Medicare (Nelson 2021), Partners Healthcare Network (Rodrigues 2017), and commercial insurance (Feuerstadt 2020) [20, 22, 27, 31].

Variations in underlying health conditions were demonstrated as measured by Charlson Comorbidity Index (CCI; mean CCI scores:1.5 [Feuerstadt et al. 2021] to 8.6 [Rodrigues et al. 2017] [21, 31]), but not all studies reported comorbidities. History of heart failure was high and was reported in two studies using the same source, Medicare fee-for-service claims data at 43.5% to 45.3% (Nelson et al. 2021 and Feuerstadt et al. 2022); history of renal disease/insufficiency ranged from 18.3% (Feuerstadt et al. 2020 and Feuerstadt et al. 2021) to 43.2% (Nelson et al. 2021 and Feuerstadt et al. 2022) [14, 20–22]. Other common comorbidities included cancer, cardiovascular disease, pulmonary disease, and immunocompromised status [19].

The majority of studies reported that patients had antibiotic treatment prior to rCDI (76.9% [Feuerstadt et al. 2020 and Feuerstadt et al. 2021, third or greater rCDI] to 89.8% [Nelson et al. 2021 and Feuerstadt et al. 2022, third or greater rCDI]) [14, 20–22]. HRU prior to rCDI was commonly reported as inpatient admission, outpatient visit, and ED visit, and varied greatly depending on patient population (**Table 3**). In Zhang et al. 2018, prior antibiotic use was reported in 66.5% [19].

HRU and Cost Publications Reporting Annual or Semi-annual Estimates

All-cause per-patient per-year HRU varied widely among four studies reporting annual estimates (Table 4). Studies reported hospitalization ranging from 1.1 visits with associated cumulative length of stay (LOS) of 8.4 days (Kuntz et al. 2017, first rCDI) to 5.8 visits with associated mean LOS of 8.5 days per hospitalization (Feuerstadt et al. 2020, third or greater rCDI). Only Kuntz et al. 2017 reported all-cause ICU admissions and estimated a mean of 0.9 days per-patient among patients with first rCDI [27]. The proportion of patients receiving care in a post-acute setting ranged from 69.8% (Nelson et al. 2021, third or greater rCDI) to 74.6% (Nelson et al. 2021, first rCDI) [22]. Moreover, the mean number of ED visits per-patient per-year ranged from 1.4 (Nelson et al. 2021, first rCDI) to 4.6 visits (Feuerstadt et al. 2020, third or greater rCDI) [20, 22]. The number of outpatient visits ranged from 15.4 (Rodrigues et al. 2017, any rCDI) to 26.3 visits (Nelson et al. 2021, third or greater rCDI) per-patient per-year [22, 31]. Only one study, Rodrigues et al. 2017, reported rCDI-attributable HRU of hospitalization visits, LOS, ICU days, ED visits, and outpatient visits

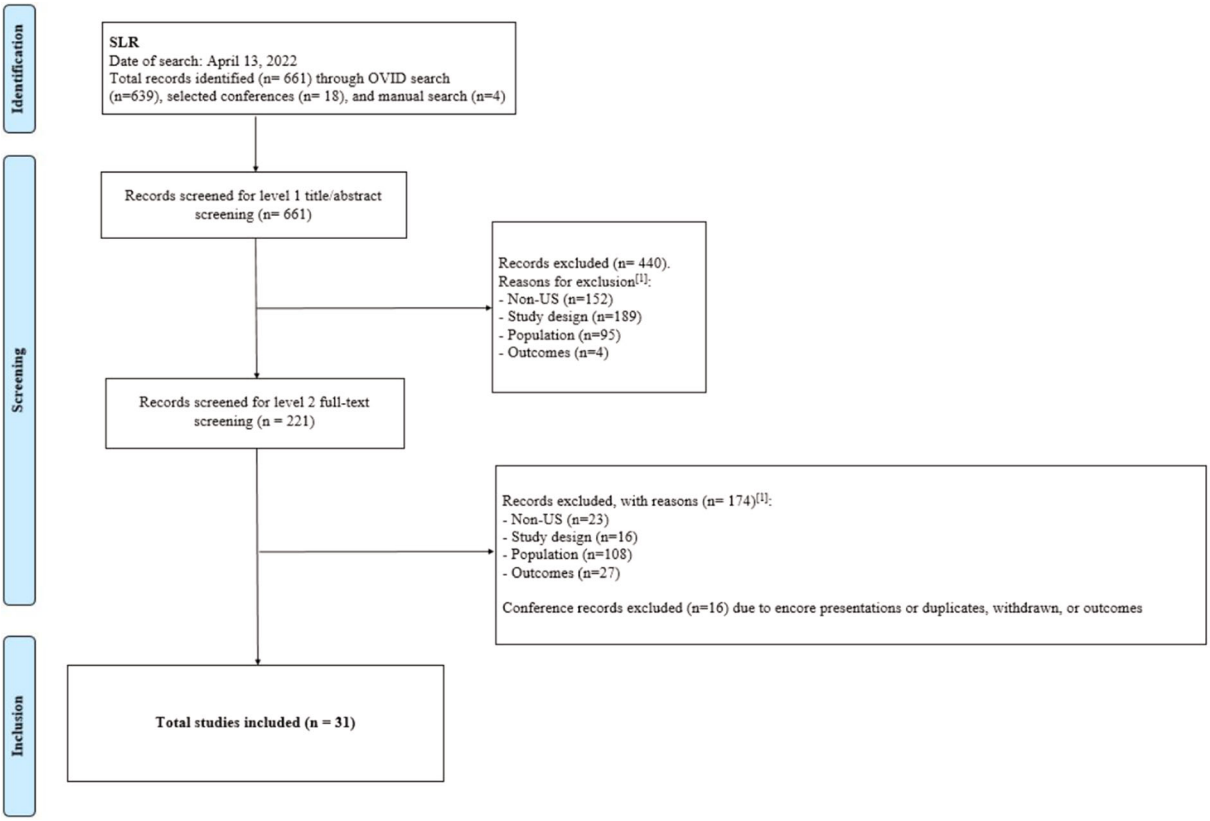

Fig. 1 PRISMA diagram. [1]The following hierarchy was applied to the exclusion criteria: (1) non-USA based, (2) study design, (3) population, (4) outcomes (e.g., if a study is both USA based and not the eligible study design, the reason for exclusion is "USA based"). *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-analyses, *SLR* systematic literature review

(Table 4) [31]. Of the two studies reporting semi-annual estimates, only Zhang et al. 2018 reported HRU [19]. This study reported an average of 9.3 cumulative hospitalized days for a rCDI cohort and 7.3 days for a matched primary CDI cohort, leading to 2.0 rCDI-attributable hospitalizations days incremental over primary CDI.

Total all-cause per-patient per-year costs varied widely in two studies of patients with any rCDI (Table 5). When inflation-adjusted to 2022 USD, estimates ranged from $93,979 (Nelson et al. 2021, second rCDI) to $231,149 (Feuerstadt et al. 2020, third or greater rCDI). Only one study, Rodrigues et al. 2017, reported rCDI-attributable total costs for the any-rCDI population: $39,668 per-patient per-year [31].

Among the studies reporting semi-annual estimates, rCDI-attributable hospitalization costs incremental over primary CDI ranged from $12,061 (Zhang et al. 2018, first rCDI) to $16,150 (Dubberke et al. 2014, any rCDI) when inflation-adjusted to 2022 USD [19, 33]. Among these studies only Zhang et al. 2018 reported a total rCDI-attributable cost incremental over primary CDI of $13,109.

Estimated Annual rCDI-attributable Medical Cost—Base-Case Estimate

To estimate the average annual total rCDI-attributable medical cost, we calculated each component cost of rCDI-attributable HRU based on literature in the SLR, as well as those from the supplemental search for hospitalization stay unit cost per day, ICU unit cost per day, post-acute care cost, outpatient visit unit cost, ileostomy reversal unit cost and rate, terminal

Table 2 Study characteristics of all included publications

Study information				rCDI populations available				Cost results available		HRU results available		Cost time period		HRU time period	
Source	**Sample and relevant subgroups**	**Sample size by arm**	**Data source**	**Any rCDI**	**First rCDI**	**Second rCDI**	**Third or greater rCDI**	**All-cause**	**rCDI-attributable**	**All-cause**	**rCDI-attributable**	**Annual**	**6-month**	**Annual**	**6-month**
Total				*31*	*17*	*9*	*10*	*8*	*8*	*21*	*17*	*4*	*2*	*8*	*1*
Zilberberg 2017	rCDI—first recurrence	4768	Claims	X	X			X	X	X	X				
Rodrigues 2017	rCDI—first recurrence	98	Other—single-center EHR + literature review	X					X	X	X	X		X	
Kuntz 2017	rCDI—first recurrence	4174	Multi-center EHR	X	X					X				X	
Razik 2016	rCDI—first recurrence	35	Multi-center EHR	X	X						X				
Jasiak 2016	rCDI—first recurrence	34	Single-center EHR	X	X					X					
Dubberke 2014	rCDI—any recurrence	421	Single-center EHR	X					X				X		
Aitken 2014	rCDI—first recurrence	64	Single-center EHR	X	X	X					X				
	rCDI—second recurrence	18													
Brandt 2012	rCDI—first recurrence	77	Survey	X	X					X					
Hamilton 2012	Non-IBD with rCDI—two or more recurrences	29	Single-center EHR	X		X				X					
	IBD with rCDI—two or more recurrences	14													
Venugopal 2012	rCDI—first recurrence	24	Single-center EHR	X	X					X					

Table 2 continued

Study information				rCDI populations available				Cost results available		HRU results available		Cost time period		HRU time period	
Source	Sample and relevant subgroups	Sample size by arm	Data source	Any rCDI	First rCDI	Second rCDI	Third or greater rCDI	All-cause	rCDI-attributable	All-cause	rCDI-attributable	Annual	6-month	Annual	6-month
Amin 2022	rCDI—first recurrence—survivors	40,277	Claims	X	X	X	X	X		X					
	rCDI—first recurrence—those that died	27,806													
	rCDI—second recurrence—survivors	24,033													
	rCDI—second recurrence—those that died	12,713													
	rCDI—third recurrence—survivors	33,428													
	rCDI—third recurrence—those that died	13,339													
Unni 2020	rCDI—first recurrence	38,163	Claims	X	X	X	X	X		X		X		X	
	rCDI—second recurrence	22,898													
	rCDI—third or greater recurrence	32,147													
Sharma 2021	rCDI	NR	National hospital database	X						X	X				
	rCDI	NR													

Table 2 continued

Study information				rCDI populations available				Cost results available		HRU results available		Cost time period		HRU time period	
Source	**Sample and relevant subgroups**	**Sample size by arm**	**Data source**	**Any rCDI**	**First rCDI**	**Second rCDI**	**Third or greater rCDI**	**All-cause**	**rCDI-attributable**	**All-cause**	**rCDI-attributable**	**Annual**	**6-month**	**Annual**	**6-month**
Essrani 2020	rCDI—first recurrence	84	Chart review	X	X					X					
	rCDI—first recurrence with prior appendectomy	15													
	rCDI—first recurrence without prior appendectomy	69													
Tariq 2021	rCDI—third or greater recurrence	522	Single-center EHR	X			X				X			X	
Sadeghi 2022a	rCDI—third recurrence with prior CDI admission	29	Single-center EHR	X			X		X		X				
Sadeghi 2022b	rCDI—fourth recurrence with prior CDI admission	13	Single-center EHR	X			X		X		X				
Haran 2018	rCDI—first recurrence	161	Multi-center EHR	X	X						X				
Meighani 2017	rCDI with no IBD	181	Multi-center EHR	X							X				
	rCDI with IBD	20													
Zhang 2018	rCDI—first recurrence	8502	Claims	X	X			X	X	X	X		X		X

Table 2 continued

Study information				rCDI populations available				Cost results available		HRU results available		Cost time period		HRU time period	
Source	Sample and relevant subgroups	Sample size by arm	Data source	Any rCDI	First rCDI	Second rCDI	Third or greater rCDI	All-cause	rCDI-attributable	All-cause	rCDI-attributable	Annual	6-month	Annual	6-month
Cheng 2019	Three to five previous CDI episodes	94	Multi-center EHR	X			X				X				
Zilberberg 2018	rCDI—secondary diagnosis	22,499	National hospital database	X					X		X				
Ashraf 2020	rCDI—any recurrence	64	Chart review	X						X	X				
Feuerstadt 2020	rCDI—first recurrence	3129	Claims	X	X	X	X	X		X		X		X	
	rCDI—second recurrence	472													
	rCDI—third or greater recurrence	134													
Feuerstadt 2021	rCDI—first recurrence	3129	Claims	X	X	X	X			X				X	
	rCDI—second recurrence	472													
	rCDI—third recurrence	134													
Reveles 2019	rCDI—first recurrence	2712	National hospital database	X	X	X				X					
	rCDI—second recurrence	858													
	Overall CDI	10,970													
Nelson 2021	rCDI—first recurrence	38,163	Claims	X	X	X	X	X		X		X		X	

Table 2 continued

Study information				rCDI populations available				Cost results available		HRU results available		Cost time period		HRU time period	
Source	Sample and relevant subgroups	Sample size by arm	Data source	Any rCDI	First rCDI	Second rCDI	Third or greater rCDI	All-cause	rCDI-attributable	All-cause	rCDI-attributable	Annual	6-month	Annual	6-month
	rCDI—second recurrence	22,898													
	rCDI—third recurrence	32,147													
Kruger 2019	Any recurrence—with cirrhosis	12,917	National hospital database	X				X		X	X				
	Any recurrence—without cirrhosis	354,009													
Amin 2022	rCDI—any recurrence—survivors	97,738	Claims	X				X	X	X	X				
	rCDI—any recurrence—decedents	53,858													
Feuerstadt 2022	Primary CDI	175,554	Claims	X	X	X	X			X				X	
	rCDI—first recurrence	38,163													
	rCDI—second recurrence	22,898													
	rCDI—third or greater recurrence	32,147													
Shah 2016	rCDI—first or greater recurrence	95	Single-center EHR	X						X	X				

CDI Clostridioides difficile infection, *IBD* inflammatory bowel disease, *EHR* electronic health record, *HRU* healthcare resource utilization, *rCDI* recurrent *Clostridioides difficile* infection

Table 3 Patient characteristics of publications reporting annual or semi-annual costs and/or HRU[1]

Source	(Sub)group	Sample size	Patient characteristics									
			Age—mean (SD)	Female—%	Prior treatments—antibiotics, n (%)	Charlson Comorbidity Index score, mean (SD)	Heart failure—%	Comorbidities—Renal insufficiency, n (%)	Comorbidities—IBD, n (%)	Comorbidities—diabetes, n (%)	Comorbidities—other, n (%)	HRU prior to rCDI
Dubberke 2014	Any recurrence	421	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rodrigues 2017	Any recurrence	98	66.7 (16.5)	62.0%	Treatment of initial episode, n (%) Metronidazole, n (%): 31 (32) Vancomycin, n (%): 31 (32) Metronidazole + Vancomycin, n (%): 25 (26)	8.6 (4.2)	NR	NR	NR	NR	NR	NR
Kuntz 2017	First recurrence	4,174	62.3 (16.1)	61.8%	NR	NR	NR	NR	NR	NR	NR	NR
Zhang 2018	First recurrence	8,502	63.7 (19.9)	63.9%	5,655 (66.5%)	3.2 (3.4)	NR	2,155 (25.4)	532 (6.3)	2,244 (26.4)	Cancer: 281 (3.3) Cardiovascular disease: 1,894 (22.3) Pulmonary disease: 5,840 (68.7) Immunocompromised: 1,996 (23.5)	Inpatient hospital visits-Mean (SD): 0.6 (0.8) ED visits-Mean (SD): 0.2 (0.5) Doctor office visits-Mean (SD): 4.7 (4.8)
Unni 2020	First recurrence	38,163	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Second recurrence	22,898	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Third or more recurrence	32,147	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 3 continued

Source	(Sub)group	Sample size	Patient characteristics									
			Age—mean (SD)	Female—%	Prior treatments—antibiotics, n (%)	Charlson Comorbidity Index score, mean (SD)	Heart failure—%	Comorbidities—Renal insufficiency, n (%)	Comorbidities—IBD, n (%)	Comorbidities—diabetes, n (%)	Comorbidities—other, n (%)	HRU prior to rCDI
Tariq 2021	Third or greater CDI episode, FMT failures	70	Median (range): 53.8 (18–89)	54.3%	1 + prior metronidazole: 43 (61.4) 1 + prior vancomycin: 69 (98.5) 1 + prior fidaxomicin: 16 (22.8)	NR	NR	NR	IBD, n (%): 24 (34.3)	NR	Immunocompromised state: 28 (40.0) Diverticulosis: 12 (17.1)	Presence of CDI-related hospitalization before FMT (yes/no): 38 (54.3%) > 1 CDI-related hospitalization before FMT (yes/no): 27 (38.7%)
Feuerstadt 2020	First recurrence	3,129	48.3 (12.8)	65.1%	2,509 (80.2)	1.5 (2.2)	NR	571 (18.3)	Ulcerative colitis, n (%): 238 (7.6) Crohn's disease, n (%): 175 (5.6)	Type 1 diabetes: 134 (4.3)	Autoimmune disease: 723 (23.1)	Pre-index (0–6 months prior) HUR, n (%) Inpatient admission: 1,307 (41.8) Outpatient hospital visit: 2,576 (82.3) ED visit: 1,581 (50.5) Outpatient office visit: 2,951 (94.3)
	Second recurrence	472	47.9 (13.0)	67.6%	381 (80.7)	1.8 (2.3)	NR	105 (22.3)	Ulcerative colitis, n (%): 39 (8.3) Crohn's disease, n (%): 22 (4.7)	Type 1 diabetes: 18 (3.8)	Autoimmune disease: 116 (24.6)	Pre-index (0–6 months prior) HUR, n (%) Inpatient admission: 236 (50.0) Outpatient hospital visit: 404 (85.6) ED visit: 268 (56.8) Outpatient office visit: 455 (96.4)
	Third or more recurrence	134	48.7 (11.5)	61.2%	103 (76.9)	2.3 (2.5)	NR	36 (26.9)	Ulcerative colitis, n (%): 21 (15.7) Crohn's disease, n (%): 11 (8.2)	Type 1 diabetes: 11 (8.2)	Autoimmune disease: 53 (39.6)	Pre-index (0–6 months prior) HRU, n (%) Inpatient admission: 81 (60.5) Outpatient hospital visit: 116 (86.6) ED visit: 77 (57.5) Outpatient office visit: 129 (96.3)

Table 3 continued

Source	(Sub)group	Sample size	Patient characteristics									
			Age—mean (SD)	Female—%	Prior treatments—antibiotics, n (%)	Charlson Comorbidity Index score, mean (SD)	Heart failure—%	Comorbidities—Renal insufficiency, n (%)	Comorbidities—IBD, n (%)	Comorbidities—diabetes, n (%)	Comorbidities—other, n (%)	HRU prior to rCDI
Feuerstadt 2021	First recurrence	3,129	48.3 (12.8)	65.1%	2,509 (80.2)	1.54 (2.2)	NR	571 (18.3)	Ulcerative colitis, n (%): 238 (7.6) Crohn's disease, n (%): 175 (5.6)	NR	Autoimmune diseases: 723 (23.1)	HRU 0–6 months pre-index, n (%) Inpatient admission: 1307 (41.8) Inpatient admission with ICU stay: 132 (4.2) Outpatient hospital visit: 2576 (82.3) ED visit: 1581 (50.5)
	Second recurrence	472	47.9 (13.0)	67.6%	381 (80.7)	1.83 (2.3)	NR	105 (22.3)	Ulcerative colitis, n (%): 39 (8.3) Crohn's disease, n (%): 22 (4.7)	NR	Autoimmune diseases: 116 (24.6) Current or history of smoking: 89 (18.9)	HRU 0–6 months pre-index, n (%) Inpatient admission: 236 (50.0) Inpatient admission with ICU stay: 21 (4.5) Outpatient hospital visit: 404 (85.6) ED visit: 268 (56.8)

Table 3 continued

Source	(Sub)group	Sample size	Patient characteristics									
			Age—mean (SD)	Female—%	Prior treatments—antibiotics, n (%)	Charlson Comorbidity Index score, mean (SD)	Heart failure—%	Comorbidities—Renal insufficiency, n (%)	Comorbidities—IBD, n (%)	Comorbidities—diabetes, n (%)	Comorbidities—other, n (%)	HRU prior to rCDI
	Third or more recurrence	134	48.7 (11.5)	62.2%	103 (76.9)	2.29 (2.5)	NR	36 (26.9)	Ulcerative colitis, n (%): 21 (15.7) Crohn's disease, n (%): 11 (8.2)	NR	Autoimmune diseases: 53 (39.6) Current or history of smoking: 30 (22.4)	HRU 0–6 months pre-index, n (%) Inpatient admission: 81 (60.5) Inpatient admission with ICU stay: 13 (9.7) Outpatient hospital visit: 116 (86.6) ED visit: 77 (57.5)
Nelson 2021	First recurrence	38,163	78.1 (7.9)	69.1%	Outpatient medication exposure Antimicrobials, %: 85.3	5.2 (3.4)	45.3%	Renal disease, %: 39.7	NR	Diabetes, %: 45.8	Chronic pulmonary disease, %: 50.6 CVD, %: 39.9 PVD, %: 44.6	0–6 months pre-index Patients with inpatient admission, %: 58.0 Patients with ED visit, %: 41.6 Number of outpatient visits per patient, mean (SD): 11.2 (8.4) 7–12 months pre-index Patients with inpatient admission, %: 27.7 Patients with ED visit, %: 27.5 Number of outpatient visits per patient, mean (SD): 9.2 (7.6) Procedures, % GI surgery: 4.5 Transplant: 2.3

Table 3 continued

Source	(Sub)group	Sample size	Patient characteristics									
			Age—mean (SD)	Female—%	Prior treatments—antibiotics, n (%)	Charlson Comorbidity Index score, mean (SD)	Heart failure—%	Comorbidities—Renal insufficiency, n (%)	Comorbidities—IBD, n (%)	Comorbidities—diabetes, n (%)	Comorbidities—other, n (%)	HRU prior to rCDI
	Second recurrence	22,898	78.3 (7.9)	69.0%	Outpatient medication exposure Antimicrobials, %: 86.8	5.2 (3.4)	44.5%	Renal disease, %: 40.4	NR	Diabetes, %: 45.2	Chronic pulmonary disease, %: 50.5 CVD, %: 39.1 PVD, %: 44.1	0–6 months pre-index Patients with inpatient admission, %: 59.4 Patients with ED visit, %: 43.7 Number of outpatient visits per patient, mean (SD): 11.5 (8.5) 7–12 months pre-index Patients with inpatient admission, %: 27.5 Patients with ED visit, %: 28.3 Number of outpatient visits per patient, mean (SD): 9.2 (7.5) Procedures, % GI surgery: 4.2 Transplant: 3.4

Table 3 continued

Source	(Sub)group	Sample size	Patient characteristics									
			Age—mean (SD)	Female—%	Prior treatments—antibiotics, n (%)	Charlson Comorbidity Index score, mean (SD)	Heart failure—%	Comorbidities—Renal insufficiency, n (%)	Comorbidities—IBD, n (%)	Comorbidities—diabetes, n (%)	Comorbidities—other, n (%)	HRU prior to rCDI
	Third or more recurrence	32,147	77.9 (8.0)	67.5%	Outpatient medication exposure Antimicrobials, %: 89.8	5.2 (3.5)	43.5%	Renal disease, %: 43.2	NR	Diabetes, %: 44.3	Chronic pulmonary disease, %: 49.4 CVD, %: 37.3 PVD, %: 43.0	0–6 months pre-index Patients with inpatient admission, %: 60.7 Patients with ED visit, %: 44.8 Number of outpatient visits per patient, mean (SD): 12.4 (9.1) 7–12 months pre-index Patients with inpatient admission, %: 27.7 Patients with ED visit, %: 27.8 Number of outpatient visits per patient, mean (SD): 9.6 (7.9) Procedures, % GI surgery: 4.3 Transplant: 12.4
Feuerstadt 2022	First recurrence	38,163	Mean (SD): 78.1 (7.9)	69.1%	Antimicrobials, %: 85.3	5.2 (3.4)	45.30%	Renal disease, %: 39.7	Crohn's disease, %: 2.4 Ulcerative colitis, %: 6.3	Diabetes, %: 45.8	Chronic pulmonary disease, %: 50.6 CVD, %: 39.6 PVD, %: 44.6	0–6 months pre-index: Patients with inpatient admission, 58.0% Patients with ED visit, 41.6% Outpatient visits per patient, mean 11.2 (8.4) 7–12 months pre-index: Patients with inpatient admission, 27.7% Patients with ED visit, 27.5% Outpatient visits per patient, mean 9.2 (7.6)

Table 3 continued

Source	(Sub)group	Sample size	Patient characteristics									
			Age—mean (SD)	Female—%	Prior treatments—antibiotics, n (%)	Charlson Comorbidity Index score, mean (SD)	Heart failure—%	Comorbidities—Renal insufficiency, n (%)	Comorbidities—IBD, n (%)	Comorbidities—diabetes, n (%)	Comorbidities—other, n (%)	HRU prior to rCDI
	Second recurrence	22,898	Mean (SD): 78.3 (7.9)	69.0%	Antimicrobials, %: 86.8%	5.2 (3.4)	44.50%	Renal disease, %: 40.4	Crohn's disease, %: 2.5 Ulcerative colitis, %: 6.5	Diabetes, %: 45.2	Chronic pulmonary disease, %: 50.5 CVD, %: 39.1 PVD, %: 44.1	0–6 months pre-index: Patients with inpatient admission, 59.4% Patients with ED visit, 43.7% Outpatient visits per patient, mean 11.5 (8.5) 7–12 months pre-index: Patients with inpatient admission, 27.5% Patients with ED visit, 28.3% Outpatient visits per patient, mean 9.2 (7.5)
	Third or more recurrence	32,147	Mean (SD): 77.9 (8.0)	67.5%	Antimicrobials, %: 89.8	5.2 (3.5)	43.50%	Renal disease, %: 43.2	Crohn's disease, %: 2.2 Ulcerative colitis, %: 6.2	Diabetes, %: 44.3	Chronic pulmonary disease, %: 49.4 CVD, %: 37.3 PVD, %: 43.0	0–6 months pre-index: Patients with inpatient admission, 60.7% Patients with ED visit, 44.8% Outpatient visits per patient, mean 12.4 (9.1) 7–12 months pre-index: Patients with inpatient admission, 27.7% Patients with ED visit, 27.8% Outpatient visits per patient, mean 9.6 (7.9)

CDI Clostridioides difficile infection, *CVD* cardiovascular disease, *ED* emergency department, *EHR* electronic health record, *FMT* fecal microbial transplantation, *GI* gastrointestinal, *HRU* healthcare resource utilization, *IBD* inflammatory bowel disease, *NR* not reported, *PVD* peripheral vascular disease, *rCDI* recurrent Clostridioides difficile infection

[1]Data in this table are as reported in each respective study

Table 4 Per-patient per-year HRU in publications reporting annual or semi-annual estimates

	HRU				
	Hospitalization	**Intensive care unit**	**Post-acute care**	**Emergency department visit**	**Outpatient visit**
Any rCDI (all-cause)					
Minimum values	1.1 visits; 8.4 days LOS	0.9 days	69.8% patients	1.4 visits	15.4 visits
Source and population[1]	*Kuntz 2017-Kaiser Permanente rCDI (1st)*	*Kuntz 2017-Kaiser Permanente rCDI (1st)*	*Nelson 2021-Medicare rCDI (3rd +)*	*Nelson 2021-Medicare rCDI (1st)*	*Rodrigues 2017-Partners Healthcare Network Boston rCDI*
Maximum values	5.8 visits; 8.5 days LOS		74.6% patients	4.6 visits	26.3 visits
Source and population	*Feuerstadt 2020-Commercial rCDI (3rd +)*		*Nelson 2021-Medicare rCDI (1st)*	*Feuerstadt 2020-Commercial rCDI (3rd +)*	*Nelson 2021-Medicare rCDI (3rd +)*
Any rCDI (rCDI-attributable)					
Source and population	1.6 visits; 15.8 days LOS	0.2 days	–	0.1 visits	2.2 visits
	Rodrigues 2017-Partners Healthcare Network Boston rCDI	*Rodrigues 2017-Partners Healthcare Network Boston rCDI*		*Rodrigues 2017-Partners Healthcare Network Boston rCDI*	*Rodrigues 2017-Partners Healthcare Network Boston rCDI*

HRU healthcare resource utilization, *LOS* length of stay, *rCDI* recurrent Clostridioides difficile infection, *SLR* systematic literature review
[1] Numbers in parentheses indicate the recurrence number of rCDI

Table 5 Per-patient per-year costs in publications reporting annual or semi-annual estimates, inflation-adjusted to 2022 USD

	Costs						
	Hospitalization	**Intensive care unit**	**Post-acute care**	**Emergency department visit**	**Outpatient visit**	**Other costs[2]**	**Total costs**
Any rCDI (all-cause)							
Minimum value	$16,714	$13,949	$17,241	$1107	$10,377	$1206	$93,979
Source and population[1]	*Nelson 2021-Medicare rCDI (1st)*	*Nelson 2021-Medicare rCDI (3rd +)*	*Nelson 2021-Medicare rCDI (3rd +)*	*Nelson 2021-Medicare rCDI (1st)*	*Nelson 2021-Medicare rCDI (1st)*	*Nelson 2021-Medicare rCDI (2nd)*	*Nelson 2021-Medicare rCDI (2nd)*
Maximum value	$157,385	$17,703	$26,357	$1269	$50,040	$23,724	$231,149
Source and population	*Feuerstadt 2020-Commercial rCDI (3rd +)*	*Nelson 2021-Medicare rCDI (1st)*	*Nelson 2021-Medicare rCDI (1st)*	*Nelson 2021-Medicare rCDI (3rd +)*	*Feuerstadt 2020-Commercial rCDI (3rd +)*	*Feuerstadt 2020-Commercial rCDI (3rd +)*	*Feuerstadt 2020-Commercial rCDI (3rd +)*
Any rCDI (rCDI-attributable)							
Available value	–	–	–	–	–	–	$39,668
Source and population							*Rodrigues 2017-Partners Healthcare Network Boston rCDI*

rCDI recurrent *Clostridioides difficile* infection, *SLR* systematic literature review, *USD* US dollar.

[1] Numbers in parentheses indicate the recurrence number of rCDI

[2] Other costs include costs of surgery, pharmacy, diagnostic tests, medical equipment use, and physician services

Table 6 Per-patient per-year rCDI-attributable medical cost calculation details

Cost categories	Total costs		Cost input option(s)	HRU input option(s)	Sources[1]
	Min-Average annual cost with min input values	Max-Average annual cost with max input values			
Hospitalization	$45,298	$51,547	$2039 (A) $1792 (B)	25.3 days/year	Cost (A): general-HCUPnet Cost (B): rCDI-Zilberberg 2018 HRU: rCDI-Rodrigues 2017
Intensive care unit	$942	$942	$5232	0.2 days/year	Cost: general-Halpern 2016 HRU: rCDI-Rodrigues 2017
Post-acute care	$11,849	$11,849	$562	21.1 days/year	Cost: rCDI-Nelson 2021 HRU: rCDI-Nelson 2021; Rodrigues 2017
Emergency department visit	$120	$120	$1004	0.1 visits/year	Cost: rCDI-Nelson 2021 HRU: rCDI-Rodrigues 2017
Outpatient visit	$459	$459	$209	2.2 visits/year	Cost: general-Optum360 National Fee Analyzer HRU: rCDI-Rodrigues 2017
Stool test	$257	$257	$58	4.4 tests/year	Cost: rCDI-Rodrigues 2017 HRU: rCDI-Rodrigues 2017
Colectomy	$6243	$6950	$54,421	7.3% annual rate (A) 6% annual rate (B)	Cost: rCDI-Rodrigues 2017 HRU (A): rCDI-Feuerstadt 2021 HRU (B): rCDI-Feuerstadt 2022
Ileostomy reversal			$42,237	7.1% annual rate	Cost: rCDI-Wilson 2013 HRU: rCDI-Feuerstadt 2021; Neal 2011

Table 6 continued

Cost categories	Total costs		Cost input option(s)	HRU input option(s)	Sources[1]
	Min-Average annual cost with min input values	Max-Average annual cost with max input values			
Terminal care/mortality	$2668	$10,142	$53,333 (A) $29,565 (B)	10.9% annual rate (A) 9.0% annual rate (B) 34.3% annual rate (C)	Cost (A): general-Byhoff 2016 Cost (B): rCDI-Amin 2022b HRU (A): rCDI-Olsen 2019 HRU (B): rCDI-Amin 2022b HRU (C): all-cause-Amin 2022b
Total costs	**$67,837**	**$82,268**			

[1] *rCDI* and general indicate whether the study was conducted in an rCDI or a general population. All-cause indicates all-cause HRU

care unit cost for end of life care, and mortality rate [44–50]. Rodrigues et al. 2017 was the only study reporting annual rCDI-attributable HRU and provided estimates of HRU components that are relevant for a payer [31]. It was used to inform the following HRU components in the base case cost calculation: rCDI-related hospitalizations and associated LOS (1.6 mean rCDI-related hospitalizations per patient × 15.8 mean LOS = 25.3 total days/year), rCDI-related ICU LOS (0.2 days/year), rCDI-related ED visits (0.1 visits/year), rCDI-related outpatient visits (2.2 visits/year), and rCDI-related stool tests (4.4 tests/year) per patient. [44–50]. The HRU estimates post-acute care was 21.1 days/year (Nelson et al. 2021 and Rodrigues et al. 2017); mortality rates included 11.0%, 9.0%, and 34.3% (Olsen et al. 2019 and Amin et al. 2022b); the colectomy rate ranged from 7.3% and 6.0% (Feuerstadt et al. 2021 and Feuerstadt et al. 2022); and the ileostomy reversal rate was 7.1% (Feuerstadt et al. 2021 and Neal et al. 2011) [14, 17, 21, 22, 31, 48, 50]. Table 6 includes the detailed HRU estimates used in the cost estimation. Unit costs for post-acute care ($562/day) and ED visits ($1,004/visit) as well as the lower bound colectomy rate (6.0%) were calculated as weighted averages based on results reported for the subgroups of patients 1, 2, and 3 + rCDI from Nelson et al. 2021 and Feuerstadt et al. 2022, respectively [14, 22].

The per-patient per-year rCDI attributable direct medical cost, estimated from the component-based cost synthesis approach, ranged from $67,837–$82,268 (Table 6). The cost drivers in order from largest to smallest were hospitalizations (62.7–66.8%), post-acute care (14.4–17.5%), colectomy and ileostomy reversals (8.4–9.2%), terminal care/morality (3.9–12.3%), ICU (1.1–1.4%), outpatient visits (0.6–0.7%), stool tests (0.3–0.4%), and ED visits (0.1–0.2%).

HRU and Cost Publications Informing Sensitivity Analyses

As rCDI-attributable hospitalization cost per year was the largest driver of the base case total cost calculation (approximately two-thirds),

alternative values for hospitalization parameters were tested as sensitivity analyses. Four publications were identified that had 90-day or longer follow-up, included relevant HRU or cost data, and were conducted in a study population that could potentially be generalized to a wider rCDI population. Two of these publications (Aitken et al. 2014 and Zhang et al. 2018) were excluded due to potential bias in estimating rCDI-attributable hospitalization LOS or cost for the given study design or data source (**Appendix 1**) [19, 34].

Shah et al. 2016 and Dubberke et al. 2014 were included in the sensitivity analyses [33, 40]. Shah et al. 2016 was a prospective, single-center cohort study including of 540 adult patients (aged ≥ 18 years) who were hospitalized for CDI at a tertiary care hospital in Houston, Texas between 2007 and 2013 [40]. Patients were followed for 3 months to assess rCDI episodes, with HRU data prospectively obtained from patients' online medical chart and/or by direct patient interview. rCDI-attributable hospitalization was defined as CDI diagnosis within 72 h of admission. Costs were estimated based on publicly available Healthcare Cost and Utilization Project data; however, the methods are not clearly reported, so only HRU results were considered for the sensitivity analysis. Over 3 months, 95 (17.6%) patients (mean age: 66 years) experienced 101 rCDI episodes, for which 38 patients (40.0%) had an rCDI-attributable hospitalization. The median LOS attributable to rCDI was 15 days.

Dubberke et al. 2014 was a retrospective, single-center cohort study of data from an academic tertiary care facility in St. Louis, Missouri, among 3958 adult patients (aged ≥ 18 years) hospitalized with a CDI episode from 2003 through 2009 [33]. Patients were followed for 180 days from the end of the hospitalization or end of antibiotic treatment (whichever occurred later). Data were collected from hospital administrative databases with supplemental data from chart review. Zero-inflated lognormal models were used to assess rCDI-attributable hospitalization costs of patients with rCDI versus those without a recurrence. Over 180 days, 421 (10.6%) patients experienced an rCDI episode (mean age for rCDI patients was not reported; overall population age quartiles were reported as 24.1% under 49 years, 26.0% 49– < 62 years, 24.5% 62–< 74 years, and 25.3% ≥ 74 years). The study estimated an rCDI-attributable hospitalization cost of $11,631 in 2010 USD (95% confidence interval, $8937–$14,588).

Estimated Average Annual rCDI-attributable Medical Cost—Sensitivity Analyses

Sensitivity analysis 1 (Shah et al. 2016) incorporates an alternative LOS input reported for admissions attributable to rCDI over 3 months [40]. To calculate the sensitivity analysis input, the median reported LOS value of 15 days was annualized to 60 days. A weighted average was then calculated to determine the LOS for the overall population, conducted among those who had an rCDI-attributable hospitalization and those who did not (LOS of 0 days). The weights used the number of patients who had an rCDI-attributable hospitalization and those who did not (38 patients with and 57 without). The resulting sensitivity analysis LOS input was 24 days. Sensitivity analysis 1 yielded a total result of a $65,543–$79,658 per-patient per-year rCDI-attributable direct medical cost.

Sensitivity analysis 2 (Dubberke et al. 2014) uses an alternative rCDI-attributable hospitalization cost input. The 180-day rCDI-attributable hospitalization cost relative to primary CDI reported in Dubberke et al. 2014 was $32,770 when inflation-adjusted to 2022 USD and annualized [33]. Using this alternative cost input in the sensitivity analysis yielded a range of $55,309 to $63,491 for the per-patient per-year rCDI-attributable direct medical cost.

DISCUSSION

We conducted an SLR of the direct economic burden of managing patients with rCDI with current approaches from the perspective of the third-party payers in the USA. In the SLR, eight publications were identified that reported annual HRU and/or direct medical costs to US third-party payers. Key differences were

observed in study designs, patient populations, identification of rCDI, and analytic approaches for estimating CDI-attributable costs and HRU. This heterogeneity in the published data is consistent with the findings of a recent SLR by Malone et al. 2022 on real-world evidence of HRU and burden of illness associated with CDI (including rCDI). Similar to our study, Malone et al. (2022) found a large variation in data sources, comparison groups, methodologies, and reporting across studies [51].

The large variation found from this search made it infeasible to perform a meta-analysis to synthesize the results. To estimate the average annual per-patient rCDI-attributable medical costs based on the SLR findings, we performed a component-based cost synthesis analysis given the lack of comprehensive rCDI-attributable annual medical costs data. By employing a component-based cost synthesis approach that relied primarily on studies identified in the SLR with an annual time horizon, we were able to estimate the annual per-patient rCDI-attributable direct medical costs from the US third-party payer's perspective using aggregated relevant HRU and cost inputs from multiple sources in a systematic fashion. This method allows for each relevant component that contributes to the average medical cost on payers to be considered directly from the available literature. Overall, the results of component-based cost synthesis analysis suggest that the annual rCDI-attributable costs range from $67,837 to $82,268 for an average rCDI patient in the base-case analysis.

Not surprisingly, the main cost driver of annual cost in the base-case component-based cost synthesis analysis was hospitalization (62.7–66.8% of total costs), driven by a mean 25.2 day LOS calculated based on data reported by Rodrigues et al. 2017 [31]. Of note, the inpatient days per year reported by Rodrigues and colleagues may be higher than some other clinical settings due to potentially more severely ill and older patients included in this study. As a result, sensitivity analyses were conducted to test alternative rCDI-attributable hospitalization LOS or cost input based on studies with at least 60-days follow-up and with a study population that could be generalized to a wider rCDI population. Four studies were identified, and two were excluded due to potential for bias in estimating rCDI-attributable hospitalization LOS or cost based on the study design or data source (Aitken et al. 2014 and Zhang et al. 2018) [19, 34]. The sensitivity analyses included alternative rCDI-attributable hospitalization LOS and cost inputs reported in two studies: Shah et al. 2016 and Dubberke et al. 2014 [33, 40]. The sensitivity analysis results varied from $55,309 to $63,491 (sensitivity analysis 2: Dubberke et al. 2014) and $65,543–$79,658 (sensitivity analysis 1: Shah et al. 2016), supporting the high burden of rCDI and demonstrating that our results were sensitive to the hospitalization assumptions [33, 40]. Collectively, our cost estimation findings from the base-case and sensitivity analyses highlight the importance and urgency of understanding the broad economic burden of recurrent CDI and provide a benchmark for assessing the economic benefit of novel treatments to prevent and reduce recurrence in CDI.

Several limitations should be noted when interpreting the findings of the component-based synthesis cost analysis. Firstly, the results reflect the patient populations, study design, and limitations of the underlying source publications reporting on the economic burden of rCDI. For example, the recommendations on antibiotic treatment for primary CDI and the first and subsequent rCDI have evolved. In the 2017 Clinical Practice Guideline Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), vancomycin or fidaxomicin were recommended for initial CDI episodes, whereas in their 2021 update, fidaxomicin is the preferred first-line antibiotic over vancomycin, given the clinical benefits in reducing CDI recurrences found with fidaxomicin [4, 52, 53]. Evolution of treatment options and recommendations over time would impact treatment patterns and subsequently the associated HRU cost in the care settings reported in our analysis. Due to the complexity of the disease, all-cause costs and HRU were not surprisingly more frequently reported than rCDI-attributable costs or HRU. However, all-cause values may not correctly reflect the specific burden associated with

rCDI. From our search, only one study (Rodrigues et al. 2017) reported annual rCDI-attributable costs [31]. This single-center study included a small sample size of 98 rCDI patients (any recurrence) treated at Partners HealthCare in 2013 who had a high number of comorbid conditions (mean CCI score of 8.6) and a mean age of 66.7 years [31]. These characteristics were consistent with rCDI patient profiles (older with multiple comorbidities) as observed in other large-scale studies (e.g., Nelson et al. 2021, Feuerstadt et al. 2022) [14, 22, 31]. However, this study likely underestimates the true rCDI disease burden, as it did not include post-acute care or terminal care costs, nor capture costs for patients who sought additional care outside of the Partners HealthCare network or dropped out of the network.

Secondly, all key HRU/cost elements of interest were not available from the SLR. Therefore, a supplemental search of publications in similar or general populations was conducted to complete the calculation. As an example, rCDI-attributable costs for outpatient visits were obtained from the Optum360 National Fee Analyzer [43]. Thirdly, most of the HRU data were from Rodrigues et al. (2017), which is the sole publication identified in the SLR reporting annual rCDI-attributable HRU estimates [31]. As noted above, the inpatient days per year is a key driver of the cost calculation. Uncertainty around this parameter was addressed in sensitivity analyses to inform potential alternative ranges of the estimated economic burden of rCDI. However, because the sensitivity analyses required extrapolation of findings from a <1-year timeframe these studies may not be comprehensive in the evaluation; for example, there may be missing hospitalizations that occurred after their defined follow-up period. Using such data required assumptions of a constant rate of hospitalization to extrapolate to an annual value. Furthermore, one of the studies used in the sensitivity analyses defined rCDI-attributable hospital costs or HRU in relativity to experience of other patients (Dubberke 2014), so it could have underestimated the true medical costs to the payer due to the insufficiency in absolute cost values [33]. Finally, while Rodrigues et al. 2017 is based on data from 2013, it is among the most recent data of the studies (Shah et al. 2016: 2007–2013; Dubberke et al. 2014: 2003–2009) [31, 33, 40]. Studies of recent clinical practice with longer follow-up (1 year or longer) are warranted, as well as research on rCDI-attributable cost burden directly on patients (e.g., out of pocket expenses, burden on caregivers).

CONCLUSION

Our SLR study found a high economic burden of rCDI in the USA with currently available treatments, with much variability in study design, populations, and reporting approaches. We provided an estimate of the annual average per-patient rCDI-attributable medical costs to a third-party payer in the USA using a component-based cost synthesis approach and provided a benchmark for assessing the economic benefit of novel treatments to prevent and reduce recurrence in CDI. Given the high-cost burden for managing rCDI with current approaches, having an established annual per-patient disease-attributable medical costs under the current standard of care will help set an initial benchmark to inform the economic benefit of novel therapies for rCDI. Future research will be warranted to report on the real-world economic burden of rCDI and evaluate the impact when more novel and effective therapies become available for these patients.

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Compliance with Ethics Guidelines. This article is based upon previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. This article is based upon previously conducted studies, and all data are publicly available in the referenced publications.

APPENDIX

Two studies were not included for sensitivity analyses due to study design or a data source that may not fully reflect rCDI-attributable hospitalization HRU or cost; these were Aitken et al. 2014 (3-month follow-up), and Zhang et al. 2018 (6-month follow-up) [19, 34].

Aitken et al. 2014 was a prospective, single-center study of adult patients within 3 months following discharge from a CDI hospitalization at a tertiary care hospital between 2007 and 2012 [34]. The study identified patients with rCDI via follow-up phone call after a CDI hospitalization. The study was not included in the sensitivity analyses due to the potential for response bias of healthier patients who responded to this recruitment method. Further, it used a narrow definition of rCDI attributable as CDI in primary diagnosis position and positive stool test within 3 days of admission, which would miss instances of a secondary diagnosis.

Zhang et al. 2018 was a retrospective MarketScan claims database analysis of propensity-score-matched patients with CDI and CDI with at least one rCDI followed for 6 months from the earliest CDI diagnosis from 2010–2014 [19]. The MarketScan data included: (1) the Commercial Claims and Encounters database and (2) the Medicare Supplemental and Coordination of Benefits database. The study was not included in the sensitivity analyses as the database would

not include claims where Medicare is the primary payer and covered all of the service. Given that 46.6% of the study population was aged over 65 years, a substantial number of claims for rCDI may have been missed.

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