**Comparative Epidemiology of *Clostridium difficile* Infection in England and the US**

1Alice King PhD†

2Benjamin H Mullish MBBChir MRCP

2Horace RT Williams MBBS PhD FRCP\*

1Paul Aylin MBChB FFPH\*

1 Dr Foster Unit at Imperial College London, 3 Dorset Rise London, EC4Y 8EN, UK

2 Division of Digestive Diseases, Department of Surgery and Cancer, Faculty of Medicine, St Mary’s Hospital Campus, Imperial College London, South Wharf Road, London W2 1NY, UK \*Joint senior authors † Corresponding author.

Dr Foster Unit at Imperial College, 3 Dorset Rise, London EC4Y 8EN, UK. Tel: +44 (0)20 7332 8864. Fax: +44 (0) 20 7332 8888. alice.king@imperial.ac.uk

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**Abstract**

**Objective:** To examine whether there is an epidemiological difference between *Clostridium difficile* infection (CDI) inpatient populations in England and the United States.

**Design:** A cross-sectional study.

**Setting:** National administrative inpatient discharge data from England (Hospital Episode Statistics) and the United States (National Inpatient Sample) in 2012.

**Participants:**  De-identifiable non-obstetric inpatient discharges from the national datasets were used to estimate national CDI incidence in the United States and England using ICD9-CM(008.45) and ICD10(A04.7) respectively.

**Main outcome measures:** The rate of CDI was calculated per 100,000 population using national population estimates. Rate per 100,000 inpatient discharges was also calculated separated by primary and secondary diagnosis of CDI. Age, sex and Elixhauser comorbidities profiles were examined.

**Results:** The US had a higher rate of CDI compared to England: 115.1/100,000 vs. 19.3/100,000 population (p<0.001). CDI age profiles differed between the countries (p<0.001): in England, patients ≥75years constitute a larger proportion of CDI cases, whilst those aged 25-70 constitute more cases in the US(p<0.001). Overall adjusted odds of CDI in females compared to males was elevated in both England (OR1.26 95%CI[1.21,1.31] p<0.001) and the US (OR1.20 95%CI[1.18,1.22] p<0.001). The proportion of CDI patients with comorbidities was greater in the US compared to England apart from dementia, which was greater in England (9.63% vs. 1.25%,p<0.0001).

**Conclusions:** The 2012 inpatient CDI rate within the US was much higher than in England. Age and co-morbidity profiles also differed between CDI patients in both countries. The reasons for this are likely multi-factorial but may reflect national infection control policy.

**Keywords:** Clostridium difficile; gastrointestinal microbiome; incidence; infection control; comorbidity

**Introduction**

*Clostridium difficile* infection (CDI) remains the predominant cause of healthcare-associated gastrointestinal infection and causes significant morbidity and mortality [1]. A number of factors contribute to the global healthcare challenge of CDI. Firstly, a significant rise in rates of severe CDI began approximately 15 years ago in high-income countries [2]. Furthermore, whilst the conventional therapies for CDI (with the antibiotics vancomycin or metronidazole) are well-established, such treatment is not universally effective. Reasons for this include a rise in rates of metronidazole failure [3], along with an increasing recognition of the problem of recurrent CDI [4]. Therefore, novel therapeutic strategies are required. One such treatment that has come to prominence recently has been faecal microbiota transplantation (FMT) [1,5]. Randomised trial evidence demonstrates FMT to be a much more efficacious treatment for recurrent/refractory CDI than conventional antibiotic treatment [6, 7]. Furthermore, the use of FMT for this indication has now been approved in England by NICE [8], and in national [9] and international guidelines [10].

 The general experience of clinicians caring for people affected by CDI in England is that affected people often have many typical risk factors. Specifically, they tend to be very old, with multiple co-morbidities, and often require care within a hospital or institutional setting. The only cohort of patients with recurrent CDI treated with FMT reported from the UK [11] described a cohort similar to that familiar to UK clinicians, with median age 81.5 years, multiple comorbidities, and >70% of the cohort being inpatients at the time of receiving FMT (the rest of the cohort had been recent inpatients). However, cohorts with recurrent CDI treated with FMT reported from elsewhere in Europe [6,7,12] and North America [13-15] have a markedly different epidemiological profile to the UK cohort. Those affected people appear much younger, with fewer comorbidities, and are often ambulatory. One explanation for this finding may be inclusion bias (i.e. in countries with high prevalence rates of CDI such as the US, investigators may be more selective about inclusion into FMT trials), but there are no data to support this.

Given these striking observations, we hypothesised that there was a true epidemiological difference between the population with CDI in England and the US. We used routinely-collected administrative data from both countries to investigate this.

**Methods**

Study design and Setting

A cross-sectional retrospective study was performed using national discharge data from National Inpatient Sample (NIS) in the US and Hospital Episode Statistics (HES) in England. HES and NIS represent national de-identifiable administrative databases for hospital inpatient discharges in England and the US respectively. The most up-to-date complete year of data available for analyses was used (2012).

The NIS is a Healthcare Cost and Utilization Project (HCUP) publically available database sponsored by Agency for Healthcare Research and Quality (AHRQ). It is an all-payer stratified inpatient sample of approx. 20% hospital inpatient discharges (excludes rehabilitation and long-term care hospitals) in participating states. It is self-weighting to produce estimates representing 95% of the US population.

The use of NIS data is held with data agreement with HCUP AHRQ. All authors responsible for the data had performed the required training and certification for use of NIS data and this project was approved by HCUP. De-identified HES data were acquired from HSCIC which is a national administrative database of all discharges from NHS hospitals in England. The principal investigator has approval from the Secretary of State and the Health Research Authority under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to hold confidential data and analyse them for research purposes (CAG 15/CAG/0005) with approval to use them for research and measuring quality of delivery of healthcare, from the London - South East Ethics Committee (REC 15/LO/0824).

Data and variables

CDI was identified in the US and England using ICD9-CM (008.45) and ICD10 (A04.7) respectively. Principal/primary diagnosis is the predominant condition treated/ investigated in that period of healthcare. Secondary diagnoses are concurrent/new conditions during the hospital period. Obstetric cases were omitted. In processed NIS data, age is grouped into infants under 1 year (0) and then 5 year bands (1-4, 5-9, 10-14…≥90); these were applied to HES data for comparisons. Population estimates for use with NIS data in the US used ≥85 as one group instead of 85-89 and >90 years; therefore this was applied to both countries for population estimates. Rates per population were calculated for each country by using population estimates for the denominators. Elixhauser comorbidities consistently coded in both countries were applied to the data using standard ICD9-CM and ICD10 codes [18].

Statistical analyses

Risk adjusted models included the age and sex. Univariate analyses were performed with χ2. Proc surveyfreq and proc survey logistic in SAS (V.9.3forWindows©2011SAS Institute Inc.Cary,NC,USA) were used for NIS data to estimate national rates and adjust for sex to produce age specific odds ratios (OR). Weights and stratum were provided in the dataset. Logistic regression was used for England to produce age specific OR in unweighted HES data.

**Results**

There were 13,371,542 inpatient discharges in 2012 in England (HES), and the rate of CDI was 19.3/100,000 population. In the US (NIS-weighted sample), there were 32,296,255 inpatient discharges in 2012; the rate of CDI was 115.11/100,000 population.

The US had a higher rate of CDI overall (OR14.9 95%CI[13.8-16.1]p<0.001) compared to England (Figure 1a). In England, apart from a peak in infants, the rate stayed relatively constant as age increased starting to increase at ~50-55 years until it exceeded 100/100,000 population at age >75-79 years (Figure 1a & 1b). Those ≥85 years had the highest CDI rate of all age groups in both England (207.8/100,000 population) and the US (1049.0/100,000 population); compared to younger ages; (p<0.001)(Figure 1a & 1c).

The proportion of CDI cases by age was significantly different between the countries (Figure 2)(p<0.001). The only ages that did not differ in the proportion of CDI cases between the two countries were those 15-24 years. Young children contribute a greater proportion of the overall CDI cases in England compared to the US (p<0.001). Those ≥75 years in England contribute more to overall CDI cases than in the US (p<0.001). In the US, those aged 25-70 years contribute a larger proportion of CDI cases than England (p<0.001). Comorbidities that are consistently coded are shown in Table 1. Proportions of these comorbidities in patients with CDI were greater in the US compared to England apart from dementia, which was greater in England (9.63% vs. 1.25%, p<0.0001).

The overall adjusted odds of a CDI diagnosis being made in females vs. males was elevated in both England (OR1.26 95%CI[1.21,1.31]p<0.001) and the US (OR1.20 95%CI[1.18,1.22]p<0.001). Sex differences predominantly occurred in those with a primary diagnosis of CDI compared to those with secondary diagnoses of CDI (Figure 3a and b). Rates of CDI per 100,000 inpatient discharges for those with a primary diagnosis in the US were significantly greater in females than males for ages 14-89 years, with OR from 1.5 to 1.8 p<0.001; females aged ≥90 years compared to males (OR1.16 95%CI [1.04, 1.29] p=0.008)(Figure 3a). Rates of CDI per 100,000 inpatient discharges as secondary diagnoses were more consistent across sexes in the US and differed only for ages 1-4 years and those aged 60-84 years (p<0.05) (Figure 3c). In England, females with a primary diagnosis had a greater OR at ages 1-4(p<0.05), 55-59(p<0.05) and 65-89 years(p<0.001); those aged ≥90 (OR1.41 95%CI[1.15, 1.75]p=0.001)(Figure 3b). In England, differences between the sexes were less marked across all ages, with differences only occurring in those 50-54(p<0.05), 60-64(p<0.05) and 75-79 and 80-89 years(p<0.001)(Figure 3B and 3D).

The higher rate of CDI at younger ages in the US was investigated, Urinary tract infections (UTI’s) were significantly more common in women with CDI (OR1.42 95%CI[1.37,1.47]p<0.001) (Figure 4). The rate of UTIs was higher in women at all ages (p<0.05) apart from three age groups (ages 10-24). The rate of irritable bowel syndrome (IBS) in women was also 4-5 times greater than men (1.35% vs. 0.34% p<0.0001) in the US. UTI’s most often occurred concurrently with CDI (OR2.43 95%CI[2.42-2.44]p<0.001), and were more common in the US vs. England (OR4.10 95%CI[3.92-4.29]p<0.001). In England IBS was 3 times greater in women than men (0.6% vs. 0.2% p<0.0001) and UTI’s were more common in women (OR1.55 95%CI[1.54-1.56]p<0.001).

**Discussion**

The most striking finding in these data are the higher rates of CDI within the US than in England in 2012. This had not previously been the case: in 2007, there was a peak in CDI in Europe and North America, with rates of 108/100,000 population in England [9, 19], whilst rates in the US were almost identical at 107.8/100,000 population [3]. In the UK, the peak in CDI rates reported in 2007-2008 led to a government-imposed target for a 30% reduction by 2010-2011 [19]. Whilst no co-ordinated change in US healthcare policy was instigated at the time, the UK government responded by creating a mandatory national enhanced surveillance system and robust changes in infection control policy, including patient isolation and antibiotic stewardship [20]. Over the next two years, the rates of CDI in England fell by over 50% [4,21]; they have continued to decline since (particularly in BI/NAP1/027), with rates as low as 26.3/100,000 population in April 2014-March 2015 [19,21]. This improvement has also manifested in a reduction in mentions of CDI on UK death certificates by ~70% between 2007-2010 [22-23]. A close temporal association between restrictions of high-risk antibiotics for CDI in healthcare settings within the UK has been described with marked decline in CDI rates [24-26]. Whilst causality cannot be attributed through association studies, the observation that declining rates in England was accompanied by a national infection control initiative - whilst US rates did not decline, where these had not been robustly instigated – might suggest the success of such infection control initiatives.

Such data could suggest that a similar programme should be considered within the US and in other healthcare settings with rising CDI rates. The US administration recently announced a plan to combat antibiotic resistance, which has included the Centre for Disease Control and Prevention (CDC) pledging to reduce CDI by 50% from 2011 rates [27,28]. The CDC has recently reported a 10% reduction in CDI from 2011-2013 overall [29]; Illinois, Massachusetts, and New York have reduced their CDI rate by 20% in 2 years using a targeted prevention program [1]. However, elsewhere in the US (where infection control policies and antibiotic stewardship remain more variable), CDI rates are persistently high. Specifically, CDI levels have increased compared to last year in some states (with annual increases estimated at 1.5% in hospital and 0.02% for community-acquired infection) [1-3], and have plateaued at high levels in other states [29], with BI/NAP1/027 remaining the most common ribotype [4].

Other marked epidemiological differences are also demonstrated in our data. Most notably, different age profiles in those with CDI were found between the US and England, with both countries showing an increased rate of CDI in those >65 years; however, in the US, there are also high rates at younger ages which are not observed in England. In addition, differences in CDI rates in people with key comorbidities were shown between the two countries; e.g., there are a higher number of people with CDI and dementia in England. The causes for these differences are unclear, although some hypotheses may be proposed including differences in geography, demographics and in healthcare systems between both countries. These may impact vulnerability to infection, disease prevelance, strain prevelance, severity and spread. Even within the US, CDI rates have been shown to be different between states and regions [1, 29]. Furthermore, it has been shown that diet, antibiotics and environment may all influence the structure of the gut microbiota, which may also influence vulnerability to CDI [30-31]. However, antibiotic use was estimated to be broadly similar in the US and England in 2010 at 22.0 and 23.0 units per person respectively [32].

In both countries, a higher rate of CDI was observed in women compared to men, particularly in those with a primary diagnosis of CDI. Investigating the higher rates in women, we found that the increase in CDI rates may have been partially due to the higher numbers of in UTIs in women. Anatomical differences between sexes predispose to UTI to women, resulting in higher antibiotic usage and a increased potential risk of CDI in women. Sex differences may be due to a higher rate of functional gastrointestinal disease in women. Some may be healthily-colonised with *C. difficile* without true CDI*,* but are more likely to be tested for – and potentially misdiagnosed with – CDI, given that diarrhoea may be a component of IBS.

There are limitations to this study. Firstly, coding practices differ between England and the US, with the US system having more payment-based detailed coding, reflecting the differences in the heathcare systems between the two countries. However, the numbers derived from HES in England are in line with the mandatory UK national surveillance system [19] and the US NIS estimates are in line with the estimates given by the Emerging Infections Program [1]. The differences observed in comorbidities, age and sex are those that are rigorously coded in each country. Furthermore, these data have previously been shown to correlate with clinical findings [33]. Another limitation is that these data only apply to inpatients with CDI, when community-associated CDI is well-recognised in both countries. However, it is still the case that the majority of CDI cases within England and the US are hospital-associated; furthermore, even though a greater proportion of CDI cases within the US than England appear to be community-associated [21, 34], recent data indicate that 81% of apparently community-associated CDI occurs in people who have had at least some recent contact with a clinical setting [35]. As such, there is likely to be some overlap in both countries between those diagnosed with CDI in hospital and a proportion of those diagnosed in the community. We were also unable to identify readmissions for CDI, which may therefore overestimate rates. Length of stay (LOS) differences between England and the US could also partly explain these data, although the fact that the LOS is longer in England than in the US [36] would if anything be expected to increase CDI testing compared to the US. In addition, mandatory UK surveillance data demonstrate that the median time between admission to positive stool sample is only four days [19], so it seems unlikely that differences in LOS are a significant contributory factor to our findings here.

Criteria for testing for CDI also differs between the two countries, with a lower threshold in England than within the US[1,9]. In England, testing is advocated after one episode of diarrhoea (Bristol Stool Chart types 5-7) “that is not clearly attributable to an underlying condition (e.g. inflammatory colitis, overflow) or therapy (e.g. laxatives, enteral feeding)” [19]. In the US, clinicians are advised to test for CDI if the patient has had three episodes of loose stool in 24 hours and a recent history of antibiotics [1-2]. However, such differences in testing thresholds would clearly be expected to cause increased testing in the UK compared to the USA. The laboratory method used to diagnose CDI might also explain differences between the two countries. When toxin tests initially became available, they were cheap, fast, easy and underwent widespread use [37]; however, their sensitivity for exclusive use is questionable [9]. Subsequent studies showed molecular testing had better sensitivity and specificity [38]. However, more recent studies suggest samples positive on molecular testing (but negative on toxin testing) may just represent asymptomatic carriers [39]. In April 2012, the UK Department of Health released updated guidance on the diagnosis and mandatory reporting of CDI [9], stating samples should undergo a two-stage approach to be eligible for mandatory reporting: 1) a NAAT/PCR test to screen samples 2) positive samples then undergoing a sensitive toxin EIA test, with negative samples not tested after screening. Only those positive on both steps should undergo mandatory national reporting. These guidelines would have been incorporated into practise during the time period studied. It was estimated that the more accurate tests would show the true prevalence; resulting in a 17% reduction in rates of CDI on mandatory reporting [9]. However, in the following year, this reduction was not observed; instead, the rate continued to decline at a similar rate as it had before these guidelines were introduced [9]. In contrast, in the US, toxin testing remained the reference standard for most laboratories in 2012 [39], although molecular testing was estimated to be used by one-third of US laboratories at this point [37]. It has been reported that molecular testing may increase detection of CDI by 24% [38]; as such, if one-third [37] of the US inpatient discharges in our samples were from laboratories performing molecular testing, an estimate for the overall CDI rate in the US would decrease by ~ 9.2% to 105.9 per 100,000 population, which still does not bring levels down to the rates shown in England. Even if all laboratories in the US were using molecular testing, the estimated 24% increase by using molecular testing [38] would mean the estimates in the US would still be elevated at 87.5/100,000 population.

In conclusion, in these analyses of administrative data, clear epidemiological differences are shown in the profile of CDI between the two countries. In contrast to the situation in 2007, in 2012 these rates of CDI were much higher within the US than in England. This marked difference may be indicative of the benefit that infection control measures (including antibiotic stewardship programmes) may generate. In addition, there are also significant differences in other epidemiological aspects (including age distribution, and co-morbidity profile) between the cohort with CDI in the US and England. There are many possible explanations for these findings - including differences in environmental and biological factors - which merit further investigation.

**Declaration of interests**

The Dr Foster Unit is an academic unit in the Department of Primary Care and Public Health, within the School of Public Health, Imperial College London. The unit receives research funding from the National Institute of Health Research (NIHR) and Dr Foster Limited, an independent health service research organisation (a wholly owned subsidiary of Telstra). The unit is affiliated with the Patient Safety Translation Research Centre at Imperial which is funded by the National Institute of Health Research. We are grateful for support from the NIHR Health Protection Research Unit and NIHR Biomedical Research Centre funding scheme. BHM receives funding from the Imperial College Healthcare Charity (grant number: 141516/161722s). The use of NIS data is held with data agreement with HCUP AHRQ. The use of this data for this project was approved by HCUP. De-identified HES data were acquired from HSCIC which is a national administrative database of all discharges from NHS hospitals in England. The principal investigator has approval from the Secretary of State and the Health Research Authority under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to hold confidential data and analyse them for research purposes (CAG 15/CAG/0005). We have approval to use them for research and measuring quality of delivery of healthcare, from the London - South East Ethics Committee (REC 15/LO/0824). All authors are guarantors. All authors report no conflicts of interest relevant to this article.

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**Figure Titles and Legends**

**Figure 1:** CDI by sex and age in England & US in 2012. Rates are shown per 100,000 population split by sex over 5 year age groups for both countries in 2012. Rate in 2007 (dot-dashed line) is also shown for reference when it was consistent in both countries. Overall rates per 100,000 population in 2012 are also shown in each country. A) Rates of CDI by sex and age in England & US in 2012. B) Rates of CDI in England in 2012. C) Rates of CDI in United States in 2012.

**Figure 2:** The proportion of CDI from each age group in the US & England. A comparison of the proportion each 5 year age group contributes to the overall rate of CDI cases in each country.

**Figure 3:** Rate of CDI per 100,000 inpatient discharges separated by whether it was listed as a primary or secondary diagnosis in the England and the US.A) CDI as Primary Diagnosis in US, B) CDI as Primary Diagnosis in England, C) CDI as Secondary Diagnosis in US, D) CDI as Secondary Diagnosis in England.

**Figure 4:** Rate of Urinary Tract Infections in CDI cases in US by age & sex

**Table 1-** Proportions of comorbidities consistently coded in the two countries

|  |  |  |
| --- | --- | --- |
|  | US | England |
| Comorbidity | No CDI | CDI | No CDI | CDI |
|  | n | % | n | % | n | % | n | % |
| **Dementia** | 184940 | **0.58** | 4530 | **1.25** | 282099 | **2.11** | 995 | **9.63** |
| **Congestive cardiac failure** | 4202400 | **13.2** | 86930 | **24.1** | 302408 | **2.26** | 1017 | **9.85** |
| **Diabetes** | 7027901 | **22.0** | 107460 | **29.7** | 1273815 | **9.53** | 1745 | **16.9****18** |
| **COPD** | 5580281 | **17.5** | 86800 | **24.0** | 1412306 | **10.6** | 1854 | **18.0** |
| **Hypertension, simple** | 11664011 | **36.5** | 136395 | **37.7** | 2808595 | **21.0** | 3746 | **36.3** |
| **Alcohol abuse** | 2715456 | **8.50** | 44745 | **12.4** | 362750 | **2.71** | 485 | **4.70** |
| **Psychoses** | 581515 | **1.82** | 7320 | **2.03** | 49338 | **0.37** | 72 | **0.70** |