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Cost burden of *Clostridioides difficile* infection to the health service: A retrospective cohort study in Scotland

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SUMMARY

Background: *Clostridioides difficile* infection (CDI) is associated with high healthcare demands and related costs.
Aim: To evaluate the healthcare and economic burden of CDI in hospitalized patients with community- (HOCA-CDI) or hospital-associated CDI (HOHA-CDI) in the National Health Service in Scotland.
Methods: A retrospective cohort study was conducted, examining data between August 2010 and July 2013 from four patient-level Scottish datasets, linked to death data. Data examined included prior antimicrobial prescriptions in the community, hospitalizations, length of stay and mortality. Each CDI case was matched to three hospital-based controls on the basis of age, gender, hospital and date of admission. Descriptive economic evaluations were based on bed-day costs for different types of wards.
Findings: Overall, 3304 CDI cases were included in the study. CDI was associated with additional median lengths of stay of 7.2 days for HOCA-CDI and 12.0 days for HOHA-CDI compared with their respective, matched controls. The 30-day mortality rate was 6.8% for HOCA-CDI and 12.4% for HOHA-CDI. Overall, recurrence within 90 days of the first CDI episode occurred in 373/2740 (13.6%) survivors. The median additional expenditure for each initial CDI case compared with matched controls was £1713. In the 6 months after the index hospitalization, the cost associated with a CDI case was £5126 higher than for controls.

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Conclusion: Using routinely collected national data, we demonstrated the substantial burden of CDI on healthcare services, including lengthy hospital stays and readmissions, which increased the costs of managing patients with CDI compared with matched controls.

Introduction

Clostridioides difficile infection (CDI) is the most common cause of healthcare-associated diarrhoea in developed countries and a major public health problem [1]. It is associated with high healthcare demands and related costs, with recurrence of infection and the need for readmission to hospital contributing to the burden of CDI [2]. Moreover, a recent study estimated an excess 30-day all-cause mortality of 10.9% in patients with CDI compared with matched patients without CDI [3]. While CDI is mainly a hospital-associated infection, a substantial proportion of cases have onset in or association with the community setting [4]. It is, therefore, important to explore both hospital- and community-associated CDI to obtain a comprehensive account of its impact on healthcare burden.

In a study from Germany, the direct treatment cost of CDI was €18,463, compared with €14,531 for controls, with CDI prolonging the mean overall length of stay (LOS) by 8 days [5]. A study from Scotland found that LOS was extended by ≥15.8% in patients aged ≥65 years with CDI compared with younger patients aged 15–64 years with CDI [6]. Furthermore, recurrence of CDI appears to prolong the LOS compared with an initial CDI episode, with some estimating a doubling of LOS [7]. Consequently, recurrent CDI substantially increases healthcare costs [7,8]. Dubberke *et al.* estimated the attributable inpatient cost of recurrent CDI to be US$11,631 over the 6-month period after the initial CDI episode [9].

Owing to the considerable economic and healthcare burden of CDI, including recurrence, an accurate assessment of associated healthcare demands could help in the planning and prioritization of resources.

Methods

Study design and data collection

This was a cohort study, which examined linked data from four patient-level Scottish datasets. Scotland has mandatory reporting of CDI cases to Health Protection Scotland, with data held on the Electronic Communication of Surveillance in Scotland (ECOSS) system. Healthcare encounters also have mandatory recording of a unique patient identifier (Community Health Index (CHI) number), enabling patient-level linkage of data. Each CDI case from the diagnostic laboratories in Scotland was linked to community-based antimicrobial prescriptions and hospital admissions data. Prescriptions for antimicrobials dispensed in primary care were obtained from the Prescribing Information System (PIS). The PIS captures 96% of CHIs for all prescriptions dispensed in the community in Scotland [10].

Hospital admissions data were obtained from the general/acute and inpatient day case Scottish Morbidity Record (SMR01) dataset [11]. Mortality data were obtained from National Records of Scotland and were linked to SMR01.

Using ECOSS data, all CDI cases aged ≥15 years diagnosed during a hospital stay were identified covering the period between 1st August 2010 and 31st July 2013. Each hospital-onset CDI case was matched to up to three hospital-based controls, who were hospitalized at the same time as the case, on the basis of age (±5 years), gender, hospital and date of admission (±7 days). The index date for comparisons of outcomes for the controls was taken to be the date of diagnosis for the matched case.

All data analysed were de-identified before being made available to researchers for analysis in the National Safe Haven, a secure repository for storing and sharing data for health research. Ethics permission for this study was not required as it used only non-identifiable routine data. Approval for the study was granted by the National Health Service (NHS) National Services Scotland Privacy Advisory Committee (study number XRB14037).

Definitions

A CDI case was defined as a hospitalized patient who tested positive for *C. difficile* toxin in stool concurrent with diarrhoea not attributable to any other cause, or a patient with *C. difficile* culture-positive stool concurrent with pseudomembranous colitis diagnosis. Cases were defined as hospital-onset community-associated (HOCA-CDI) if the diagnostic sample was taken 0–2 days after admission. CDI diagnosed from samples taken from day 3 of admission was defined as hospital-onset hospital-associated (HOHA-CDI). If a patient was diagnosed twice with CDI within a 28-day period, the second positive test was considered part of the same infection episode. CDI recurrence was defined as a second CDI diagnosis ≥28 days after the initial positive CDI test. Presumed cure of CDI occurred for patients who had a period of ≥28 days after the first positive *C. difficile* test with no positive result and no death. Any result reported in the ECOSS system as equivocal (i.e. positive for glutamate dehydrogenase but negative for *C. difficile* toxin) was removed from the final dataset.

The exact date of CDI symptom onset is not systematically reported. A proxy for the onset date of CDI from the ECOSS system was the date that specimens were collected from patients or, when this was unavailable, the date that specimens were received by the testing laboratory or the date that results were reported.

Assessments and statistical analyses

LOS, additional LOS owing to CDI, mortality rates for ≤2 months post-CDI diagnosis and the recorded cause of death were assessed in cases and matched controls. If cases had multiple CDI episodes, one episode was randomly selected for

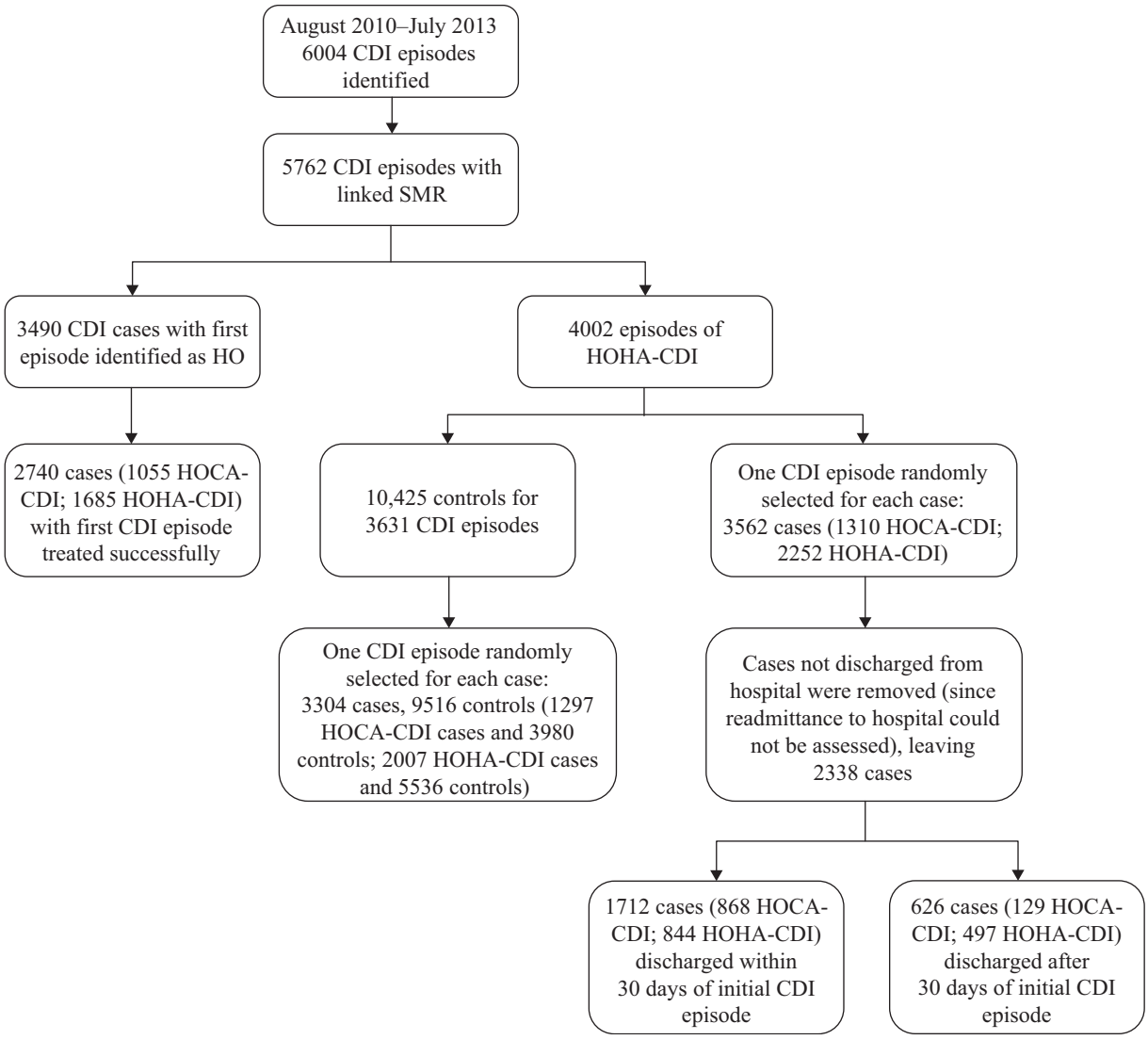


Figure 1. Identification and selection of *Clostridioides difficile* infection cases and controls. CDI, *Clostridioides difficile* infection; HO, hospital onset; HOCA-CDI, hospital-onset community-associated CDI; HOHA-CDI, hospital-onset hospital-associated CDI; SMR, Scottish Morbidity Record.

analysis of LOS, readmission and survival. Additional LOS for both cases and controls was analysed using a multivariable parametric survival regression model with a log-normal distribution assumed for time to event. A robust sandwich covariance matrix estimator was used to account for the matched design. Additional LOS due to CDI was calculated by comparing the median outcomes predicted by the survival regression model, adjusting for deprivation, comorbidities and time in hospital before CDI, for the cases and controls. The 95% confidence intervals (CIs) for the additional LOS was obtained by parametric bootstrapping 500 times. Patients who were transferred to another hospital environment, ending the continuous inpatient stay, were censored at the date of transfer.

Analyses of CDI recurrence and its determinants included cases who survived the first CDI episode (i.e. did not die or were not censored within 28 days after the initial CDI diagnosis). Analysis of secondary CDI recurrence included all cases who survived at least two CDI recurrences. Multivariable competing risks models [12,13] were used to account for mortality when investigating recurrence. A sensitivity analysis was conducted in relation to CDI recurrence, replacing 28 days with 6 and 8 weeks as the presumed date of cure.

A multivariable Cox proportional hazards survival model was applied to investigate the determinants of hospital readmission. The analysis was stratified by whether the first discharge was pre- or post-30 days after CDI diagnosis. Readmission rates within 6 months after CDI diagnosis and factors that may predict readmission were assessed in cases who were discharged from hospital before censor/date of death.

A multivariable Cox proportional hazards survival model was used to compare survival between cases and matched controls. Matched cases and controls were included as strata in the model providing a different baseline hazard for each stratum to account for the matched design.

In the analysis of potential risk factors, the following were recorded: comorbidities for the index admission; comorbidities reported in hospital admissions in the previous 5 years; number

Table I
Demographics and characteristics of *Clostridioides difficile* infection cases and controls.

Variable	Cases $N = 3304$	Controls $N = 9516$
Gender		
Male	1385 (41.9)	3907 (41.1)
Female	1919 (58.0)	5609 (58.9)
Age group, years		
15–64	807 (24.4)	2263 (23.8)
65–74	730 (22.1)	2080 (21.9)
75–84	1049 (31.8)	3159 (33.2)
≥85	718 (21.7)	2014 (21.2)
Origin of CDI		
HOCA	1297 (39.3)	–
HOHA	2007 (60.7)	–
Admitted from a care home		
No	3132 (94.8)	9125 (95.9)
Yes	172 (5.2)	391 (4.1)
Charlson Comorbidity Index		
0	1650 (49.9)	4676 (49.1)
1	524 (15.9)	1399 (14.7)
2	600 (18.2)	1658 (17.4)
3	218 (6.6)	535 (5.6)
≥4	180 (5.5)	385 (4.1)
Unknown	132 (4.0)	863 (9.1)
Characteristic, median (IQR)		
Antimicrobial prescriptions in previous year	1 (0–3)	1 (0–3)
Number of admissions in previous year	2 (1–3)	1 (0–3)
Total prescriptions in previous year	58 (30–95)	48 (22–82)
Different prescriptions in previous year	13 (8–18)	11 (6–16)
Length of stay (days) before the date of CDI	5 (1–19)	4 (1–15)

Data are n (%) unless otherwise indicated.
CDI, *Clostridioides difficile* infection; HOCA, hospital onset community-associated; HOHA, hospital onset hospital-associated; IQR, interquartile range.

of hospital admissions in the previous year; number of antimicrobial prescriptions in primary care, total number of prescriptions (all drugs) and number of different prescriptions (based on approved name) dispensed in primary care in the previous year; Charlson Comorbidity Index [14–16] based on ICD-10 discharge codes from all hospital admissions in the 5 years prior to the CDI episode; care home residency (yes/no); and Scottish Index of Multiple Deprivation (SIMD) quintile [17].

Cost analysis included LOS for both cases and matched controls. The first CDI episode was selected for the cost analysis if cases had multiple episodes. Costs were based on daily costs for different types of beds, such as beds on a general or critical care ward; see Supplementary Table S1. Descriptive economic evaluations were conducted for the NHS cost of managing the index CDI episode, the additional cost of managing the index CDI episode compared with matched controls, and NHS costs for hospital stay in the 6 months following the index CDI/matched control episodes.

All statistical analyses were stratified by HOHA-CDI and HOCA-CDI. Analyses were performed using statistical software R (version 3.2.1) [18].

Results

Cases and matched controls

There were 1297 HOCA-CDI cases and 3980 matched controls, and 2007 HOHA-CDI cases and 5536 matched controls. The identification and selection of cases and controls are shown in Figure 1. A greater number of previous hospital admissions and prescriptions for any medications were recorded in the cases, but other covariates were reasonably balanced between cases and controls (Table I and Supplementary Table S2).

Outcomes

Length of stay

Adjusting for comorbidities on admission, previous admissions and social deprivation, the median LOS was more than double for CDI patients compared with controls and HOCA-CDI cases had an additional median LOS of 7.2 days (95% CI 4.7–12.0), while HOHA-CDI cases had an additional 12.0 days (95% CI 7.7–18.9) compared with their respective controls (Table II).

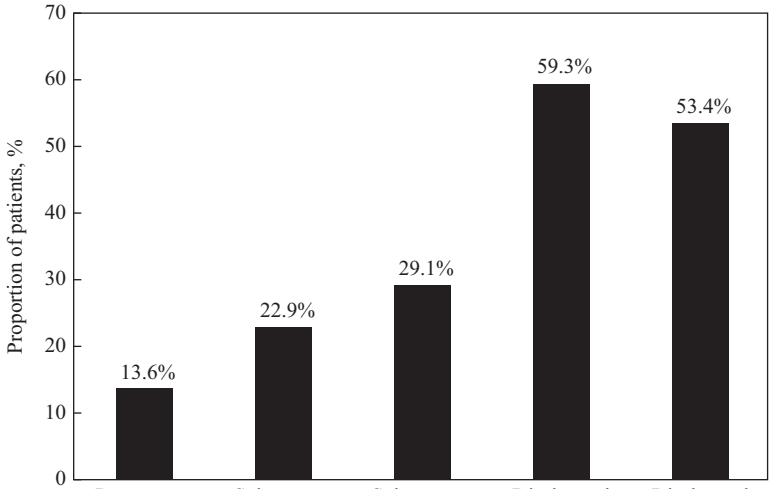
CDI recurrence

There were 1055 HOCA-CDI and 1685 HOHA-CDI cases eligible for analysis of recurrence (Figure 1). Overall, recurrence

Table II
Additional length of stay, in-hospital mortality and discharge from hospital according to *Clostridioides difficile* infection type.

	HOCA-CDI		HOHA-CDI	
	Cases $N = 1297$	Controls $N = 3980$	Cases $N = 2007$	Controls $N = 5536$
Median (95% CI) additional length of stay, days[a]	11.6 (7.7–18.8)	4.4 (3.0–6.9)	22.8 (14.8–35.5)	10.8 (7.0–16.2)
Died in hospital, *N* (%)	204 (15.7)	211 (5.3)	527 (26.3)	644 (11.6)
Discharged within 2 months, *N* (%)	966 (74.5)	3535 (88.8)	1056 (52.6)	4007 (72.4)

CI, confidence interval; HOCA-CDI, hospital onset community-associated *Clostridioides difficile* infection; HOHA-CDI, hospital onset hospital-associated *Clostridioides difficile* infection.
[a] Additional length of stay was adjusted according to comorbidities on admission, previous admissions, length of stay in hospital before CDI, and social deprivation.



No. events/ Total no. patients	373/2740	85/371	108/371	1015/1712	334/626

Figure 2. Recurrence of *Clostridioides difficile* infection and readmission to hospital for any reason. CDI, *Clostridioides difficile* infection.

within 90 days of the first CDI episode occurred in 373/2740 (13.6%) survivors (Figure 2). Recurrence rates over the 1-year period after the initial CDI diagnosis were similar for patients with HOCA-CDI and HOHA-CDI (Supplementary Table S3). Recurrence occurred in 161/1055 (15.3%) HOCA-CDI cases and 212/1685 (12.6%) HOHA-CDI cases. The hazard ratio (HR, 95% CI) for recurrence relative to patients aged ≤64 years was 1.51 (0.94–2.43) in patients aged 65–74 years, 1.98 (1.26–3.12) in patients aged 75–84 years and 2.16 (1.30–3.60) in patients aged ≥85 years.

After the first recurrent CDI episode, 371 cases were presumed cured. Rates of a second CDI recurrence in the next 12 months were 48/196 (24.6%) for cases with initial HOCA-CDI and 61/175 (34.8%) for cases with initial HOHA-CDI. The sensitivity analyses revealed that the recurrence rates had little variation if replacing 28 days post-infection with 6 and 8 weeks as the presumed date of cure (Supplementary Table S3).

Readmission to hospital

There were 868 HOCA-CDI and 844 HOHA-CDI cases that had been discharged from hospital within 30 days of the initial CDI episode and were eligible for analysis of readmission. Readmission within 6 months of the CDI episode occurred in 526/868 (60.6%) HOCA-CDI cases and 489/844 (57.9%) HOHA-CDI cases. The reason for readmission did not differ substantially from the reason for index admission (Supplementary Table S4). For patients discharged from hospital ≥30 days after the initial CDI episode, 71/129 (55.0%) HOCA-CDI cases and 263/497 (52.9%) HOHA-CDI cases were readmitted to hospital within 6 months.

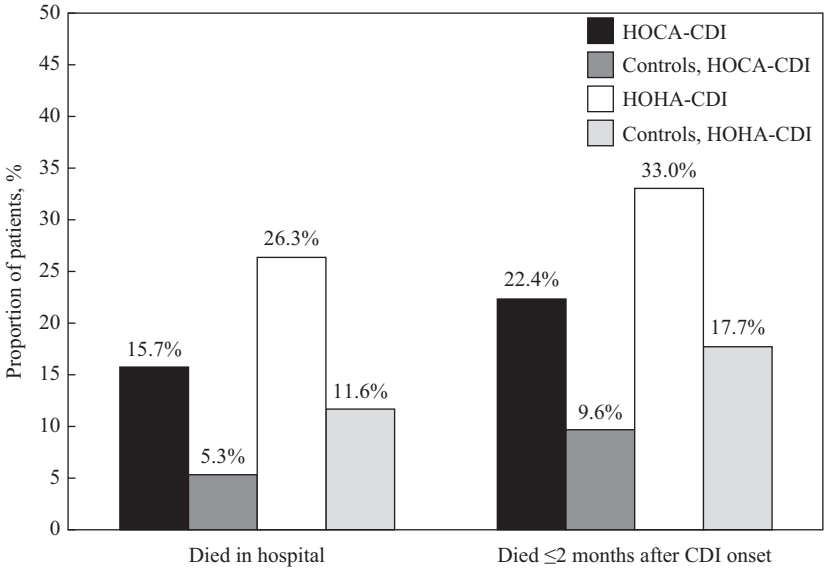
Mortality

Within 2 months of CDI diagnosis, 15.7% of cases with HOCA-CDI and 26.3% of cases with HOHA-CDI died in hospital, while the corresponding rates in control patients were 5.3% and 11.6%, respectively (Table II). The in-hospital mortality rates and mortality rates within 2 months after CDI onset are shown in Figure 3. The 30-day mortality rate was 6.8% for HOCA-CDI cases and 12.4% for HOHA-CDI cases. Adjusting for comorbidities on admission, previous hospital admissions and social deprivation score, compared with the corresponding controls, the HR for mortality was 2.47 (95% CI 2.04–3.00) for HOCA-CDI cases and 2.01 (95% CI 1.79–2.25) for HOHA-CDI cases.

Regardless of the origin of CDI, only comorbidities associated with the current admission were positively associated with mortality. There was no impact of social deprivation, antimicrobial or any medication prescriptions, or the number of hospital admissions in the 12 months prior to admission. Admission from a care home was positively associated with mortality (HR 1.52, 95% CI 0.94–2.45 for HOCA-CDI and HR 1.57, 95% CI 1.19–2.08 for HOHA-CDI).

Economic evaluation

The median (lower quartile (LQ), upper quartile (UQ)) index inpatient cost was more than double for cases (£7456 (3728, 16,060)) compared with controls (£2796 (932, 8388)), (Figure 4a). The median (LQ, UQ) additional cost associated with the index inpatient stay, calculated as the difference in median costs between cases in the index inpatient stay and matched controls, was £1713 (-1864, 8396; Figure 4b). Median (95% CI) longer-term costs based on all hospital stays in the 6 months



No. events/ Total no. patients	204/ 1297	211/ 3980	527/ 2007	644/ 5536		290/ 1297	381/ 3980	663/ 2007	981/ 5536

Figure 3. Mortality by origin of *Clostridioides difficile* infection. CDI, *Clostridioides difficile* infection; HOCA-CDI, hospital onset community-associated CDI; HOHA-CDI, hospital onset hospital-associated CDI.

after the index inpatient stay were £11,650 (5126, 23750) for cases and £6524 (2324, 16170) for controls (Figure 4c).

Discussion

Using routinely collected national data, the present study identified and characterized the additional burden of CDI on the NHS in Scotland, not only in relation to patient outcome and hospital resource use, but also its impact on hospitalization costs. Compared with matched controls, CDI is associated with additional median lengths of stay of 7.2 days for HOCA-CDI and 12.0 days for HOHA-CDI. The median additional expenditure for each CDI case is £1713. In the 6 months after the index hospitalization, the cost associated with a CDI case is £5126 higher than for controls. As far as we are aware, this study offers the first European data on the economic burden of hospitalized cases of community-associated CDI [2]. It highlights the substantial healthcare and economic burden of CDI, including recurrent infection, and therefore provides a key rationale for campaigns that promote the early detection and treatment of cases and/or instigate infection control strategies to lessen the impact of CDI. Our findings could also help service providers to plan and prioritize resources.

From our study, patients with CDI had longer lengths of stay and poorer outcomes than matched controls, and one in seven patients had a second recurrence within 90 days of the initial infection. The LOS for patients with CDI is comparable to that in other studies based on European data [19], including a recently published study of CDI cases over a 6-year period in Scotland [6]. While our study did not compare the costs associated with index CDI and recurrent CDI episodes, we calculated the costs of admissions with recurrent CDI, contributing to the evidence that recurrent CDI adds substantially to the total cost of treating CDI.

Our study also enabled a comparison of outcomes between community- and hospital-associated CDI, when identified in the hospital. It has long been assumed that community-associated CDI is less acute than hospital-associated CDI, but a substantial proportion of patients with community-associated CDI have serious sequelae, including severe infection, treatment failure, recurrent CDI and need for hospitalization [20,21]. Although there is a greater burden of hospital-associated disease, our study highlights that the mortality rate is similar in hospital- and community-associated CDI groups, when the latter is diagnosed in hospital. During the study period, ~801 community-associated, community-onset CDI cases were reported. The 30-day mortality rate of 12.4% for HOHA-CDI cases in our study was lower than the 17.5% reported for patients with hospital-associated CDI in a recent study from Scotland, although a greater proportion of patients in this other study had a higher Charlson Comorbidity Index compared with our study [6].

While a recently published study also reported on the impact of CDI on LOS and mortality in patients in Scotland [6], no data on costs, recurrent infection or readmissions were included. The present study considers the current economic burden in the NHS in the United Kingdom and highlights the substantial cost associated with the acute management of CDI. We demonstrate that the burden of financial cost continues over an extended period of time, such that 6 months after the acute episode there is still a clear and significant difference in cost between cases and controls. Recent data from both 2016/17 and 2017/18 suggest that 31% of all patients admitted to hospital have more than one admission within a year [22,23]; in our study, 57.7% of all hospital-onset CDI patients, from an earlier period (2010–2013), were readmitted within 6 months, suggesting that hospital-onset CDI is associated with particularly high rates of hospital readmission.

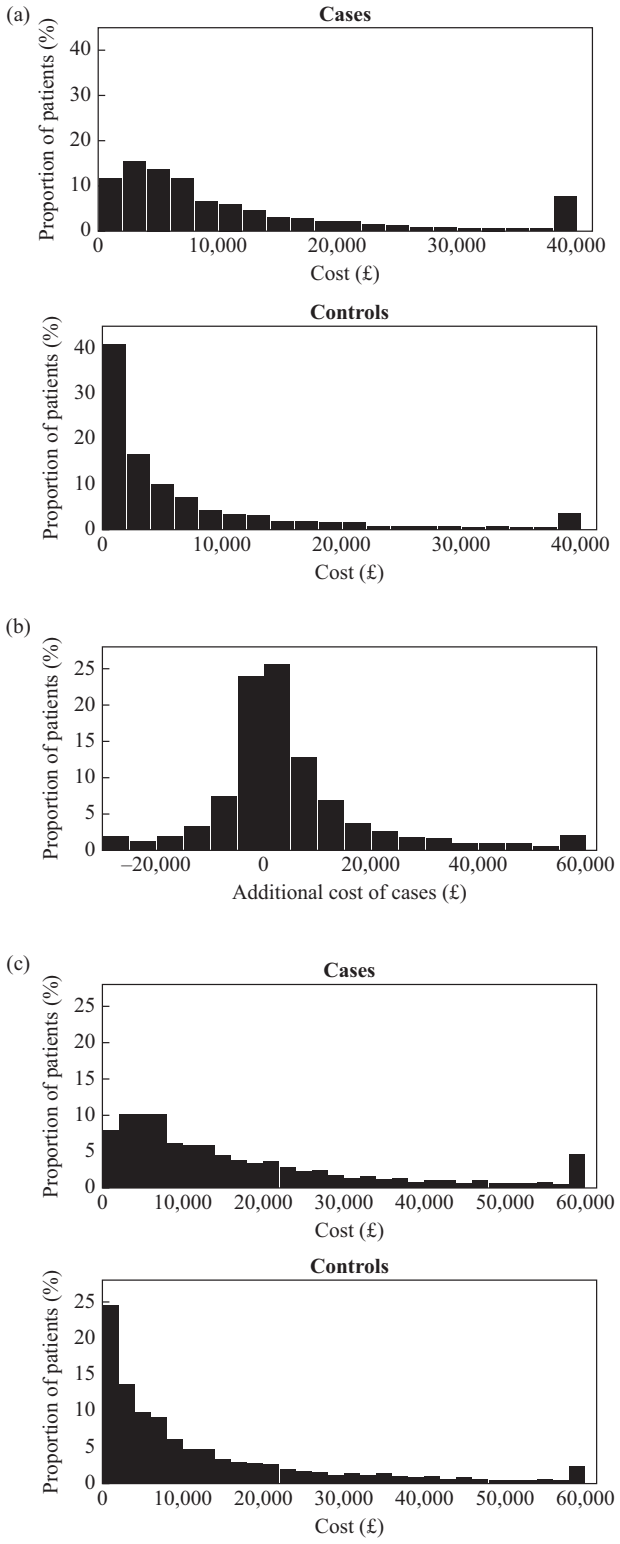


Figure 4. Economic evaluation of *Clostridioides difficile* infection (CDI) cases and controls in relation to (a) costs associated with first continuous inpatient stay after CDI diagnosis, (b) additional costs of cases versus controls for first continuous inpatient stay, and (c) longer term costs in the 6 months after CDI diagnosis. For (a), all costs valued above £40,000 were revalued as £40,000, while for (b) and (c), all costs valued above £60,000 were revalued as £60,000.

A key strength of this study was the matched design for estimating costs. The study design also minimized the impact of bias and confounding factors on our analyses. As a limitation, we recognize that the quality of the retrospective data relies on the accuracy and completeness of the medical records, although it is presumed that cases and controls were subject to the same issues. Additionally, and unlike the definition provided by the European Centre for Disease Prevention and Control (ECDC), our definition of HOCA-CDI did not take into account previous hospital discharges $\leq$4 weeks of the current admission [24], and therefore some HOCA-CDI cases may have been healthcare-associated CDI. Likewise, our definition of recurrent CDI incorporated a different timeline (second CDI diagnosis $\geq$28 days after the initial positive CDI test) than that from the ECDC (second CDI $>$2 weeks and $<$8 weeks after onset of previous episode) [24]. Consequently, the current study may have under- or over-estimated HOCA-CDI and recurrent CDI. Also, the prescribing data used in our study were derived from primary care, rather than prescriptions received during the hospital stay. Furthermore, our analysis did not include cost data associated with prescribing or management within the community. Finally, by selecting the first CDI episode within the time period for individuals with multiple CDI episodes, we estimated the total additional costs of CDI within 6 months, which may have resulted in an overestimate compared with the selection of an episode at random, as had been done for the estimation of recurrence and readmission rates.

In conclusion, CDI poses a substantial burden on healthcare services, including lengthy hospital stays, and after the infection, patients are at greater risk of readmission to hospital, even for non-CDI reasons. Consequently, there are increased costs associated with the management of patients with CDI compared with matched controls.

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Author contributions

Conception: A.L., C.R., I.F., C.McC., C.M. Study design and conduct: A.L., C.R., I.F., C.McC., K.K., M.B. Data acquisition: C.R., K.K., J.P., C.M., C.McC. Analysis and interpretation: J.P., K.K., C.R., C.McC., I.F., C.M. Writing: A.L., C.R., J.P., K.K., I.F., C.McC., M.B., C.M.

Conflict of interest statement
All authors report financial support from Astellas Pharma for conduct of the study reported here and for medical writing support. In addition, A.L. has received funding from Astellas Pharma relating to attendance at an educational meeting.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2020.07.019.

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