Estimating excess mortality and economic burden of *Clostridioides difficile* infections and recurrences during 2015–2019

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Highlights

- Around 20% of CDI patients in England died of any cause within 12-months.
- Excess mortality of 1.81 deaths per 100 patient-months in CDI patients.
- Higher excess mortality of 2.53 deaths per 100 patient-months in ≥1 rCDI patients.
- HCRU and costs were higher in CDI patients, particularly due to hospitalisations.
- Incremental costs of hospitalisations increased with the number of recurrences.

Manuscript Title: Estimating excess mortality and economic burden of *Clostridioides difficile* infections and recurrences during 2015–2019: The RECUR England study

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Abstract

Objective: To generate real-world evidence on all-cause mortality and economic burden of *Clostridioides difficile* infections (CDIs) and recurrences (rCDIs) in England.

Methods: We conducted a cohort study using retrospective data from Clinical Practice Research Datalink linked to Hospital Episode Statistics. Patients diagnosed with CDI in hospital and community settings during 2015–2018 were included and followed for ≥1year. All-cause mortality was described at 6-, 12-, and 24-months. Healthcare resource usage (HCRU) and associated costs were assessed at 12-months of follow-up. A cohort of non-CDI patients, matched by demographic and clinical characteristics including Charlson Comorbidity Index score, was used to assess excess mortality and incremental costs of HCRU.

Results: All-cause mortality among CDI patients at 6-, 12-, and 24-months was 15.87%, 20.37%, and 27.03%, respectively. A higher proportion of rCDI patients died at any point during follow-up. Compared with matched non-CDI patients, excess mortality was highest

at 6-months with 1.81 and 2.53 deaths per 100 patient-months among CDI and ≥1 rCDI patients. Hospitalisations were the main drivers of costs, with an incremental cost of £1,209.21 per CDI patient. HCRU and costs increased with rCDIs.

Conclusions: CDI poses a substantial mortality and economic burden, further amplified by rCDIs.

Keywords: *Clostridioides difficile*; recurrence; mortality; healthcare costs; England; RECUR

Introduction

Clostridioides difficile is a common source of healthcare-associated infection, with symptoms ranging from mild diarrhoea to life-threatening colon damage [1, 2]. While most *C. difficile* infection (CDI) cases are acquired in healthcare facilities, the incidence of community-associated CDIs has been increasing [1, 3]. Nearly a quarter of patients experience a recurrent CDI (rCDI) episode. The recurrence rate increases with each subsequent episode, and 40%–65% of patients with one recurrence experience ≥2 recurrences [4].

The therapeutic management of CDI is based on the setting of infection, severity, and presence of rCDIs. Treatment is usually based on antibiotics (metronidazole, vancomycin, and fidaxomicin). Surgical intervention and faecal microbiota transplantation are recommended for patients with severe complications and multiple rCDIs [1]. The US Food and Drug Administration's recent approval of faecal microbiota products for preventing rCDIs in adults may extend the treatment landscape of the disease [5-7].

The latest CDI surveillance data in acute care hospitals from the European Centre for Disease Prevention and Control showed a crude incidence density of ~3.5 cases per 10,000 patient-days [8]. In England, the incidence of hospitalised CDI reported by the National Health Service (NHS) acute trusts has been relatively stable since 2014, with approximately 22–25 episodes per 100,000 population per year [9]. Recent real-world data (RWD) from England showed a similar trend, with the incidence of CDI and rCDI in both hospital and community settings estimated at ~103.4 episodes per 100,000 population between 2015 and 2019 [10].

Despite cross-country variations, CDI has been linked to substantial mortality. In Europe and North America, studies using data from 2002 to 2013 have estimated the 12-month mortality rate for CDI in the range of 21%–50% [11-14]. In England, 30-day and 12-month

mortality rates of 16.3% and 49.9%, respectively, were reported in patients with healthcare-associated CDI [13]. CDI also represents a substantial economic burden to healthcare systems owing to prolonged hospital stays, readmissions, and treatment [15]. An annual cost of 3 billion euros has been estimated in Europe which is expected to double in the future [15]. Recurrences have been associated with an increased risk of death and higher healthcare resource usage (HCRU) and associated costs [4, 13, 16].

While the burden of CDI and rCDI has been widely evaluated in hospital settings, only a few studies have focused on community settings. This study aims to address this gap by generating RWD on mortality and costs in CDI patients treated in both hospital and community settings in England during 2015–2019.

Methods

Study design, data sources, and patient selection

This observational retrospective study conducted in England used primary and secondary care data from the Clinical Practice Research Datalink (CPRD) Aurum and Hospital Episode Statistics (HES) (hospitalisation data including Admitted Patient Care [APC], Accident and Emergency [A&E] and HES Outpatient [OP]) databases, respectively. These data were linked to the Office for National Statistics database, which captures death registration data (date and cause) in the UK.

The study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol number: 21_000471). Access to CPRD data and linked data such as HES, can be requested directly from CPRD and

is made available subject to protocol approval via CPRD's Research Data Governance (RDG) Process. The study team is not able to share data directly.

The study design has been described in detail in a parallel publication [10]. An overview of the study design is provided in Figure S2. The study included adult patients (≥18 years) with a CDI diagnosis recorded between 1st January 2015 and 31st December 2019 in primary care (community) (CPRD MedCode ID) or in a hospital (International Classification of Diseases version 10 [ICD-10] code: A04.7, primary or secondary diagnoses). Detailed criteria for patient selection are available in Table S1.

The first CDI episode experienced during the inclusion period was defined as the index CDI episode and was classified based on the setting of treatment (hospitalised or community-treated CDI) and setting of infection (healthcare-associated or community-associated CDI or unknown) (Figure S1). An rCDI episode was defined as a subsequent episode experienced ≤60 days from the start date of the last CDI episode (index CDI or previous rCDI).

Analyses were restricted to CDI patients diagnosed between 1st January 2015 and 31st December 2018, thereby allowing for at least 12-months of potential follow-up. Patients with a CDI episode within 6-months preceding the index CDI date were excluded. Patients were followed from the index date until death, loss to follow-up, 24-months after inclusion, or the end of the study period (31st December 2019), whichever occurred first. A matched cohort analysis with a cohort of non-CDI patients was performed to estimate excess mortality and incremental costs among CDI patients.

CDI patients for matched cohort analysis

CDI patients were categorised into four groups (based on the setting of treatment and infection, Figure S1) for the matched cohort analysis – Group 1: healthcare-associated and hospitalised CDI; Group 2: community-associated and hospitalised CDI; Group 3: healthcare-associated and community-treated CDI; and Group 4: community-associated and community-treated CDI. Patients with an unknown infection setting were not selected for matching.

Non-CDI patients for matched cohort analysis

A cohort of non-CDI patients was selected from patients in the CPRD/HES databases that had no record of a CDI diagnosis during the study period and in the 12-months preceding the index date. Non-CDI patients were matched to each of the four groups of CDI patients previously described to ensure a similar pattern of healthcare use. For each CDI patient, up to three non-CDI patients were matched. Matching (without replacement) was based on age (±5 years), sex, region, Charlson Comorbidity Index (CCI) score, prior antibiotic consumption, previous hospitalisation, and record of primary or secondary healthcare consultations (Table S2). Non-CDI patients were required not to have CDI at any point during the study period. The index date for non-CDI patients matched with hospitalised CDI patients (Groups 1 and 2) was set to the date of hospitalisation closest to the index date of the matched CDI patients (±1 month). For non-CDI patients matched with community-treated CDI patients (Groups 3 and 4), it corresponded to the index date of the matched CDI patient.

Outcomes

Outcomes of interest included all-cause mortality and excess mortality at 6-, 12- and 24-months post-index date, HCRU (i.e., hospitalisations [day-case and overnight admissions], outpatient consultations, A&E admissions, primary care consultations, and pharmacological treatments prescribed at primary care) and associated costs, and incremental HCRU costs.

Data analysis

The data were analysed using R software version 3.4.1. CPRD small number rules were applied to all study outputs to prevent identification of individual patients. Any number <7 in a column was replaced by a '*' along with the next lowest number so that the suppressed numbers could not be derived. For continuous variables, descriptive statistics were reported as mean, standard deviation (SD), median, 25th and 75th percentiles, and minimum and maximum. For categorical variables, absolute numbers and percentages were computed.

All-cause mortality (with corresponding 95% confidence intervals [CIs]) at 6-, 12-, and 24-months of follow-up was derived as the proportion of CDI/rCDI patients who died (of any cause) during follow-up among all included CDI patients. To estimate all-cause mortality at 24-months, the analysis was restricted to patients with an index date recorded before 31st December 2017 (i.e., patients with a potential follow-up of ≥24 months). Excess mortality (per 100 patient-months) was computed as the difference in the mortality rate between matched CDI patients and matched non-CDI patients and presented along with the corresponding 95% CIs.

HCRU and associated costs were estimated for the overall population of CDI patients (including patients with no record of resource usage), and per resource type over a 12-month period of follow-up. The start of follow-up was set at the index date for community-

treated CDI patients. For hospitalised CDI patients, follow-up began post-hospital discharge following the index episode. HCRU related to hospitalisations included day-case admissions (i.e., discharge on the same day). For these, a length of stay (LOS) of zero days was adopted in alignment with the data reported by the National Tariff Payment System and as available in the database [17].

Total costs, derived as the sum over all patients and average costs per patient, were expressed in pounds (£) and inflated to rates for 2020. The difference in total and average costs between matched CDI and matched non-CDI patients was used to determine the total and average incremental costs per patient, respectively. Patients with missing cost data in at least one HCRU category were excluded from cost analyses for that particular HCRU category and total cost analyses. In addition, CDI patients with non-missing costs were excluded from the incremental cost evaluation analyses if all their matched patient pairs were excluded due to missing costs.

Results were presented for non-CDI patients as well as all CDI patients and stratified by the number of rCDIs. The reference group to estimate excess mortality and incremental costs of HCRU only included the respective matched non-CDI patients of each group of interest according to the number of rCDIs.

Results

Demographic and clinical characteristics

A population of 29,340 patients with a CDI diagnosis between 1st January 2015 and 31st December 2018 was included in this study (Table 1). Their median age was 73 years, 75.19% (n=22,061) were ≥65 years of age and 58.99% (n=17,309) were women. A slightly higher proportion of women experienced 2 (n=716, 62.92%) or ≥3 rCDIs (n=546, 63.64%). The median age-adjusted CCI score at the

index date was 4.0, with little variation across different subgroups. Proton-pump inhibitors (PPIs) (n=15,963, 54.41%) and antibiotics (n=13,701, 46.7%) were the most common pre-index medications. The setting of infection of the index CDI episode was classified for 89.58% (n=26,283) of patients. Among these, most had a community-associated index CDI episode (n=19,194, 73.03%) and 26.97% (n=7,089) had a healthcare-associated index CDI episode. Most patients (n=21,304, 72.61%) were treated in community settings at the index date. All CDI and matched CDI patients showed a similar distribution of baseline characteristics.

All-cause mortality and excess mortality rate

All-cause mortality among CDI patients at 6-, 12-, and 24-months was estimated at 15.87% (n=4,657), 20.37% (n=5,978), and 27.03% (n=5,817), respectively (Table 2). A higher proportion of patients with ≥1 rCDI died at 6-months of follow-up (1,283 of 6,254 patients at index date, i.e., 20.51%) compared with patients with no rCDIs (3,374 of 23,086 patients at index date, i.e., 14.61%). The same trend was observed at 12- and 24-months of follow-up.

The mortality rate among matched CDI patients at 6-, 12-, and 24-months of follow-up was 2.83, 1.94, and 1.39 per 100 patients-months, respectively (Table 3). This corresponded to an excess mortality of 1.81, 1.13, and 0.72 per 100 patient-months at 6, 12, and 24-months, respectively, when compared with matched non-CDI patients. While excess mortality among patients with ≥1 rCDI (2.53 per 100 patient-months, 95% CI: 2.29–2.78) was higher than that among those without any rCDI (1.64 per 100 patient-months, 95% CI: 1.54–1.74), experiencing ≥3 rCDIs did not appear to increase excess mortality.

HCRU

More than half of the CDI patients (n=13,998, 53.32%) were hospitalised during the 12-months of follow-up compared with 43.11% (n=33,071) of non-CDI patients (Table 4). The proportion of patients hospitalised during follow-up increased with the number of rCDIs, varying from 66.79% (n=2,413) of patients with 1 rCDI to 81.60% (n=590) of patients with ≥3 rCDIs. The mean LOS per hospitalisation was greater for CDI patients, with a mean of 4.81 days (SD: 13.60), compared with 3.52 days (SD: 10.44) for non-CDI patients. Patients with 1 rCDI showed a slightly higher mean LOS of 5.66 days (SD: 13.83), with the maximum being observed among patients with 2 rCDIs (7.02 days, SD: 15.72). CDI patients showed a ~2-fold increase in the number of inpatient care days compared with non-CDI patients (mean 9.49 [SD: 25.19] vs. 4.48 [SD: 15.55], respectively). The number of inpatient care days increased with the number of rCDIs: patients experiencing 1 rCDI spent 15.89 days in the hospital on average, compared with 25.96 days for patients with ≥3 rCDIs. A higher proportion of CDI patients (n=11,425, 43.52%) had A&E visits as compared with non-CDI patients (n=25,703, 33.50%). The mean number of A&E visits also increased with the number of rCDIs (1.38 vs. 2.19 in matched CDI patients with one and ≥3 rCDIs, respectively). While the proportion of CDI and non-CDI patients was similar in the other HCRU categories (i.e., intensive care unit [ICU] admissions, outpatient visits, primary care consultations, and pharmacological treatments), a higher resource utilisation was observed among rCDI patients.

HCRU costs

The overall median HCRU cost during the 12-month follow-up period was £1,393.69 per CDI patient, compared with £791.53 among matched non-CDI patients and increased with each rCDI episode to £6,407.89 in patients with ≥3 rCDIs (Table 4).

While the median cost of hospitalisations and A&E visits was estimated at £0 in the CDI and non-CDI population, mean costs were £3,111.24 (vs. £1,849.09 for non-CDI patients) and £181.98 (vs. £120.05 for non-CDI patients), respectively (for zero-cost admissions, please see Discussion). Costs increased with the number of rCDIs. Costs associated with all other HCRU categories were higher for CDI patients as compared with non-CDI patients (median cost for outpatient visits: £148.35 vs. £69.87; primary care consultations: £374.78 vs. £236.63; and pharmacological treatments: £255.61 vs. £154.00) and increased with the number of recurrences.

Incremental HCRU costs

Hospitalisations incurred the highest incremental costs in CDI patients compared with non-CDI patients, with a mean incremental cost of £1,209.21 (Table 5). Mean incremental costs per patient for matched CDI patients (vs. respective non-CDI patient reference group) in the other resource categories evaluated were £59.46, £97.51, £155.91, and £202.10 for A&E visits, outpatient visits, primary care consultations, and pharmacological treatments, respectively. The average total incremental cost per patient was £1,179.80 for matched CDI patients, increasing alongside the number of recurrences to £6,044.45 in patients with ≥3 rCDIs.

Discussion

This real-world observational retrospective study estimated the mortality and economic burden of CDI and rCDI in England during 2015–2019. At the index CDI episode, most patients were treated in community settings (~73%), which may be reflective of the healthcare system in the UK, where primary care services act as the first point of contact in the NHS. A majority (~65%) of CDI cases were community-associated.

Overall, ~16% of CDI patients died of any cause within 6-months of follow-up, increasing to ~20% and ~27.0% at 12- and 24-months of follow-up, respectively. A higher proportion of patients with ≥1 rCDI died at any point of follow-up compared with those without rCDI. When compared with matched non-CDI patients with similar demographic and clinical characteristics, the excess mortality (at 6-months of follow-up) was estimated at 1.81 deaths per 100 patient-months in the overall CDI population and 2.53 deaths per 100 patient-months in patients with ≥1 rCDI. These differences in mortality gradually reduced over time (0.72 and 1.2 excess deaths per 100 patient-months at 24-months of follow-up, respectively).

Overall, the all-cause mortality estimates obtained were lower when compared to a prior retrospective study conducted using the CPRD during 2002–2013, in which all-cause mortality rates of 44.8% and 49.9% were estimated at 6- and 12-months of follow-up [13]. These differences are likely related to both the age of patients (median age: 81 years) and restriction of the study population to hospitalised patients with healthcare-associated CDI only, who tend to present with higher mortality compared with patients with community-associated CDI [3, 13]. Despite this difference, the previous CPRD-based study also indicated a higher risk of death among CDI patients compared with non-CDI patients, even if estimates were not comparable because of their nature (risk difference in the current study vs. hazard ratio [HR] in the previous CPRD study, HR [95% CI]=1.77 [1.67–1.87]) [13]. Similar findings (HR [95% CI]=1.51 [1.05–2.19]) were observed in a study using the UK National Death Register from 2005–2007 [18]. Excess mortality of the same magnitude has been observed in other countries. A multicentre Dutch study conducted from 2006–2009 reported 1.5 times higher mortality in CDI patients compared with matched controls within one year of follow-up [14]. These studies only included hospitalised patients, both CDI and non-CDI. Thus, our results, with only a quarter of CDI patients treated in hospitals, provides new insights regarding the excess mortality

of CDI in the overall population of CDI patients. In the US, a study leveraging 2011 Medicare claims data of elderly patients (mean age: 80.5 years) estimated a 1-year risk difference in all-cause mortality of 10.9% through propensity score-matched pairs analyses, close to that observed in the current study [11]. However, even if no restriction had been imposed on the CDI population, the 1-year mortality rate (40.9%) was closer to that observed in the previous CPRD-based English study, and age appears to be the major contributor to CDI mortality, ahead of treatment and infection settings [11, 13].

Aligned with prior research, all-cause mortality rates decreased with the number of recurrences. A US study using Medicare claims data during 2009–2017 estimated 1-year all-cause mortality rates of 40.8%, 34.6%, and 28.5% for patients with 1, 2, or subsequent rCDIs, respectively [16]. However, CDI-associated mortality rates increased with the number of recurrences (2.7%, 16.4%, 30.9%, and 39.0% in patients with 0, 1, 2, or ≥3 rCDI episodes, respectively) [16]. Notably, unlike our study, the all-cause mortality rate was higher in CDI patients without any recurrence than in patients presenting with rCDI (45.9% vs. 35.5%, respectively) [16]. This study only included elderly patients (≥65 years) and consequently more frail patients, which might explain this result.

HCRU and associated costs within a year after the index CDI were consistently higher in CDI patients compared with non-CDI patients. Hospitalisation use (inpatient care days) was twice as high in CDI patients compared with matched non-CDI patients. A&E visits and all other HCRU were also significantly higher in CDI patients. Hospitalisations were the key driver of costs, representing a mean incremental cost of ~£1,209 per CDI patient. Patients with 1 rCDI versus no rCDI had a cost difference of more than £1,500 in total costs, which increased to more than £5,300 in patients with ≥3 rCDIs. Indeed, CDI patients were more frequently hospitalised, with a longer mean LOS per admission, with both the frequency and duration increasing with the number of rCDIs. Thus, our results show the

importance of breaking the vicious cycle of frequent rCDIs, emphasising the need for different stewardship initiatives and innovative treatment options [19].

The impact of rCDIs on HCRU and associated costs, particularly due to longer hospital stays, has been previously described [1, 20, 21]. A UK study in six acute care hospitals (2013–2014) reported a median LOS of 15.5 and 21 days for a first CDI and rCDI episode, respectively. The corresponding median costs varied from £6,294 to £7,539 [22]. A micro-costing analysis (2014–2017) in England (London) showed the total LOS to be 17 and 33 days, respectively, for primary and rCDI, with mean total costs of £12,710 for primary and £31,121 for rCDI episodes [23].

To the best of our knowledge, this study provides the most comprehensive assessment of the mortality and economic burden associated with CDI and rCDI in England, accurately diagnosed in both hospital and community settings. While our study population consisted exclusively of patients from England (i.e., eligible for linkage with HES), the CPRD has been shown to be representative of the UK population, allowing generalisability of results [24]. Despite this, limitations inherent to the use of secondary RWD should be acknowledged, such as data completeness and accuracy. Firstly, an algorithm was developed to determine the setting of infection, as this information was not available in the CPRD/HES data. However, it could not be ascertained for ~10% of patients. These patients were excluded from matched cohort analyses, which may have introduced selection bias. However, matched CDI and non-CDI patients were very similar in terms of demographic and clinical characteristics. Secondly, regarding the assessment of HCRU, the accurate matching of A&E visits to their respective inpatient admissions where the A&E visit resulted in an admission was not possible (i.e., respective datasets are produced and curated separately), introducing a potential risk of double counting. Fortunately, this potential risk

does not extend to cost assessment, since costs are applied separately depending on the part of the health system in which a patient is treated [25]. Additionally, costs related to hospitalisation may be underestimated due to the inclusion of zero-cost hospitalisations. Zero-cost admissions can be observed, and generally occur when the reason for an inpatient admission is a procedure that should be performed in outpatient settings. These are set up to penalise inefficiency, and since these are reflective of the incentive system within the tariff system, they were retained in the analyses.

It should be noted that for hospitalised CDI patients at index, follow-up began post-hospital discharge, which was not accounted in HCRU and costs assessment. Finally, despite a rigorous selection of matching criteria to identify non-CDI patients for matched cohort analysis, using regression modelling could have provided a more efficient strategy to adjust for potential confounding factors. The interpretation of results on all-cause and excess mortality according to the number of rCDIs is also limited, since it reflects immortal time bias as patients need to survive long enough to experience each rCDI episode [13].

Despite these limitations, the study provides a robust assessment of the excess mortality and economic costs associated with CDI and widened by the presence of rCDIs. The findings highlight the urgent need for therapeutic advances, particularly in the context of an increasingly complex elderly population with multiple comorbidities and growing antibiotic resistance [26].

Declaration of competing interest

FLA was, at the time of the study, employed by Ferring Pharmaceuticals A/S. AA, HRK, SL-F, EC, AT are employed by IQVIA. SG is a member of steering committees for Janssen, Bristol Myers Squibb and Abbvie, participates in drug monitoring committees for Janssen, has speaker commitments for Abbvie, Takeda, Janssen, Pfizer, Gilead, Galapagos, Ferring Pharmaceuticals A/S, Eli-Lilly, Celltrion, and is a member of advisory committees for Janssen, Abbvie, Takeda, Gilead, Galapagos, Eli-Lilly, Pfizer, Celltrion, and Ferring Pharmaceuticals A/S.

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Ethical approval

Approval to conduct this study was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency.

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Author contributions

FLA conceptualized the study. SG, AA, HRK, SL-F, EC, and AT contributed to the study design, data analysis, and interpretation of results. SG, AA, AT, and FLA drafted the manuscript. All authors critically reviewed and approved the manuscript.

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Table 1. Demographic and clinical characteristics of the CDI/rCDI and matched non-CDI patients (longitudinal cohort).

	All CDI patients	**Patients without rCDI (0 rCDI)[a]**	**Patients with 1 rCDI[a]**	**Patients with 2 rCDIs[a]**	**Patients with ≥3 rCDIs[a]**	**Patients with ≥1 rCDIs[a]**	**All matched CDI patients**	**Matched non-CDI patients**
Total number of patients								
N	29,340	23,086	4,258	1,138	858	6,254	26,254	76,715
Age at index date (years)								
Mean (SD)	70.41 (16.83)	70.11 (16.83)	71.40 (16.90)	71.99 (16.40)	71.39 (16.77)	71.51 (16.79)	70.18 (16.91)	69.94 (16.92)
Median; Q1–Q3	73.00; 65.00–82.00	73.00; 65.00–82.00	75.00; 64.00–84.00	75.00; 65.00–84.00	75.00; 64.00–83.00	75.00; 64.00–84.00	73.00; 65.00–82.00	73.00; 64.00–82.00
Min; Max	18.00; 105.00	18.00; 105.00	18.00; 105.00	19.00; 103.00	19.00; 103.00	18.00; 105.00	18.00; 105.00	18.00; 105.00
Missing	0	0	0	0	0	0	0	0
Age group at index, n (%)								
18–64	7,279 (24.81%)	5,703 (24.7%)	1,086 (25.5.29%)	270 (23.73%)	220 (25.64%)	1,576 (25.2%)	6,528 (24.86%)	19,369 (25.25%)
≥65	22,061 (75.19%)	17,383 (75.3%)	3,172 (74.5%)	868 (76.27%)	638 (74.36%)	4,678 (74.8%)	19,726 (75.14%)	57,346 (74.75%)
Gender, n (%)								
Female	17,309 (58.99%)	13,565 (58.76%)	2,482 (58.29%)	716 (62.92%)	546 (63.64%)	3,744 (59.87%)	15,517 (59.1%)	45,341 (59.1%)
Male	12,031 (41.01%)	9,521 (41.24%)	1,776 (41.71%)	422 (37.08%)	312 (36.36%)	2,510 (40.13%)	10,737 (40.9%)	31,374 (40.9%)
Charlson Comorbidity Index, age-adjusted, at index date								
Mean (SD)	4.02 (2.31)	3.90 (2.28)	4.42 (2.34)	4.49 (2.30)	4.42 (2.48)	4.43 (2.35)	3.91 (2.28)	3.62 (2.27)
Median; Q1–Q3	4.00; 3.00–5.00	4.00; 2.00–5.00	4.00; 3.00–6.00	5.00; 3.00–6.00	5.00; 3.00–6.00	4.00; 3.00–6.00	4.00; 2.00–5.00	3.00; 2.00–5.00
Min; Max	0.00; 15.00	0.00; 15.00	0.00; 14.00	0.00; 12.00	0.00; 13.00	0.00; 14.00	0.00; 15.00	0.00; 16.00
Missing	0	0	0	0	0	0	0	0
Pre-index medical procedures and treatments, n (%)								
Pre-index medications								
Antibiotics[b]	13,701 (46.7%)	10,381 (44.97%)	2,203 (51.74%)	636 (55.89%)	481 (56.06%)	3,320 (53.09%)	11,948 (45.51%)	33,065 (43.1%)
Laxatives	8,814 (30.04%)	6,641 (28.77%)	1,461 (34.31%)	417 (36.64%)	295 (34.38%)	2,173 (34.75%)	7,525 (28.66%)	14,959 (19.5%)

	All CDI patients	Patients without rCDI (0 rCDI)[a]	Patients with 1 rCDI[a]	Patients with 2 rCDIs[a]	Patients with ≥3 rCDIs[a]	Patients with ≥1 rCDIs[a]	All matched CDI patients	Matched non-CDI patients
Proton-pump inhibitors	15,963 (54.41%)	12,460 (53.97%)	2,375 (55.78%)	634 (55.71%)	494 (57.58%)	3,503 (56.01%)	13,996 (53.31%)	28,454 (37.09%)
H2-receptor antagonists	2,254 (7.68%)	1,732 (7.5%)	341 (8.01%)	106 (9.31%)	75 (8.74%)	522 (8.35%)	1,902 (7.24%)	3,191 (4.16%)
Selective immunosuppressants	178 (0.61%)	130 (0.56%)	29 (0.68%)	13 (1.14%)	* (*)	48 (0.77%)	154 (0.59%)	170 (0.22%)
TNF-α inhibitors	29 (0.1%)	21 (0.09%)	* (*)	* (*)	0 (0.00%)	8 (0.13%)	26 (0.1%)	30 (0.04%)
Interleukin inhibitors	* (*)	* (*)	* (*)	0 (0.00%)	0 (0.00%)	* (*)	* (*)	7 (0.01%)
Calcineurin inhibitors	178 (0.61%)	126 (0.55%)	29 (0.68%)	13 (1.14%)	10 (1.17%)	52 (0.83%)	153 (0.58%)	194 (0.25%)
Other immunosuppressants	651 (2.22%)	504 (2.18%)	92 (2.16%)	25 (2.2%)	30 (3.5%)	147 (2.35%)	572 (2.18%)	1,072 (1.4%)
Chemotherapies/Antineoplastic agents	201 (0.69%)	153 (0.66%)	31 (0.73%)	10 (0.88%)	7 (0.82%)	48 (0.77%)	175 (0.67%)	307 (0.4%)
Monoclonal antibody indicated in CDI (Zinplava)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pre-index medical procedures	1,200 (4.09%)	859 (3.72%)	222 (5.21%)	69 (6.06%)	50 (5.83%)	341 (5.45%)	987 (3.76%)	1,350 (1.76%)
Setting of infection at index								
Healthcare-associated	7,089 (24.16%)	4,967 (21.52%)	1,424 (33.44%)	397 (34.89%)	301 (35.08%)	2,122 (33.93%)	7,075 (26.95%)	20,273 (26.43%)
Community-associated	19,194 (65.42%)	16,018 (69.38%)	2,192 (51.48%)	562 (49.38%)	422 (49.18%)	3,176 (50.78%)	19,179 (73.05%)	56,442 (73.57%)
Unknown	3,057 (10.42%)	2,101 (9.1%)	642 (15.08%)	179 (15.73%)	135 (15.73%)	956 (15.29%)	0 (0.00%)	0 (0.00%)
Setting of treatment at index								
Hospitalised	8,036 (27.39%)	5,533 (23.97%)	1,703 (40%)	462 (40.6%)	338 (39.39%)	2,503 (40.02%)	6,809 (25.94%)	19,842 (25.86%)
Community-treated	21,304 (72.61%)	17,553 (76.03%)	2,555 (60%)	676 (59.4%)	520 (60.61%)	3,751 (59.98%)	19,445 (74.06%)	56,873 (74.14%)

CDI: *Clostridioides difficile* infection; Min: Minimum; Max: Maximum; Q1: 1st quartile; Q3: 3rd quartile; rCDI: Recurrent *Clostridioides difficile* infection; SD: Standard deviation; TNF-α: Tumour necrosis factor-alpha.

[a]*Non-rCDI patients (0 rCDI), patients with 1 rCDI, patients with 2 rCDIs, patients with ≥3 rCDIs are subgroups of "All CDI patients".*

[b]Antibiotics, including cephalosporins, fluoroquinolones, macrolides, penicillins with extended spectrum, clindamycin, and rifaximin.

Table 2. All-cause mortality at 6-, 12-, and 24-months of follow-up in CDI patients, overall and according to the number of rCDIs.

Time	Statistical parameters	All CDI patients	Patients without rCDI	Patients with 1 rCDI	Patients with 2 rCDIs	Patients with ≥3 rCDIs	Patients with ≥1 rCDI
Death[a] at 6-months	Number of patients at index	29,340	23,086	4,258	1,138	858	6,254
	Number of deaths	4,657	3,374	921	226	136	1,283
	6-month mortality rate (%)	15.87	14.61	21.63	19.86	15.85	20.51
	95% CI for proportion	[15.45; 16.29]	[14.16; 15.07]	[20.39; 22.87]	[17.54; 22.18]	[13.41; 18.29]	[19.51; 21.52]
Death[a] at 12-months	Number of deaths	5,978	4,303	1,176	304	195	1,675
	12-month mortality rate (%)	20.37	18.64	27.62	26.71	22.73	26.78
	95% CI for proportion	[19.91; 20.84]	[18.14; 19.14]	[26.28; 28.96]	[24.14; 29.28]	[19.92; 25.53]	[25.69; 27.88]
Death[a] at 24-months	Number of patients at index[a]	21,524	16,887	3,152	847	638	4,637
	Number of deaths	5,817	4,184	1,115	305	213	1,633
	24-month mortality rate (%)	27.03	24.78	35.37	36.01	33.39	35.22
	95% CI for proportion	[26.43; 27.62]	[24.13; 25.43]	[33.71; 37.04]	[32.78; 39.24]	[29.73; 37.04]	[33.84; 36.59]

CDI: *Clostridioides difficile* infection; CI: Confidence interval; rCDI: Recurrent *Clostridioides difficile* infection.
[a]Death at 24-months restricted to patients with a potential follow-up of at least 24-months.

Table 3. Mortality rate (/100 patient-months) and excess mortality in CDI patients compared with matched non-CDI patients, overall and according to number of rCDIs.

Time	Statistical parameters	Non-CDI patients	All CDI patients	Patients without rCDI	Patients with 1 rCDI	Patients with 2 rCDIs	Patients with ≥3 rCDIs	Patients with ≥1 rCDI
	Number of patients at index date	76,715	26,254	20,962	3,613	956	723	5,292
6-month mortality	Number of deaths	4,418	3,877	2,829	754	178	116	1,048
	Follow-up time in patient-months	432964.60	136873.37	109901.67	18019.23	5010.40	3942.07	26971.70
	Mortality rate (/100 patient-months)	1.02	2.83	2.57	4.18	3.55	2.94	3.89
	Excess mortality (/100 patient-months)[a]	Ref.	1.81	1.64	2.82	2.27	1.59	2.53
	95% CI for excess mortality	-	[1.72; 1.91]	[1.54; 1.74]	[2.5; 3.13]	[1.72; 2.82]	[1.01; 2.16]	[2.29; 2.78]
12-month mortality	Number of deaths	6,745	4,994	3,629	958	244	163	1,365
	Follow-up time in patient-months	830,542.00	257442.97	208313.27	32822.77	9118.50	7188.43	49129.70
	Mortality rate (/100 patient-months)	0.81	1.94	1.74	2.92	2.68	2.27	2.78
	Excess mortality (/100 patient-months)[a]	Ref.	1.13	1	1.83	1.61	1.22	1.7
	95% CI for excess mortality	-	[1.07; 1.18]	[0.93; 1.06]	[1.63; 2.02]	[1.26; 1.97]	[0.85; 1.6]	[1.54; 1.86]
24-month mortality	Number of deaths	9,748	6,201	4,491	1,169	320	221	1,710
	Follow-up time in patient-months	1457044.00	444884.80	361971.60	55513.33	15330.53	12069.33	82913.20
	Mortality rate (/100 patient-months)	0.67	1.39	1.24	2.11	2.09	1.83	2.06

	Excess mortality (/100 patient-months)[a]	Ref.	0.72	0.62	1.23	1.24	0.98	1.2
	95% CI for excess mortality	-	[0.69; 0.76]	[0.58; 0.66]	[1.1; 1.36]	[1; 1.48]	[0.72; 1.24]	[1.09; 1.3]

CDI: *Clostridioides difficile* infection; CI: Confidence interval; rCDI: Recurrent *Clostridioides difficile* infection.
[a]The reference group to estimate excess mortality in CDI patients, overall and according to the number of rCDIs, was constituted by the respective matched non-CDI patients of each group of interest.

Table 4. HCRU and costs in matched non-CDI and CDI patients during 12-months of follow-up, overall, and according to number of rCDIs.

	Non-CDI patients (matched cohort)	**All CDI patients**	**Patients without rCDI**	**Patients with 1 rCDI**	**Patients with 2 rCDIs**	**Patients with ≥3 rCDIs**	**Patients with ≥1 rCDIs**
Total number of patients, N[a]	76,715	26,254	20,962	3,613	956	723	5,292
Hospitalisations							
Patients with hospital stays, n (%)	33,071 (43.11%)	13,998 (53.32%)	10,247 (48.88%)	2,413 (66.79%)	748 (78.24%)	590 (81.60%)	3,751 (70.88%)
Inpatient care days							
Mean (SD)	4.48 (15.55)	9.49 (25.19)	7.22 (22.45)	15.89 (29.74)	22.75 (35.20)	25.96 (39.01)	18.51 (32.42)
Median; Q1–Q3	0.00; 0.00–1.00	0.00; 0.00–6.00	0.00; 0.00–2.00	2.00; 0.00–18.00	8.50; 0.00–31.00	11.00; 0.00–34.00	4.00; 0.00–23.00
Min; Max	0.00; 510.00	0.00; 492.00	0.00; 492.00	0.00; 371.00	0.00; 334.00	0.00; 408.00	0.00; 408.00
Number of hospitalisations							
N	97,846	51,849	35,434	10,141	3,099	3,175	16,415
Mean (SD)	1.28 (5.62)	1.97 (7.53)	1.69 (6.72)	2.81 (10.07)	3.24 (7.53)	4.39 (12.48)	3.10 (10.05)
Median; Q1–Q3	0.00; 0.00–1.00	1.00; 0.00–2.00	0.00; 0.00–2.00	1.00; 0.00–3.00	2.00; 1.00–3.00	2.00; 1.00–4.00	1.00; 0.00–3.00
Min; Max	0.00; 162.00	0.00; 175.00	0.00; 157.00	0.00; 175.00	0.00; 114.00	0.00; 155.00	0.00; 175.00
Length of stay per hospitalisation, days							
Mean (SD)	3.52 (10.44)	4.81 (13.60)	4.27 (13.32)	5.66 (13.83)	7.02 (15.72)	5.91 (13.36)	5.97 (14.13)
Median; Q1–Q3	0.00; 0.00–2.00	0.00; 0.00–4.00	0.00; 0.00–3.00	0.00; 0.00–5.00	0.00; 0.00–7.00	0.00; 0.00–7.00	0.00; 0.00–6.00
Min; Max	0.00; 417.00	0.00; 480.00	0.00; 480.00	0.00; 250.00	0.00; 214.00	0.00; 239.00	0.00; 250.00
ICU admission, n (%)							
Yes	1,380 (1.8%)	857 (3.26%)	547 (2.61%)	206 (5.7%)	70 (7.32%)	34 (4.7%)	310 (5.86%)
No	31,691 (41.31%)	13,141 (50.05%)	9,700 (46.27%)	2,207 (61.08%)	678 (70.92%)	556 (76.9%)	3,441 (65.02%)
Total costs of hospitalisations							
Sum	134,456,265	76,623,589	49,517,587	16,186,184	5,856,773	5,063,045	27,106,003

	Non-CDI patients (matched cohort)	All CDI patients	Patients without rCDI	Patients with 1 rCDI	Patients with 2 rCDIs	Patients with ≥3 rCDIs	Patients with ≥1 rCDIs
Mean (SD)	1849.09 (4354.80)	3111.24 (6601.29)	2501.77 (5868.31)	4868.03 (7818.33)	6778.67 (9591.64)	7837.53 (10065.58)	5606.21 (8559.26)
Median; Q1–Q3	0.00; 0.00–1483.32	0.00; 0.00–3615.12	0.00; 0.00–2191.39	1508.97; 0.00–6569.97	4313.95; 252.62–9421.02	4471.80; 584.37–10960.88	2572.40; 0.00–7747.29
Min; Max	0.00; 126264.58	0.00; 182476.49	0.00; 182476.49	0.00; 90920.47	0.00; 124820.22	0.00; 79992.70	0.00; 124820.22
A&E (emergency room) visits							
Patients with A&E (emergency room) visits, n (%)	25,703 (33.50%)	11,425 (43.52%)	8,315 (39.67%)	1,961 (54.28%)	631 (66%)	518 (71.65%)	3,110 (58.77%)
Number of A&E visits							
N	54,131	27,199	19,060	4,987	1,568	1,584	8,139
Mean (SD)	0.71 (2.25)	1.04 (2.83)	0.91 (2.81)	1.38 (2.89)	1.64 (2.26)	2.19 (3.30)	1.54 (2.86)
Median; Q1–Q3	0.00; 0.00–1.00	0.00; 0.00–1.00	0.00; 0.00–1.00	1.00; 0.00–2.00	1.00; 0.00–2.00	1.00; 0.00–3.00	1.00; 0.00–2.00
Min; Max	0.00; 331.00	0.00; 199.00	0.00; 199.00	0.00; 96.00	0.00; 23.00	0.00; 42.00	0.00; 96.00
Total costs of A&E visits							
Sum	9,086,537	4,688,987	3,175,515	932,113	296,848	284,511	1,513,472
Mean (SD)	120.05 (278.50)	181.98 (382.60)	154.32 (331.66)	262.94 (536.83)	315.13 (450.37)	405.29 (541.31)	291.67 (525.03)
Median; Q1–Q3	0.00; 0.00–168.77	0.00; 0.00–247.24	0.00; 0.00–177.37	115.02; 0.00–367.64	177.37; 0.00–424.61	247.24; 0.00–514.91	168.77; 0.00–416.01
Min; Max	0.00; 12669.57	0.00; 15925.65	0.00; 8622.32	0.00; 15925.65	0.00; 5857.50	0.00; 6003.70	0.00; 15925.65
Outpatient visits							
Patients with outpatient visits, n (%)	49,407 (64.40%)	18,567 (70.72%)	14,660 (69.94%)	2,587 (71.60%)	744 (77.82%)	576 (79.67%)	3,907 (73.83%)
Number of outpatient visits							
N	352,258	160,965	123,215	24,469	7,450	5,831	37,750
Mean (SD)	4.59 (12.56)	6.13 (16.70)	5.88 (17.53)	6.77 (11.79)	7.79 (12.13)	8.07 (17.94)	7.13 (12.87)
Median; Q1–Q3	2.00; 0.00–6.00	3.00; 0.00–7.00	2.00; 0.00–7.00	3.00; 0.00–8.00	3.00; 1.00–9.00	4.00; 1.00–9.00	3.00; 0.00–9.00
Min; Max	0.00; 2002.00	0.00; 1318.00	0.00; 1318.00	0.00; 191.00	0.00; 105.00	0.00; 285.00	0.00; 285.00
Total costs of outpatient visits							
Sum	16,723,628	7,423,362	5,752,045	1,105,542	321,694	244,080	1,671,317
Mean (SD)	285.91 (637.78)	392.11 (766.03)	374.82 (723.15)	447.23 (914.78)	502.65 (971.92)	514.94 (902.80)	466.07 (923.85)

	Non-CDI patients (matched cohort)	All CDI patients	Patients without rCDI	Patients with 1 rCDI	Patients with 2 rCDIs	Patients with ≥3 rCDIs	Patients with ≥1 rCDIs
Median; Q1–Q3	69.87; 0.00–338.61	148.35; 0.00–477.54	144.05; 0.00–464.39	138.13; 0.00–535.33	208.54; 0.00–540.71	221.44; 0.00–598.76	162.32; 0.00–549.31
Min; Max	0.00; 45438.89	0.00; 20214.77	0.00; 16021.32	0.00; 20214.77	0.00; 11160.32	0.00; 9312.45	0.00; 20214.77
Primary care consultations							
Patients with primary care consultations, n (%)	69,645 (90.78%)	23,908 (91.06%)	18,995 (90.62%)	3,298 (91.28%)	905 (94.67%)	710 (98.20%)	4,913 (92.84%)
Number of primary care consultations							
N	752,367	377,509	289,686	54,817	17,312	15,694	87,823
Mean (SD)	9.81 (10.51)	14.38 (14.98)	13.82 (14.57)	15.17 (15.04)	18.11 (19.44)	21.71 (16.65)	16.60 (16.31)
Median; Q1–Q3	7.00; 3.00–13.00	11.00; 5.00–20.00	11.00; 5.00–19.00	12.00; 5.00–21.00	14.00; 7.00–24.00	18.00; 11.00–28.00	13.00; 6.00–23.00
Min; Max	0.00; 191.00	0.00; 650.00	0.00; 650.00	0.00; 147.00	0.00; 318.00	0.00; 137.00	0.00; 318.00
Total costs of primary care consultations							
Sum	25,333,404	12,804,278	9,815,193	1,867,463	589,074	532,548	2,989,085
Mean (SD)	330.23 (348.17)	487.71 (499.21)	468.24 (484.93)	516.87 (503.53)	616.19 (651.72)	736.58 (552.75)	564.83 (545.45)
Median; Q1–Q3	236.63; 97.89–448.70	374.78; 165.32–666.78	359.50; 156.92–639.59	397.70; 163.21–726.07	493.24; 239.53–795.10	617.53; 364.34–972.32	446.51; 196.15–775.18
Min; Max	0.00; 6356.84	0.00; 22588.79	0.00; 22588.79	0.00; 4945.85	0.00; 11060.30	0.00; 4944.81	0.00; 11060.30
Pharmacological treatments (primary care only)							
Patients with pharmacological treatments (primary care only), n (%)	69,328 (90.37%)	23,945 (91.21%)	19,001 (90.64%)	3,318 (91.84%)	919 (96.13%)	707 (97.79%)	4,944 (93.42%)
Number of pharmacological treatments							
N	4,447,660	1,898,621	1,459,206	293,311	79,681	66,423	439,415
Mean (SD)	57.98 (83.61)	72.32 (98.55)	69.61 (96.61)	81.18 (106.70)	83.35 (97.92)	91.87 (106.63)	83.03 (105.20)
Median; Q1–Q3	33.00; 9.00–75.00	42.00; 12.00–94.00	40.00; 11.00–90.00	47.00; 12.00–107.00	54.00; 17.00–111.00	60.00; 23.00–117.00	50.00; 15.00–110.00
Min; Max	0.00; 1862.00	0.00; 1295.00	0.00; 1295.00	0.00; 1018.00	0.00; 749.00	0.00; 721.00	0.00; 1018.00
Total costs of pharmacological treatments (primary care only)							
Sum	29,044,718	14,997,678	11,174,362	2,371,606	753,673	698,038	3,823,317
Mean (SD)	386.56 (618.07)	590.99 (919.02)	550.41 (880.57)	683.66 (993.92)	827.30 (1060.02)	1004.37 (1206.28)	753.36 (1043.40)

	Non-CDI patients (matched cohort)	All CDI patients	Patients without rCDI	Patients with 1 rCDI	Patients with 2 rCDIs	Patients with ≥3 rCDIs	Patients with ≥1 rCDIs
Median; Q1–Q3	154.00; 34.22–500.03	255.61; 57.34–771.31	226.90; 50.42–712.89	342.57; 77.46–907.35	464.13; 132.07–1142.00	641.49; 241.29–1298.92	402.67; 96.68–1019.57
Min; Max	0.00; 21228.81	0.00; 18300.34	0.00; 18300.34	0.00; 12576.36	0.00; 9572.54	0.00; 9863.09	0.00; 12576.36
Total overall HCRU costs							
Sum	127,765,015	64,226,455	44,148,898	11,967,949	4,233,379	3,876,230	20,077,558
Mean (SD)	2348.15 (4268.42)	3722.41 (6198.95)	3135.80 (5547.55)	5442.45 (7192.01)	7505.99 (8482.99)	9408.32 (10201.95)	6323.64 (8005.18)
Median; Q1–Q3	791.53; 236.33–2419.04	1393.69; 425.65–4339.15	1183.62; 368.23–3281.01	2867.89; 745.15–7182.29	5048.52; 1667.76–10103.81	6407.89; 2396.95–12540.80	3755.59; 1013.09–8565.34
Min; Max	0.00; 90618.81	0.00; 86524.44	0.00; 81622.92	0.00; 75061.39	0.00; 61583.50	137.83; 86524.44	0.00; 86524.44

CDI: *Clostridioides difficile* infection; ICU: Intensive care unit; Min: Minimum; Max: Maximum; Q1: 1st quartile; Q3: 3rd quartile; rCDI: Recurrent *Clostridioides difficile* infection; SD: Standard deviation.
For both CDI and non-CDI patients, all healthcare-related costs are estimated.
[a]All HCRU captured for 12-month follow-up after index date. Total number of patients (regardless of the use of each resource) was used as denominator for all cost analyses. Costs are expressed in pound (£), inflated to 2020 rates.

Table 5. Incremental HCRU costs (total and by type of resource) in matched non-CDI and CDI patients during 12-months of follow-up, overall and according to number of rCDIs.

Incremental costs during follow-up (£)	Non-CDI patients[a]	All CDI patients (Matched cohort)	Patients without rCDI	Patients with 1 rCDI	Patients with 2 rCDIs	Patients with ≥3 rCDIs	Patients with ≥1 rCDIs
Total number of patients, N	76,715	26,254	20,962	3,613	956	723	5,292
Incremental costs of inpatient hospitalisations							
Sum	Ref.	29,748,934	14,616,961	8,153,043	3,589,064	3,389,866	15,131,973
Mean (SD)	Ref.	1209.21 (6967.23)	739.24 (6308.55)	2455.74 (8279.53)	4158.82 (9966.07)	5247.47 (10161.53)	3133.56 (8930.55)
Incremental costs of A&E visits							
Sum	Ref.	15,131,973	800,242	407,793	147,658	176,015	731,466
Mean (SD)	Ref.	59.46 (408.64)	38.89 (363.36)	115.10 (554.55)	156.75 (495.58)	250.73 (548.12)	141.02 (545.30)
Incremental costs of outpatient visits							
Sum	Ref.	1,801,536	1,425,329	195,837	111,612	68,758	376,207
Mean (SD)	Ref.	97.51 (933.02)	95.07 (903.62)	81.80 (1060.74)	178.29 (1056.64)	148.83 (981.73)	108.04 (1050.32)
Incremental costs of primary care visits							
Sum	Ref.	4,093,279	3,049,131	555,913	230,012	258,222	1,044,147
Mean (SD)	Ref.	155.91 (531.61)	145.46 (519.33)	153.86 (541.39)	240.60 (660.84)	357.15 (590.64)	197.31 (575.88)
Incremental costs of pharmacological treatments							
Sum	Ref.	5,126,960	3,646,782	784,600	321,691	373,886	1,480,178
Mean (SD)	Ref.	202.10 (967.59)	179.68 (925.00)	226.24 (1066.64)	353.12 (1158.57)	538.74 (1264.28)	291.78 (1117.53)
Total incremental costs							
Sum	Ref.	19,563,395	10,072,573	4,707,711	2,419,730	2,363,381	9,490,822
Mean (SD)	Ref.	1179.80 (6815.65)	742.10 (6279.69)	2269.87 (7808.61)	4448.03 (9103.84)	6044.45 (10561.45)	3154.15 (8565.78)

CDI: *Clostridioides difficile* infection; rCDI: Recurrent *Clostridioides difficile* infection; SD: Standard deviation.
[a]Costs in CDI patients were compared with costs among the respective matched non-CDI patients according to the number of rCDIs. All HCRU was captured for 12-month follow-up after index date. Costs are expressed in pounds, inflated to 2020 rates. As matching of CDI patients and control non-CDI patients is usually not 1:1 (up to three non-CDI patients were matched to a CDI patient), total costs for non-CDI patients were divided by the number of non-CDI patients per case before deriving the incremental difference.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

FLA was, at the time of the study, employed by Ferring Pharmaceuticals A/S. AA, HRK, SL-F, EC, AT are employed by IQVIA. SG is a member of steering committees for Janssen, Bristol Myers Squibb and Abbvie, participates in drug monitoring committees for Janssen, has speaker commitments for Abbvie, Takeda, Janssen, Pfizer, Gilead, Galapagos, Ferring Pharmaceuticals A/S, Eli-Lilly, Celltrion, and is a member of advisory committees for Janssen, Abbvie, Takeda, Gilead, Galapagos, Eli-Lilly, Pfizer, Celltrion, and Ferring Pharmaceuticals A/S.