



# Risk of complications and mortality following recurrent and non-recurrent *Clostridioides difficile* infection: a retrospective observational database study in England

D.A. Enoch<sup>a,\*</sup>, T. Murray-Thomas<sup>b</sup>, N. Adomakoh<sup>c</sup>, D. Dedman<sup>b</sup>, A. Georgopali<sup>c</sup>, N.A. Francis<sup>d,†</sup>, A. Karas<sup>c</sup>

<sup>a</sup> Public Health England, Addenbrooke's Hospital, Cambridge, UK

<sup>b</sup> Clinical Practice Research Datalink, London, UK

<sup>c</sup> Astellas Pharma Europe Ltd, Addlestone, UK

<sup>d</sup> Division of Population Medicine, Cardiff University, Cardiff, UK

## ARTICLE INFO

### Article history:

Received 14 May 2020

Accepted 20 September 2020

Available online 25 September 2020

### Keywords:

*Clostridioides difficile*

infection

Recurrence

Mortality

Complications



## SUMMARY

**Background:** *Clostridioides difficile* infection (CDI) increases the risk of complications and mortality. We assessed the magnitude of these outcomes in a large cohort of English patients with initial and recurrent CDI.

**Aim:** To compare the risk of complications and all-cause mortality, within 12 months, among hospitalized patients  $\geq 18$  years old with hospital-associated- (HA-) CDI and recurrent CDI.

**Methods:** Patients with HA-CDI during 2002–2013 were identified using inpatient hospital data linked to primary care and death data. Each HA-CDI case was frequency matched to two hospitalized patients without CDI on age group, sex, calendar year of admission, admission method and number of hospital care episodes. A second CDI episode starting on days 13–56 was defined as recurrence. Risks of mortality and complications at 12 months were analysed using Cox proportional hazard models.

**Findings:** We included 6862 patients with HA-CDI and 13,724 without CDI. Median age was 81.0 years (IQR 71.0–87.0). Patients with HA-CDI had more comorbidities than those without CDI, and significantly higher risks of mortality (adjusted hazard ratio (95% confidence interval) 1.77 (1.67–1.87)) and complications (1.66 (1.46–1.88)) within 12 months from hospital admission. Of those with HA-CDI, 1140 (16.6%) experienced CDI recurrence. Patients with recurrent versus non-recurrent CDI also had significantly increased risk of mortality (1.32 (1.20–1.45)) and complications (1.37 (1.01–1.84)) in the 12 months from the initial CDI.

**Conclusions:** HA-CDI (versus no CDI) and recurrent CDI are both associated with significantly higher risks of complications or death within 12 months of the initial CDI episode.

\* Corresponding author. Address: Clinical Microbiology & Public Health Laboratory, National Infection Service, Public Health England, Box 236, Addenbrookes Hospital, Hills Road, Cambridge, CB2 0QW, UK. Tel.: +44 1223 257035.

E-mail address: [david.enoch@addenbrookes.nhs.uk](mailto:david.enoch@addenbrookes.nhs.uk) (D.A. Enoch).

† Present address: School of Primary Care, Population Sciences and Medical Education, University of Southampton, UK.

## Introduction

*Clostridioides difficile* is a Gram-positive, spore-forming, anaerobic bacillus that is predominantly a nosocomial pathogen [1]. Traditional risk factors for infection include older age, hospital duration, prolonged use of antimicrobials, and use of immunosuppressive or gastric-suppressive medications [2–7]. Other risk factors include a history of inflammatory bowel disease (IBD), cystic fibrosis and diabetes [8].

*C. difficile* infection (CDI) is a major cause of morbidity and mortality in hospitalized patients [9,10]. Several studies have reported increased toxic megacolon, perforation and sepsis among patients with CDI [3,11–13]. Significantly higher risks of all-cause mortality have also been observed in the USA [14] and Europe [15,16]. In the UK, one study using surveillance data from Scotland estimated an almost three-fold increase in 30-day mortality [17], and another reported a 50% increased risk of death up to 5–8 years after hospital admission among patients with CDI at an English teaching hospital [18]. The incidence of CDI recurrence ranges from 11% to 33% and recurrence is also associated with higher patient mortality and complication rates [19–21], although lower mortality rates have been reported among patients with recurrent CDI compared with first episodes [22].

Although several studies have examined complications and mortality rates among patients with CDI, they were sometimes limited by small sample sizes [16,18], focused on either in-hospital [23,24] or post-discharge mortality [21], or did not include clinical information from outside the hospital setting [16–18,25]. Some studies were also restricted to populations from specialist centres or other clinical settings that may not be representative of wider groups of patients with CDI [20,21].

To overcome these issues, we conducted a frequency-matched, longitudinal, retrospective cohort study using data from hospitalized patients linked to a primary care database and a national death registry, to assess the risk of mortality and complications among patients with hospital-associated (HA)-CDI versus no CDI, between 1<sup>st</sup> January 2002 and 31<sup>st</sup> December 2013. We separately assessed the risk of all-cause mortality and complications in patients with recurrent CDI versus patients with non-recurrent CDI.

## Methods

### Data sources

Data were extracted from the UK Clinical Practice Research Datalink General Practitioner Online Data (CPRD GOLD), a longitudinal primary care electronic database of anonymized patient records, collected from a sample of general practices in the UK. Analyses were restricted to 380 practices in England with individual record linkage to Hospital Episode Statistics (HES) Admitted Patient Care (APC) data, which comprise admission and discharge dates plus information on clinical diagnoses and procedures collected from English hospitals [26]; the Office for National Statistics (ONS) database, which holds

data on the date and cause of death [27]; and/or the Index of Multiple Deprivation (IMD), which combines a number of economic and social indicators into a single deprivation score based on area of residence [28]. In the case of the IMD, which ranks areas relative to one another from 1 to 32, 844, the raw scores were categorized into quintiles, with 1 being the least deprived and 5 the most deprived. Analyses of primary outcomes were restricted to patients in CPRD GOLD eligible for linkage to both HES APC and ONS death data. For secondary outcomes where death was not evaluated, patients were required to be eligible for linkage to HES and IMD data only.

### Study population

The risk of mortality and complications among hospitalized patients with a first episode of HA-CDI was compared with frequency-matched (1:2) hospitalized patients without CDI. Recurrence was evaluated among the sub-cohort of patients with a first episode of HA-CDI. Only patients with  $\geq 6$  months of follow up during the study period were eligible for inclusion.

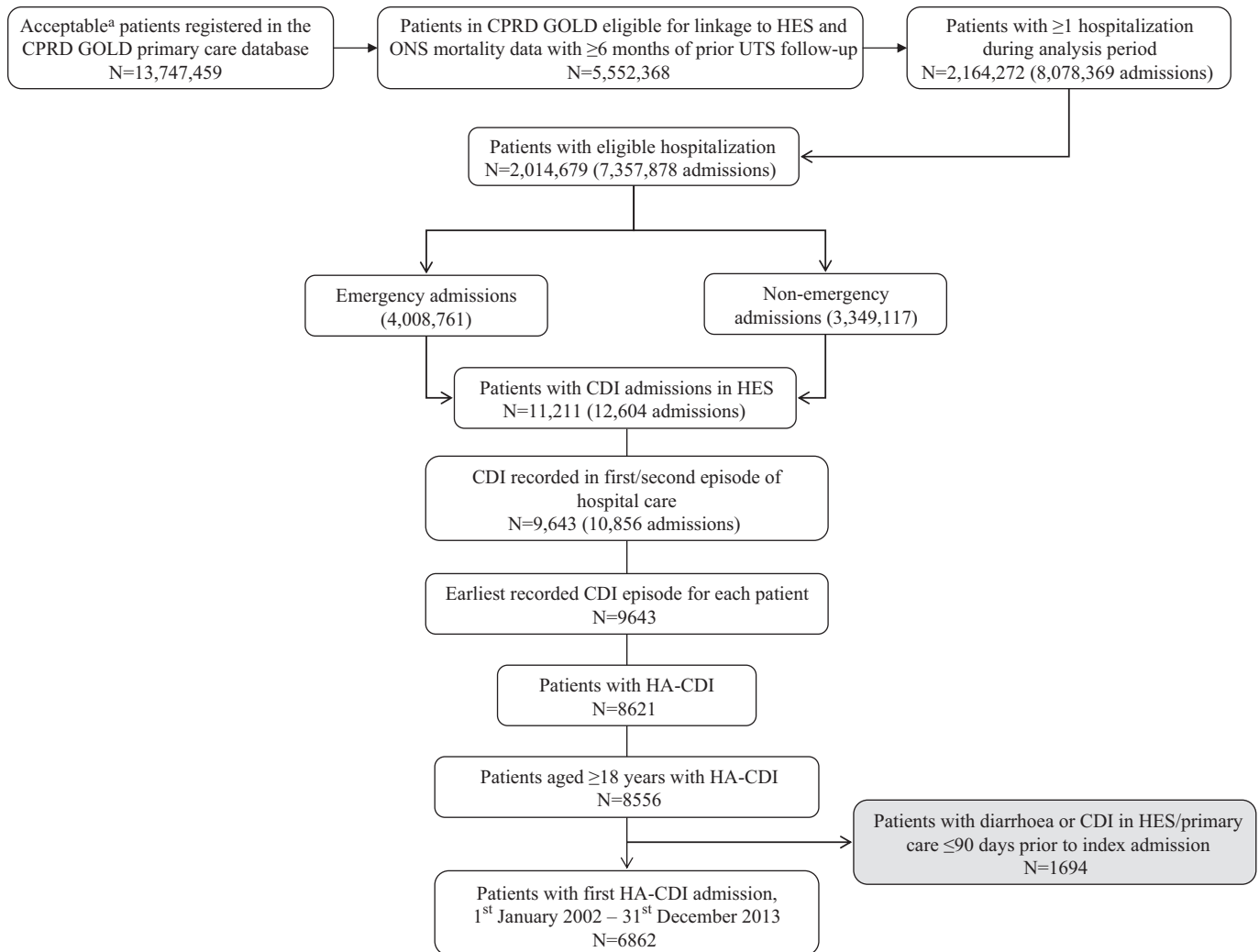
#### CDI case selection

Cases were patients with a diagnosis of HA-CDI recorded between 1<sup>st</sup> January 2002 and 31<sup>st</sup> December 2013. Eligible patients were aged  $\geq 18$  years at index hospital admission with  $\geq 1$  diagnosis of HA-CDI documented during their first or second episode of hospital care (periods during which a patient was under the care of a particular consultant [29]). Pregnancy-related admissions, between-hospital transfers and patients with a first CDI occurrence recorded in hospital care episode  $\geq 3$  were excluded.

Cases were ascertained based on ICD-10 (International Classification of Diseases 10th revision) A04.7 ‘*Enterocolitis due to Clostridium difficile*’ or related codes, recorded in HES APC data. HA-CDI was defined using an algorithm developed from previous work by Jen *et al.* [30], and was specified as a primary diagnosis of CDI (CDI recorded in the first hospital care episode and in the first diagnosis order) and a history of hospitalization within the preceding 4 weeks, or CDI recorded as a secondary diagnosis during the first or second episode of a hospital stay of  $>2$  days (Supplementary Figure S1). As the exact dates of clinical onset are not recorded in HES, the index date of the CDI episode was defined as the start of the care episode in which the CDI was recorded.

#### Control group selection

Cases were frequency matched to two hospitalized patients without CDI (unexposed patients) through random selection. Potential controls with CDI or diarrhoeal illness in HES or primary care up to 90 days prior to their index admission were excluded. Unexposed patients were selected to reflect the distribution of the case pool on the following parameters: calendar year of diagnosis, sex, age group, index admission method (emergency or non-emergency) and the number of hospital care episodes (one or more). The matched hospital care episode for each unexposed patient was randomly



**Figure 1.** Selection of cases with hospital-associated- (HA-) *Clostridioides difficile* infection (CDI) recorded in the first or second episode of hospital care. <sup>a</sup> Patients are considered acceptable by the Clinical Practice Research Datalink (CPRD) based on 15-point criteria that excludes patients with non-continuous follow up, or patients with poor data recording that raises suspicion as to the validity of those patients' records. GOLD, General Practitioner Online Data; HES, Hospital Episode Statistics; UTS, up-to-standard. Grey boxes indicate patients excluded from the dataset.

sampled to reflect the distribution of episodes in which CDI was recorded. The index date was defined as the start of the randomly selected care episode.

Recurrence of CDI was defined as a second CDI episode documented on days 13–56 inclusive, after the index episode. The date of CDI recurrence was defined as the start of the care episode in which the diagnosis was made. Otherwise, patients with a single record of CDI documented during the study period, with all CDI events recorded within 12 days of their first CDI episode or with their second CDI event recorded after day 56 were included in the non-recurrent CDI cohort. Follow-up time for these patients was censored at the date of their second CDI diagnosis.

### Outcomes

The primary outcome was time to all-cause mortality, up to 12 months, as evidenced by a record of death in the ONS mortality record. Only mortality events recorded during the patient's registration period at the practice were included.

Secondary outcomes were the time to first complication and time to the combined endpoint of complications or death, up to 12 months. Complications included ulcerative pancolitis, megacolon, intestinal perforation, toxic gastroenteritis/colitis, colectomy, renal failure and sepsis, and were identified using ICD-10 codes in HES or ONS mortality data, Read Codes in primary care, and/or Office of Population Censuses and Surveys procedure codes in hospital (Supplementary Table S1). Admission to augmented or critical care for any reason during the follow-up period was also classed as a complication. Events occurring prior to the index date were excluded.

### Study size

Assuming a cumulative risk of 21.5% for 1-year mortality among patients without diarrhoea and unexposed to CDI [31], 1571 patients with and without CDI would provide 90% power to detect a statistically significant difference between groups at a two-sided significance level of 0.05, if the real difference in 1-year mortality was  $\geq 5\%$ . Using a 1-year mortality rate of

15.3% among patients with non-recurrent CDI [32], 1228 patients with and without recurrent CDI would provide 90% power to detect a statistically significant difference between groups at a two-sided significance level of 0.05, if the real difference in mortality was  $\geq 5\%$ . We elected to use a ratio of 1:2 of cases to controls for any incremental power that this might add.

### Statistical analysis

Baseline characteristics were summarized using Chi-squared tests, *t*-tests and Mann–Whitney U-tests, where appropriate. Kaplan–Meier analysis was initially used to estimate the cumulative incidence function of time to mortality or complications up to 12 months. Cox proportional hazard regression models, with backward stepwise selection of candidate variables, were fitted to compare hazards of endpoints during the outcome periods. To assess the impact of immortal time bias [33], Cox regression models were alternatively specified with time-fixed or time-dependent covariates. For the comparison of HA-CDI versus no CDI, two models were used: CDI was specified as either a time-dependent or time-fixed covariate, the index date of CDI was set as the start of the CDI episode, and follow up was from either hospital admission or from the start of the CDI episode. The comparison of recurrent versus non-recurrent CDI used four different models, with CDI specified as either a time-dependent or time-fixed covariate; the index date of recurrent CDI specified as either the start of the recurrent episode or final CDI status; and follow up from either the episode start of the index CDI, day 13 (the start of the recurrence risk window) or day 57 (the end of the recurrence risk window). Tests for proportional hazards were undertaken visually using log–log plots and statistically by assessing Schoenfeld’s residuals. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported and two-sided *P*-values were calculated using the Wald test.

Adjustment factors measured at cohort entry using primary care and/or HES data included age in years, sex, body mass index, smoking history, alcohol use, history of comorbidities, drug therapies and socioeconomic deprivation category (Supplementary data). To further assess the robustness of our findings, we conducted sensitivity analyses taking the midpoint of the hospital care episode as the CDI index date (Supplementary Tables S2 and S3). The end of follow up was defined as the earliest of the following: practice last collection date, patient deregistration date, date of complication diagnosis or death, end of HES data collection, end of ONS mortality data collection, or study end.

All analyses were performed using STATA version 14.

### Ethics

CPRD has ethical approval for the collection and use of pseudonymized primary care records and linked data from the Health Research Authority Research Ethics Committee (reference number: 05/MRE04/87). The study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency, under protocol number 14\_187A3.

## Results

### Patient populations

Between 1<sup>st</sup> January 2002 and 31<sup>st</sup> December 2013, 5,552,368 patients registered in CPRD GOLD were eligible for linkage to HES and ONS data (Figure 1). Following the implementation of inclusion and exclusion criteria, 6862 patients met our definition of HA-CDI (Figure 1) and were matched to 13,724 hospitalized patients without CDI.

### Demographic and clinical characteristics

#### Patients with HA-CDI versus no CDI

The median age (interquartile range) of all participants was 81.0 (71.0–87.0) years; females comprised 59.0% (12,141/20,586) of patients. Compared with patients with no CDI, patients with HA-CDI had higher healthcare service use in the 12 months prior to CDI diagnosis, more recorded comorbidities (including a history of IBD and diabetes mellitus), and more antibiotics prescribed in the 90 days prior to admission (Table I). Higher prior use of proton-pump inhibitors and more admissions to augmented or intensive care were also observed (Table I).

#### Patients with recurrent CDI versus non-recurrent CDI

Within the HA-CDI sub-cohort, 16.6% (1140/6862) of patients had a recurrent CDI episode during days 13–56. Notably, patients with recurrent CDI had a longer index hospital stay and were more likely to have had an emergency index hospital admission (Table I). A history of hypertension, renal disease, moderate/severe liver disease and use of lipid-lowering therapy were also more commonly documented among those with recurrent CDI (Table I). A history of malignant cancer (up to 5 years prior to the index CDI diagnosis) and dementia were more prevalent in the non-recurrent CDI group (Table I).

### Twelve-month risk of death or complications

#### Patients with HA-CDI versus no CDI

There were 3427/6862 (49.9%) and 4146/13,724 (30.2%) deaths among patients with and without CDI, respectively, at 12 months from the initial hospital care episode ( $P < 0.001$ ) (Table II). In the time-dependent and time-fixed analyses, the adjusted HRs for death among patients with HA-CDI versus no CDI were 1.77 (95% CI: 1.67, 1.87) and 1.55 (95% CI: 1.47, 1.64), respectively (Table III).

Similarly, significantly more patients with HA-CDI experienced complications up to 12 months following index hospital admission, compared with patients with no CDI ( $P < 0.001$ ) (Table II). The adjusted HR from time-dependent analysis for complications in the group of patients with HA-CDI versus no CDI was 1.66 (95% CI: 1.46, 1.88) (Table III).

#### Patients with recurrent versus non-recurrent CDI

There were 564 (49.5%) and 2737 (47.8%) deaths among patients with recurrent and non-recurrent CDI, respectively, at 12 months from the initial hospital care episode (Table II). When evaluating the risk of death from the start of the initial CDI episode, the incidence of mortality at  $\leq 30$  days and  $\leq 90$  days was significantly lower in patients with recurrent CDI and

Table 1

Baseline characteristics of patients with hospital-associated- (HA-) *Clostridioides difficile* infection (CDI) and no CDI, and patients with recurrent and non-recurrent CDI

	HA-CDI and no CDI cohort <sup>a</sup>			P	Recurrent CDI and non-recurrent CDI cohort <sup>b</sup>			
	HA-CDI (N=6862)	No CDI (N=13,724)	Total (N=20,586)		Recurrent CDI (N=1140)	Non-recurrent CDI (N=5722)	Total (N=6862)	P
<b>Baseline characteristics</b>								
Age in years, median (IQR)	81.0 (72.0–87.0)	81.0 (71.0–87.0)	81.0 (71.0–87.0)	0.092	81.0 (72.0–87.0)	81.0 (72.0–87.0)	81.0 (72.0–87.0)	0.688
Female	4047 (59.0)	8094 (59.0)	12,141 (59.0)	1.000 <sup>c</sup>	678 (59.5)	3369 (58.9)	4047 (59.0)	0.709
<b>BMI</b>								
Median (IQR)	25.4 (22.2–29.1)	25.4 (22.5–28.9)	25.4 (22.4–28.9)	0.381	25.5 (22.1–29.1)	25.4 (22.2–29.2)	25.4 (22.2–29.1)	0.901
Unknown	1382 (20.1)	2761 (20.1)	4143 (20.1)		222 (19.5)	1160 (20.3)	1382 (20.1)	
<b>Smoking status</b>								
Non-smoker	2659 (38.7)	5772 (42.1)	8431 (41.0)	<0.001	420 (36.8)	2239 (39.1)	2659 (38.7)	0.513
Ex-smoker	2679 (39.0)	4917 (35.8)	7596 (36.9)		468 (41.1)	2211 (38.6)	2679 (39.0)	
Smoker	1136 (16.6)	2173 (15.8)	3309 (16.1)		205 (18.0)	931 (16.3)	1136 (16.6)	
Unknown	388 (5.7)	862 (6.3)	1250 (6.1)		222 (19.5)	1160 (20.3)	1382 (20.1)	
<b>Drinking status</b>								
Non-drinker	1010 (14.7)	1852 (13.5)	2862 (13.9)	<0.001	163 (14.3)	847 (14.8)	1010 (14.7)	0.513
Ex-drinker	769 (11.2)	1321 (9.6)	2090 (10.2)		122 (10.7)	647 (11.3)	769 (11.2)	
Drinker	3867 (56.4)	8005 (58.3)	11 872 (57.7)		667 (58.5)	3200 (55.9)	3867 (56.4)	
Unknown	1216 (17.7)	2546 (18.6)	3762 (18.3)		188 (16.5)	1028 (18.0)	1216 (17.7)	
<b>Socioeconomic deprivation level<sup>d</sup></b>								
1	1200 (17.5)	2787 (20.3)	3987 (19.4)	<0.001	210 (18.4)	990 (17.3)	1200 (17.5)	0.704
2	1590 (23.2)	3284 (23.9)	4874 (23.7)		262 (23.0)	1328 (23.2)	1590 (23.2)	
3	1396 (20.3)	2892 (21.1)	4288 (20.8)		215 (18.9)	1181 (20.6)	1396 (20.3)	
4	1416 (20.6)	2586 (18.8)	4002 (19.4)		237 (20.8)	1179 (20.6)	1416 (20.6)	
5	1249 (18.2)	2151 (15.7)	3400 (16.5)		215 (18.9)	1034 (18.1)	1249 (18.2)	
Unknown	11 (0.2)	24 (0.2)	35 (0.2)		1 (<0.1)	10 (0.2)	11 (0.2)	
<b>Current or prior comorbidities</b>								
Diabetes mellitus <sup>e</sup>	1369 (20.0)	1979 (14.4)	3348 (16.3)	<0.001	247 (21.7)	1130 (19.7)	1377 (20.1)	0.140
Hypertension <sup>e</sup>	5036 (73.4)	9172 (66.8)	14 208 (69.0)	<0.001	864 (75.8)	4172 (72.9)	5036 (73.4)	0.045
Inflammatory bowel disease <sup>e</sup>	214 (3.1)	81 (0.6)	295 (1.4)	<0.001	44 (3.9)	176 (3.1)	220 (3.2)	0.170
Renal disease <sup>e</sup>	2386 (34.8)	3163 (23.0)	5549 (27.0)	<0.001	440 (38.6)	1993 (34.8)	2433 (35.5)	0.015
Cerebrovascular accident <sup>e</sup>	1910 (27.8)	3249 (23.7)	5159 (25.1)	<0.001	349 (30.6)	1625 (28.4)	1974 (28.8)	0.131
Moderate-to-severe liver disease <sup>e</sup>	158 (2.3)	88 (0.6)	246 (1.2)	<0.001	40 (3.5)	132 (2.3)	172 (2.5)	0.018
Peripheral vascular disease <sup>e</sup>	1076 (15.7)	1418 (10.3)	2494 (12.1)	<0.001	191 (16.8)	899 (15.7)	1090 (15.9)	0.379
Dementia <sup>e</sup>	850 (12.4)	1694 (12.3)	2544 (12.4)	0.928	125 (11.0)	758 (13.2)	883 (12.9)	0.036
Malignant cancer ≤5 years previously	1485 (21.6)	1781 (13.0)	3266 (15.9)	<0.001	213 (18.7)	1299 (22.7)	1512 (22.0)	0.003
Transplantation ≤24 months previously	87 (1.3)	15 (0.1)	102 (0.5)	<0.001	14 (1.2)	75 (1.3)	89 (1.3)	0.822
<b>Medication prescriptions ≤90 days previously</b>								
Any antibiotic	2749 (40.1)	3961 (28.9)	6710 (32.6)	<0.001	478 (41.9)	2254 (39.4)	2732 (39.8)	0.110
Lipid-lowering drugs	1904 (27.7)	3492 (25.4)	5396 (26.2)	<0.001	344 (30.2)	1547 (27.0)	1891 (27.6)	0.030
Immunosuppressants excluding hydrocortisone and prednisolone	59 (0.9)	27 (0.2)	86 (0.4)	<0.001	9 (0.8)	50 (0.9)	59 (0.9)	0.778
Hydrocortisone and/or prednisolone	788 (11.5)	1023 (7.5)	1811 (8.8)	<0.001	137 (12.0)	649 (11.3)	786 (11.5)	0.513
Proton-pump inhibitors	2285 (33.3)	2806 (20.4)	5091 (24.7)	<0.001	382 (33.5)	1888 (33.0)	2270 (33.1)	0.737
Glucocorticoids	804 (11.7)	1041 (7.6)	1845 (9.0)	<0.001	139 (12.2)	663 (11.6)	802 (11.7)	0.561

(continued on next page)

Table 1 (continued)

	HA-CDI and no CDI cohort <sup>a</sup>		Recurrent CDI and non-recurrent CDI cohort <sup>b</sup>				
	HA-CDI (N=6862)	No CDI (N=13,724)	Total (N=20,586)	Recurrent CDI (N=1140)	Non-recurrent CDI (N=5722)	Total (N=6862)	P
<b>Health service use ≤12 months previously</b>							
GP consultations, mean (SD)	17.2 (15.4)	12.3 (11.7)	13.9 (13.2)	17.8 (15.8)	17.1 (15.4)	17.3 (15.4)	0.537
≥2 prior hospitalizations	2926 (42.6)	2124 (15.5)	5050 (24.5)	574 (50.4%)	2809 (49.1%)	3383 (49.3%)	0.032
<b>Index hospitalization</b>							
Duration of hospital stay, median (IQR)	28.0 (15.0–50.0)	6.0 (1.0–15.0)	11.0 (3.0–28.0)	39.0 (24.0–62.0)	26.0 (14.0–47.0)	28.0 (15.0–50.0)	<0.001
Emergency admission	5832 (85.0)	11,664 (85.0)	17,496 (85.0)	997 (87.5)	4835 (84.5)	5832 (85.0)	0.011
Augmented/intensive care <sup>f</sup>	234 (3.4)	119 (0.9)	353 (1.7)	44 (3.9)	229 (4.0)	273 (4.0)	0.822

BMI, body mass index; GP, general practitioners; IQR, interquartile range; SD, standard deviation. Data are N (%) unless otherwise given.

<sup>a</sup> Characteristics were assessed for the specified duration prior to index hospital admission.

<sup>b</sup> Characteristics were assessed for the specified period prior to the index HA-CDI episode.

<sup>c</sup> Patients with no CDI were matched to those with HA-CDI for this parameter.

<sup>d</sup> Grouping based on Index of Multiple Deprivation scores, with 1 being the least deprived and 5 the most deprived.

<sup>e</sup> At any time previously.

<sup>f</sup> Assessed from admission to index date.

the difference in mortality at ≤365 days was not significant (Table II). Adjusted time-fixed analyses showed a seemingly implausible protective effect of recurrence on 12-month mortality (HR: 0.88, 95% CI: 0.80, 0.96) (Table III). When immortal time was correctly classified (Figure 2), 12-month survival was higher in those with non-recurrent CDI versus recurrent CDI (HR: 1.32, 95% CI: 1.20, 1.45) (Table III).

The incidence of complications (excluding death) up to 90–365 days from the start of the initial care episode was significantly higher ( $P \leq 0.005$ ) in patients with recurrent CDI (Table II). The adjusted HR for complications excluding death, up to 12 months from the start of the initial care episode, was 1.37 (95% CI: 1.01, 1.84) (Table III).

Results of further sensitivity analyses, with outcomes assessed from the midpoint of the initial hospital care episode, are included in the Supplementary data).

## Discussion

We conducted a retrospective study of patients hospitalized in England with a first episode of CDI and observed that the risk of 12-month mortality and complications was significantly higher compared with matched hospitalized patients with no evidence of CDI, a finding supported by previous research [14,17,23,34–36]. Interestingly, in a study of CDI in Scotland [17], the 30-day all-cause mortality rate of 17.5% was similar to the rate we observed in England (16.3%), despite the use of differing time periods and database methodology. Additionally, mortality and complications were increased significantly in patients with recurrent CDI compared with non-recurrent CDI, findings which align with earlier research in the USA [19,21]. It is, however, important to note that our study population was older and had more comorbidities than some populations studied in North America [19,20,35] and Europe [31]. This age difference is similar to findings from studies of fidaxomicin for the treatment of CDI, in which the median age in the UK was 70–81 years [37] whilst in North America and Europe, the mean age was 61–63 years [38,39].

We also found a higher frequency of risk factors recorded among CDI cases: more comorbidities, more patients with prior prescriptions of antibiotics and/or proton-pump inhibitors, a greater incidence of hospitalization within the previous 12 months, and significantly higher use of augmented or intensive care; these results are also consistent with previous studies [40–44]. The finding that lipid-lowering drugs had a statistically significant risk for CDI is novel and requires further study, although the difference is small. Among patients with CDI, we also found higher rates of hypertension, renal disease, moderate-to-severe liver disease, IBD and malignant cancer, compared with patients with no CDI. Conversely, the incidence of IBD was not significantly higher among patients with recurrent versus non-recurrent CDI, and the rate of malignant cancer was significantly higher in the non-recurrent CDI group. Hypertension, renal disease, liver disease and malignant cancer have been found to be associated with recurrence in previous studies [45–49]. The reason for the higher rate of malignant cancer among patients with non-recurrent CDI in our study needs to be further explored and may be due to the methodology used in the definition of the recurrence window, which is a particular challenge in this type of large database study, or the immortal time bias already described.

**Table II**  
Incidence of death or complications in patients with *Clostridioides difficile* infection (CDI)

Outcome	Time to outcome	HA-CDI versus no CDI			Recurrent CDI versus non-recurrent CDI		
		HA-CDI (N=6862)	No CDI (N=13,724)	P	Recurrent CDI (N=1,140)	Non-recurrent CDI (N=5,722)	P
Death <sup>a</sup> , N (%)	≤30 days	1117 (16.3)	2041 (14.9)	0.008	87 (7.6)	1102 (19.3)	<0.001
	≤90 days	2535 (36.9)	3094 (22.5)	<0.001	381 (33.4)	2164 (37.8)	0.005
	≤180 days	3076 (44.8)	3613 (26.3)	<0.001	492 (43.2)	2494 (43.6)	0.790
	≤365 days	3427 (49.9)	4146 (30.2)	<0.001	564 (49.5)	2737 (47.8)	0.311
Complications <sup>b</sup> , N (%)	≤30 days	1227 (17.9)	1009 (7.4)	<0.001	183 (16.1)	868 (15.2)	0.450
	≤90 days	1353 (19.7)	1096 (8.0)	<0.001	226 (19.8)	940 (16.4)	0.005
	≤180 days	1436 (20.9)	1164 (8.5)	<0.001	241 (21.1)	996 (17.4)	0.003
	≤365 days	1486 (21.7)	1240 (9.0)	<0.001	249 (21.8)	1036 (18.1)	0.003
Complications <sup>b</sup> or death <sup>a</sup> , N (%)	≤30 days	2032 (29.6)	2639 (19.2)	<0.001	247 (21.7)	1690 (29.5)	<0.001
	≤90 days	3251 (47.4)	3620 (26.4)	<0.001	520 (45.6)	2628 (45.9)	0.846
	≤180 days	3742 (54.5)	4137 (30.1)	<0.001	615 (53.9)	2943 (51.4)	0.121
	≤365 days	4055 (59.1)	4668 (34.0)	<0.001	682 (59.8)	3173 (55.5)	0.007

Follow up was from the start of the initial hospital care episode. CDI, *Clostridioides difficile* infection; CPRD, Clinical Practice Research Datalink; GOLD, General Practitioner Online Data; HA, hospital-associated; HES, Hospital Episode Statistics.

<sup>a</sup> Ascertained using death registration recorded in Office of National Statistics mortality data.

<sup>b</sup> Evaluated using primary care (CPRD GOLD), hospital (HES) and Office of National Statistics mortality data. Complications included ulcerative pancolitis, megacolon, intestinal perforation, toxic gastroenteritis/colitis, colectomy, renal failure and sepsis (Supplementary Table S1).

Strengths of this study include its use of objective death data from the ONS mortality registry to confirm vital status and its inclusion of both primary and secondary care data in risk factor and covariate definitions. This is likely to have increased outcome ascertainment in our study, as well as the accuracy and completeness of data on baseline characteristics and covariates. Our study also provides insights on the risk of outcomes in both the early and later periods following CDI diagnosis by taking account of all deaths recorded up to 12 months.

Sensitivity analyses to assess the robustness of our findings offered insights into some of the methodological issues involved in the use of real-world data for infectious disease epidemiology. For example, comparison of the mortality incidence between recurrent and non-recurrent CDI groups showed that patients with recurrent CDI had significantly lower mortality up to 90 days from the start of initial hospitalization, than those with non-recurrent CDI. This can be explained by the effects of immortal time bias: by definition, patients with recurrent CDI would need to survive long enough to experience a second CDI episode 13–56 days after the first. Similarly, our time-fixed analyses showed that recurrent CDI was protective regarding the 12-month risk of death. However, this implausible benefit was invalidated once immortal time was correctly classified by following patients from the start of the recurrence window in a time-dependent analysis or from the end of the recurrence risk window in a time-fixed analysis. In contrast with mortality, the occurrence of a non-fatal complication does not preclude a recurrent CDI episode, and the 12-month risk of complications were thus more frequently observed in the group with recurrent CDI versus non-recurrent CDI, regardless of the analyses used.

One limitation of this study was that some patients in our primary and secondary analyses may have been incorrectly classified as CDI-positive due to the lack of laboratory confirmation of infection. Secondly, a precise onset or CDI diagnosis date was not available for either the primary or recurrent episode of CDI, as clinical data in the HES database

are grouped into episodes of care rather than presented as separate encounters [29]. This limitation may have led to misclassification of initial CDI or recurrence status, and/or an inaccurate time to event in the survival analysis. Given this important limitation, throughout our study we selected analysis parameters that would provide more conservative estimates of the effect of CDI exposure on outcomes. Thirdly, the CPRD GOLD and HES databases lack information on some important factors, such as disease severity, infection strain, metabolic changes associated with CDI, severity of comorbidities and prescribing in the secondary care setting, which may introduce residual confounding. It is, however, reasonable to assume that some factors may be non-differentially distributed between exposure and comparison groups. Additionally, location and organizational information such as hospital provider codes or hospital ward are not routinely available in the HES data collected by CPRD, to minimize the potential risk of patient re-identification. Hospital and ward information was therefore not used as a matching parameter for cases and controls. Instead, we opted to take account of whether patients were admitted for emergency or elective procedures as a proxy for the severity of the patient condition at the time of admission. There is also no linkage from HES to microbiology data or outbreak surveillance systems, so we were unable to account for impact of local outbreaks. For the CDI versus no CDI analysis, we matched on year of admission, and for the recurrent CDI versus CDI analysis, we adjusted for year of admission, in an attempt to mitigate the impact of large national outbreaks or important temporal trends. Lastly, in the absence of objective laboratory or pathology evidence to link CDI to cause of death, it was not possible to estimate the proportion of deaths attributable to CDI; given this, we assessed all-cause mortality up to 12 months to capture both short and longer term, and direct and indirect effects of CDI.

In summary, this study draws on a substantial body of data from routine clinical practice to demonstrate that patients who

**Table III**

Twelve-month risk of death or complications for patients with hospital-associated- (HA-) *Clostridioides difficile* infection (CDI) versus no CDI and for recurrent CDI versus non-recurrent CDI

Model	CDI covariate specification	Index date of CDI	Start of follow up	Death <sup>a</sup>		Complications <sup>b</sup>		Complications <sup>b</sup> or death <sup>a</sup>	
				Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
HA-CDI versus no CDI									
1	Time-dependent	Start of CDI episode	Hospital admission	1.96 (1.87–2.06)*	1.77 (1.67–1.87)*	1.80 (1.58–2.03)*	1.66 (1.46–1.88)*	1.99 (1.89–2.08)*	1.75 (1.65–1.86)*
2	Time-fixed	Start of CDI episode	Start of CDI/selected hospital care episode	1.77 (1.69–1.85)*	1.55 (1.47–1.64)*	3.27 (3.00–3.56)*	3.36 (3.06–3.68)*	2.05 (1.96–2.14)*	1.88 (1.78–1.98)*
Recurrent CDI versus non-recurrent CDI									
3	Time-dependent	Start of recurrent episode	Episode start of the index CDI	1.37 (1.25–1.50)*	1.32 (1.20–1.45)*	1.37 (1.02–1.85)*	1.37 (1.01–1.84)*	1.40 (1.26–1.54)*	1.36 (1.22–1.50)*
4	Time-dependent	Start of recurrent episode	Day 13 (start of recurrence risk window) <sup>c</sup>	1.37 (1.25–1.50)*	1.34 (1.22–1.47)*	1.37 (1.02–1.85)*	1.35 (1.00–1.83)*	1.40 (1.26–1.54)*	1.36 (1.23–1.50)*
5	Time-fixed	Final CDI status <sup>d</sup>	Day 57 (end of the recurrence risk window) <sup>c</sup>	1.45 (1.27–1.64)*	1.40 (1.23–1.59)*	1.39 (0.95–2.02)	1.34 (0.91–1.95)	1.50 (1.31–1.71)*	1.46 (1.27–1.67)*
6	Time-fixed	Final CDI status <sup>d</sup>	Episode start of the index CDI	0.91 (0.83–1.00)*	0.88 (0.80–0.96)*	1.18 (1.03–1.36)*	1.17 (1.02–1.34)*	1.01 (0.93–1.10)	0.99 (0.91–1.08)

CDI, *Clostridioides difficile* infection; CPRD, Clinical Practice Research Datalink; GOLD, General Practitioner Online Data; HES, Hospital Episode Statistics; HR, hazard ratio. Recurrent CDI was defined as a second CDI episode diagnosed on days 13–56.

P<0.05 for comparison.

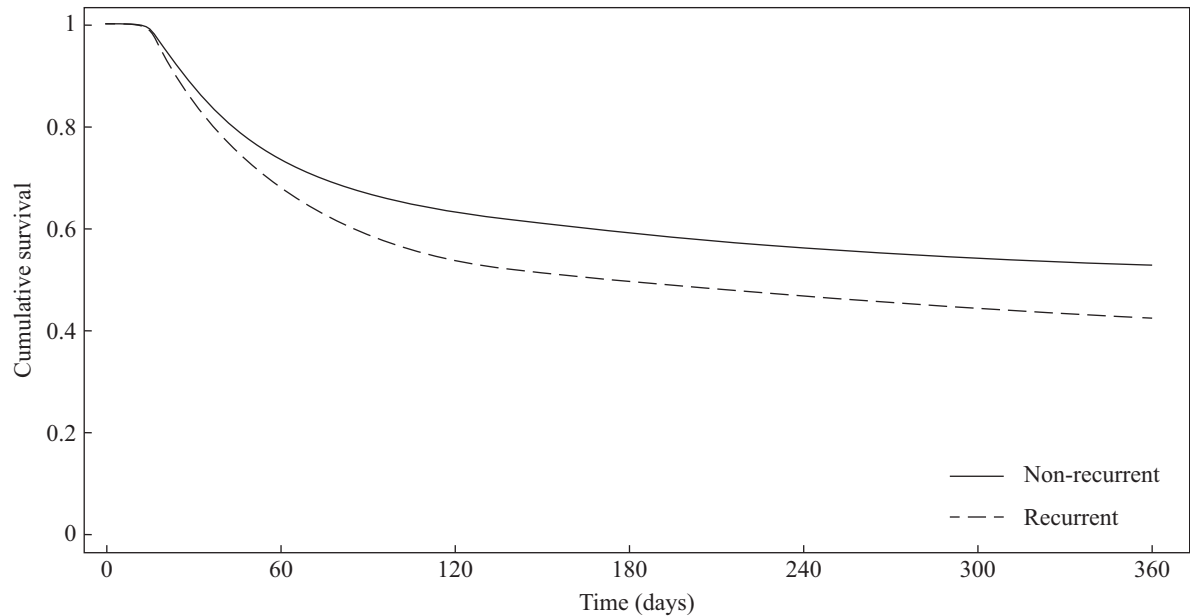
<sup>a</sup> Ascertained using death registration recorded in Office of National Statistics mortality data.

<sup>b</sup> Evaluated using primary care (CPRD GOLD), hospital (HES) and Office of National Statistics mortality data. Complications included ulcerative pancolitis, megacolon, intestinal perforation, toxic gastroenteritis/colitis, colectomy, renal failure and sepsis (Supplementary Table S1).

<sup>c</sup> As evaluated from the date of index CDI.

<sup>d</sup> Defined as ever having a diagnosis of CDI (yes or no) during the study period.





Number at risk		0	60	120	180	240	300	360
Non-recurrent		0	3684	2826	2489	2299	2157	2052
Recurrent		0	872	631	540	487	445	420

**Figure 2.** Twelve-month mortality, assessed from the start of the *Clostridioides difficile* infection (CDI) recurrence window, among patients with recurrent and non-recurrent CDI. Recurrent CDI was defined as a second CDI episode documented on days 13–56 inclusive. Time to death was assessed from the start of the CDI recurrence window at day 13. The date of recurrence was defined as the start of the hospital episode in which the recurrent CDI episode was identified.

have CDI during their hospital stay have higher mortality rates than patients who do not. Among patients who have HA-CDI, those with recurrent CDI are at greater risk of complications or death than those with non-recurrent CDI. Our data provide a comprehensive picture of the impact of CDI in England, and highlight the importance of preventing and managing initial and recurrent episodes of CDI.

## Acknowledgements

This study was funded by Astellas Pharma Europe Ltd. We wish to thank Reiner Tretter, statistician at Astellas Pharma Inc. at the time of this study, for his contribution to the analysis and Iona Easthope, DPhil, of Cello Health MedErgy for medical writing services. Previous presentations: oral presentation at the 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 25<sup>th</sup>–28<sup>th</sup> April 2015, Copenhagen, Denmark; e-poster at the 27th ECCMID, 22<sup>nd</sup>–25<sup>th</sup> April 2017, Vienna, Austria.

## Author contributions

D.A.E., T.M-T., N.A., D.D., N.F. and A.K. were involved in the concept and design of the study. T.M-T., N.A., D.D., A.G. and A.K. were involved in the acquisition, analysis and/or interpretation of the data. All authors participated in drafting the manuscript and its critical revisions for important intellectual content. All authors approved the final submitted article.

## Conflict of interest statement

D.A.E. has received fees for conference attendance from Astellas Pharma, Eumedica, Pfizer, Gilead and MSD, and for consultancy work from Cardiome. T.M-T. and D.D. are full-time employees of CPRD, which provides contract research services and which received payment from Astellas Pharma for work on the study. N.A. and A.G. were full-time employees of Astellas Pharma at the time of the study. A.K. was a full-time employee of Astellas Pharma at the time of the study, and has patents WO2015169451 A1 and EP17167541.6 pending, which are licenced to Astellas Pharma.

## Funding sources

This research study and medical writing services were funded by Astellas Pharma Europe Ltd. Astellas Pharma Europe Ltd. was involved in the study design; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the article for publication.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhin.2020.09.025>.

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