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The impact of *Clostridium difficile* infection on resource use and costs in hospitals in Spain and Italy: a matched cohort study

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SUMMARY

Objective: To assess the impact of *Clostridium difficile* infection (CDI) on hospital resources and costs in Spain and Italy.

Methods: CDI data were collected from institutions in Spain and Italy. Each patient was matched with two randomly selected uninfected controls in the same institution. Patient outcomes were assessed for the first and second episodes of CDI and for patients aged ≤65 and >65 years. The impact of CDI on hospital length of stay (LOS) was used to calculate CDI-attributable costs. A multivariate analysis using duration of stay as the continuous outcome variable assessed the independent effect of CDI on hospital costs and LOS.

Results: LOS attributable to CDI ranged from 7.6–19.0 days in adults and was 5.0 days in children; the increases were greater in adults in Italy than in Spain. Attributable costs per adult patient ranged from €4396 in Madrid to €14 023 in Rome, with the majority of the cost being due to hospitalization. For children, the total attributable cost was €3545/patient.

Conclusions: These data show that the burden of CDI is considerable in Spain and Italy. Treatments that can reduce LOS, disease severity, and recurrence rates, as well as effective infection control measures to prevent transmission, have the potential to reduce the burden of CDI.

1. Introduction

Clostridium difficile infection (CDI), which is caused by an anaerobic, Gram-positive, spore-forming bacillus, is the leading cause of infectious diarrhoea in hospitalized adult patients, causing infections ranging from mild diarrhoea to pseudomembranous colitis.[1–3] The most important risk factor for CDI is prior or ongoing antimicrobial therapy, which can disrupt the normal intestinal flora and allow *C. difficile* to colonize the gut.[1–3] Other risk factors include chemotherapy, solid organ and bone marrow transplantation, and chronic treatment with proton pump inhibitors.[2,4] Specific patient groups are also considered to be at risk, e.g. elderly, chronically ill, and immunocompromised patients.[2,3] However, CDI is becoming an increasingly common cause of community-acquired diarrhoea in low-risk populations, such as children, healthy adults, and pregnant women.[1,4]

Although viral infections (rotavirus, norovirus) remain the leading causes of diarrhoea in the paediatric population, CDI is also considered to be an increasingly common cause of hospital-acquired diarrhoea and an emerging cause of community-acquired diarrhoea in children.[2,5] In contrast to adults, no relationship with antibiotic exposure or comorbid conditions has been observed in children with community-acquired CDI.[2–4,6]

Many reports have shown that the incidence and severity of CDI are increasing and that it is associated with increasing morbidity and mortality; however, most studies have been performed in

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North America or northern Europe.[7–9] A pan-European study conducted by the European Centre for Disease Prevention and Control in 2008 showed that the incidence of CDI differs between countries; the reported rates in Italy and Spain were 3.6 and 4.3 episodes per 10 000 patient-days, respectively.[10] Although the study had a uniform design with a fixed 3-month follow-up, some studies have suggested that the diagnostic testing approach used causes variations in estimates of the incidence of CDI.[11–13] However, country-specific studies in Spain and Italy indicate that the prevalence of CDI is increasing: between 1999 and 2007, the prevalence rate increased from 3.9–12.2 per 100 000 population in Spain,[14] with more recent data indicating that rates remain high (13.4–22.5 per 100 000) and suggesting that CDI is under-diagnosed due to the diagnostic methods used;[15,16] in Italy, the incidence of CDI in five large hospitals in Rome increased significantly ($p < 0.001$) over the 6-year period between 2006 and 2011 (from 0.3–2.3 episodes per 1000 patient-days).[17]

The resource burden of CDI is considerable. A retrospective cohort study of infected ($n = 38$) and matched non-infected ($n = 76$) patients conducted during an outbreak of nosocomial CDI in Spain in 2006, demonstrated that patients who developed CDI were exposed to more antibiotics, had higher mortality, and were hospitalized for longer.[18] A retrospective cross-sectional study in Italy showed that CDI is associated with considerable costs in an Italian hospital setting, with length of stay (LOS) being the most important factor in determining costs,[19] although this study had methodological limitations. CDI in hospitalized children has been shown to increase the risk of death, extend hospital LOS, and increase hospital costs.[20] The general conclusion that CDI has a considerable resource impact is supported by a report showing that CDI is associated with a significant increase in attributable healthcare costs.[21] The increasing economic burden of CDI in healthcare facilities in Europe has been demonstrated, with incremental costs of infection in the range of €1857–€4266.[22] However, this study included only limited data from Spain and no information from Italy.[22]

As evidence regarding the impact of CDI on healthcare resources in southern Europe is generally scarce, the aim of this study was to analyse data on the burden of CDI in terms of hospital resources and costs, and in particular CDI-attributable LOS, in Spain and Italy.

2. Methods

2.1. Patient selection

Patients with CDI were diagnosed based on a positive *C. difficile* toxin immunoassay or positive culture for toxigenic *C. difficile* and signs and symptoms compatible with CDI (three or more unformed stools within 24 h). All patients with CDI diagnosed at the Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain (tertiary care referral hospital with a large solid organ transplantation programme and approximately 650 beds; period of data collection January 2011–November 2013), Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain (tertiary care hospital with approximately 400 beds, including 18 in an intensive care unit; data collected February–November 2011), and Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy (tertiary care hospital, including specialist paediatric medical and surgical departments with 50 beds; data collected 2006–2012) were included. Patients for inclusion in the study were selected randomly at the National Institute for Infectious Diseases "L. Spallanzani", Rome, Italy (tertiary care hospital with medical, surgical, and diagnostics departments and approximately 200 beds; data collected January 2011–August 2013).

2.2. Data extraction protocol

A protocol for data extraction from patient records was developed and used to collect data. For each institution, data for hospital-onset cases of CDI (infected cohort) and uninfected control patients (non-infected cohort) were collected. Hospital-onset was defined as >48 h after admission or <4 weeks after discharge from a healthcare facility (Naples only).

2.3. Matched cohort design

Each patient in the infected cohort was matched with two randomly selected uninfected control patients in the same institution. Patients were matched by ward and period of hospital admission (±15 days). For each patient in the infected and non-infected cohorts, data regarding main disease diagnosis at hospital admission, demographics, hospital department in which they were treated, and other factors potentially associated to LOS were collected. This matched cohort design was used to overcome the problem of how to assign hospital LOS data directly to *C. difficile*.

For the patients in the infected cohort, the index day was defined as the day of hospital stay when the patient was diagnosed with CDI. For those in the non-infected cohort, patients were selected randomly from those whose duration of stay was at least as long as that from the date of admission to the index day for the case with which they were matched. For these patients, the index day was defined as the same day of hospitalization as the index day of the case with which they were matched.

2.4. Data collected

To control for severity of illness before CDI infection, data required for the calculation of a modified Acute Physiology and Chronic Health Evaluation III (APACHE) score[23] were collected for all patients 48 h before the index day. The modified APACHE score did not include blood pH, pulmonary arterial oxygen saturation, pulmonary arterial gradient, urine output, or scoring for neurological abnormalities, because these data were not available for all patients in the study, particularly those not in the intensive care unit (ICU). To control for underlying disease, the Charlson comorbidity index was calculated using patient medical history.[24] It should be noted that while data for these two measures were collected for the paediatric patients, the validity of the measures for paediatric patients is uncertain.

To control for prognosis of primary disease, the McCabe–Jackson index was estimated.[25] Finally, information about previous antibiotic use was collected from the date of hospital admission to date of infection for cases, and from the date of hospital admission to the index day for controls.

The following data on CDI were collected: duration of diarrhoea, treatment for CDI, hospital LOS (including ICU and isolation days), whether sigmoidoscopy/colonoscopy was performed, and clinical outcomes, including cure, mortality at 30 days, attributable mortality, and recurrence. Based on the guidelines available at the time that patients were diagnosed,[26] recurrence was defined as a second episode of CDI based on clinical symptoms, a positive diagnostic test for *C. difficile*, or both, occurring within 2–8 weeks of the index case and within the hospital stay.

2.5. Treatment protocols

In Spain, adult patients with mild-to-moderate CDI received metronidazole 250 mg every 6 h for 10 days, whereas in Italy they received metronidazole 500 mg every 8 h for 10 days. Severe infections were treated using oral vancomycin 125–500 mg every 6 h for 10 days. Recurrences were treated using oral vancomycin

125–500 mg every 6 h for 10 days or fidaxomicin 200 mg twice daily for 10 days.

Paediatric patients with mild-to-moderate CDI were usually treated with metronidazole 125 or 250 mg every 8 h according to body weight for 7–14 days; patients with severe or recurrent infections received vancomycin 10 mg/kg/dose every 6 h (to a maximum of 1500 mg/day).

2.6. Costs

In Spain, the costs of metronidazole and vancomycin were €1.08 (20 units of 250 mg) and €3.45 (1 unit of 125 mg), respectively.[27] The daily cost of a hospital in-patient stay was €443.59 and the daily cost of ICU was €1156.07.[27] An estimated average daily cost of stay was calculated by comparing the total number of days patients spent in the ICU with the total days spent in hospital and calculating a weighted average cost.

In Italy, costs of €708.54 and €1214.64 were used for daily adult hospitalization and ICU costs. These are based on the value reported by Magalini et al.[19] inflated to 2013 values using the Italian Consumer Price Index.[28] The costs of metronidazole and vancomycin were €1.30 (per g) and €4.60 (per g), respectively. The cost of hospitalization per day in children was €708.54, also based on the value reported by Magalini et al.[19]

2.7. Analyses performed

In the adult population, the following analyses were performed. First, patient outcomes were assessed both for the first and second episodes of CDI and by therapy used. The impact of CDI on hospital LOS, including time in the ICU, was also calculated. Furthermore, the number of isolation days (contact precautions) was assessed. Each of these outcomes was analysed both in the overall population and in patients aged ≤65 and >65 years. These measures were used to calculate CDI attributable costs.

For the paediatric patients, the type and outcome of therapy was captured for the first and subsequent episodes of CDI. The impact of CDI on hospital LOS, isolation days, and costs was analysed.

2.8. Statistical analyses

To analyse the independent effect of CDI on hospital costs and LOS, a multivariate analysis using a continuous outcome variable of duration of stay (post-infection duration of hospitalization for the infected cohort and duration of hospitalization after the index day for the non-infected cohort) was performed. Potential confounding variables were taken into account: modified APACHE III score (incorporates age), Charlson comorbidity index score, and McCabe–Jackson disease classification.

Median rather than mean values were used for the outcome measures to reduce the influence of extreme or outlier values. This approach was considered more appropriate than using mean values, which have been used in other studies. By not adjusting for skewed data, the use of mean values tends to overestimate difference. The alternative – log transformation of data – tends to underestimate difference.

Median regression analysis using the qreg function in the statistical program Stata version 12 (StataCorp., College Station, TX, USA) was regarded as valid.

3. Results

3.1. Patient and disease characteristics

In total, data were collected for 232 adult infected patients and 426 matched non-infected patients in Madrid ($n = 94$), Barcelona ($n = 12$), and Rome ($n = 126$). Nineteen patients in Madrid had community-onset CDI and were not matched to non-infected patients. In addition, data for 19 paediatric infected patients and 38 matched non-infected patients were also collected in Naples.

Table 1
Patient and disease characteristics

	Institution							
	Madrid		Barcelona		Rome		Naples	
Characteristic	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected	Infected	Non-infected
Adult/paediatric	Adult	Adult	Adult	Adult	Adult	Adult	Paediatric	Paediatric
n	94	150	12	24	126	252	19	38
Mean age, years (range)	70.4 (21–98)	65.7 (20–100)	55.3 (21–80)	53.8 (25–80)	65.8 (19–95)	55.2 (18–101)	9.0 (0.8–17)	11.1 (1–18)
Male (%)	50.0	62.0	58.3	58.3	57.1	54.4	68.4	36.8
Prior antibiotic use (%)	74.5		75.0		91.3		43.4	
Admission service (%)								
Medical	71	67	75	75	89	77	–[a]	–[a]
Surgical	23	28	8	8	6	20		
ICU	4	5	17	17	5	3		
Other	2	1	0	0	0	0		
Mean serum albumin, g/l (range)	3.05 (0.3–4.0)	3.42 (2.0–5.2)	2.70 (1.4–4.2)	3.13 (1.2–4.0)	2.86 (0.1–4.3)		4.1 (2.8–4.9)	4.46 (3.5–4.9)
McCabe–Jackson disease classification (%)								
Non-fatal	59.6	62.7	66.7	70.8	82.5	94.1	100.0	36.8
Rapidly fatal	17.0	12.7	0.0	4.2	4.0	1.6	0	
Ultimately fatal	23.4	24.7	33.3	25.0	13.5	4.4	0	63.2[b]
Mean Charlson comorbidity index score (range)[c]	6.3 (0–14)	5.33 (0–12)	2.8 (0–9)	2.7 (0–10)	6.0 (0–18)	3.7 (0–13)	NR	NR
Mean APACHE score (range)[d]	34.7 (0–68)	28.8 (0–73)	9.3 (2–16)	11.5 (0–35)	NR	NR	NR	NR

ICU, intensive care unit; NR, not reported.
[a] All paediatric patients were admitted to the paediatric department.
[b] For paediatric patients, disease was classified as non-fatal or ultimately fatal only.
[c] Used to assess the risk of 10-year mortality based on the scoring of 19 medical conditions, which are weighted to provide a score in the range 0–45; higher scores are associated with a higher risk of death.
[d] APACHE III is a severity-of-disease classification system used in ICUs; scoring ranges from 0–299, with higher scores associated with a higher risk of death.

Patient and disease characteristics are shown in Table 1. Differences in age were observed, most likely because the matching criteria used did not specify age, and probably contributed to the difference in Charlson index scores observed in Italy. Data on antibiotic use prior to the diagnosis of CDI are shown in the **Supplementary Material** (Online Resources 1 and 2).

3.2. First episode of CDI

3.2.1. Adults

Data regarding the disease characteristics of the initial episode of CDI, its treatment, and the outcomes of treatment for the overall population and patients aged ≤65 and >65 years (Madrid and Rome only) are shown in Table 2 (data for patients who did not have a recurrence and those who had a recurrence are shown in the **Supplementary Material** (Online Resources 3 and 4)). It should be noted that a proportion of patients received non-oral therapy: 26 patients in Madrid (intravenous metronidazole $n = 19$, intracolonic vancomycin $n = 2$, both $n = 5$), four in Barcelona (intravenous metronidazole $n = 3$, intracolonic vancomycin $n = 1$), and 16 in Rome (all intravenous metronidazole). Disease characteristics were generally similar for adult patients at the different sites, both for the overall population and the patients aged >65 years, although the incidence of ulceration and colonic wall thickening appeared to be lower in Italy than in either Madrid or Barcelona. However, this could be due to differences in the proportions of patients who underwent computed tomography in different institutions. Finally, while outcomes in Spain were generally similar for patients aged >65 and ≤65 years, patients aged >65 years had worse outcomes than those aged ≤65 years in Rome.

3.2.2. Children

Data regarding the disease characteristics of the initial episode of CDI, its treatment, and the outcomes of treatment for paediatric patients in Naples are shown in Table 2. Disease characteristics were generally comparable to those in adults, but the incidence of ulceration and colonic wall thickening was higher than that in the adult patients in Rome. In contrast to adult patients, the first episode of CDI in children was exclusively treated with oral therapy. No deaths due to the first episode of CDI were reported.

3.3. CDI recurrence

A total of 34 adult patients (12.5%) and two paediatric patients (10.5%) experienced a first recurrence of CDI. Three of the 34 adult patients and one of the two paediatric patients had a further recurrence. Although fidaxomicin was included in the treatment protocols for recurrent CDI in Spain and Italy, no patient was treated with this agent. Two deaths occurred in patients with a first recurrence, both attributable to CDI and both occurring in Rome. No deaths were reported in this patient group in the other centres, whether attributable to CDI or not. No CDI-attributable mortality was reported in patients with a second CDI recurrence. No statistical analysis of potential differences in outcomes was performed due to the small sample size of the recurrent CDI groups.

3.4. Attributable hospital LOS

Data for hospital LOS, including days spent in isolation and the ICU, and hospital LOS attributable to CDI are shown in Tables 3–5. LOS attributable to CDI was generally similar in adults aged ≤65 and >65 years. However, the data suggest that the LOS attributable to CDI was longer in adults with CDI in Italy than in adults with CDI in Spain. LOS attributable to CDI in children was shorter than in adults in both Spain and Italy.

In Madrid, the LOS attributable to CDI was shorter for the first episode (6.4 days) than for the first recurrence (45 days) (Tables 4 and 5). This was also the case in Rome, although the

Table 2
Initial CDI, treatment, and outcomes

	Institution							
	Madrid			Barcelona[a]	Rome			Naples
	All	≤65 years	>65 years	All	All	≤65 years	>65 years	Paediatric
n	94	33	61	12	126	54	72	19
Mean duration of diarrhoea, days (range)	10.1 (1–48)	8.7 (2–33)	10.9 (1–48)	11.8 (2–25)	12.9 (2–50)	11.5 (2–50)	14.0 (2–42)	7.8 (0–30)
Diarrhoea contains blood (%)	15.0	15.6	14.7	16.7	6.3	7.4	5.6	36.8
Fever (%)	15.0	18.8	13.1	8.3	18.2	22.2	15.3	21.0
Ileus (%)	3.2	3.1	3.3	8.3	2.4	1.9	2.8	0.0
Leukocyte count $\geq 15 \times 10^9$/l (%)	31.2	37.5	27.9	25.0	32.5	24.1	70.8	36.8
Serum creatinine increase >50% (%)	24.7	12.5	31.1	0.0	21.4	11.1	29.2	0.0
Sigmoidoscopy/colonoscopy (%)	7.5	9.4	6.6	8.3	7.1	5.6	8.3	15.8
Pseudomembranes (%)	8.6	9.4	8.2	8.3	0.0	0.0	0.0	0.0
Ulceration (%)	3.2	3.1	3.3	0.0	3.2	1.8	4.2	10.5
Colonic wall thickening (%)	14.0	21.9	9.8	33.3	7.1	5.6	8.3	5.3
Pericolonic fat (%)	4.3	3.1	4.9	0.0	0.8	0.0	1.4	0.0
Treatment, *n* (%)[b]								
Metronidazole, oral	79 (84.0)	27 (81.8)	53 (86.9)	10 (83.3)	83 (65.9)	39 (72.2)	44 (61.1)	10 (52.6)
Metronidazole, intravenous	24 (25.5)	7 (22.6)	17 (25.0)	3 (25.0)	16 (12.7)	3 (5.6)	13 (18.1)	0
Vancomycin, oral	13 (13.8)	5 (15.2)	8 (13.1)	1 (8.3)	36 (28.6)	12 (22.2)	24 (33.3)	5 (26.3)
Vancomycin, intracolonic	7 (7.5)	4 (12.1)	3 (4.9)	1 (8.3)	0	0	0	0
Outcomes (%)[c]								
Cure	75 (80.6)	26 (81.3)	49 (80.3)	12 (100.0)	79 (64.8)	42 (80.8)	37 (52.9)	17 (89.5)
Failure	13 (14.0)	5 (15.6)	8 (13.1)	0 (0.0)	5 (4.1)	3 (5.8)	2 (2.9)	1 (5.3)
30-day mortality	14 (15.1)	5 (15.6)	9 (14.8)	1 (8.3)	18 (14.8)	4 (7.7)	14 (20.0)	0 (0.0)
1-year mortality	19 (20.4)	6 (18.8)	13 (21.3)	1 (8.3)	19 (15.6)	4 (7.7)	15 (21.4)	0 (0.0)
Attributable mortality	4 (4.3)	1 (3.1)	3 (4.9)	0 (0.0)	7 (5.7)	1 (1.9)	6 (8.6)	0 (0.0)
Recurrence[d]	7 (7.5)	2 (6.3)	5 (8.2)	2 (16.7)	25 (20.5)	6 (11.5)	19 (27.1)	2 (10.5)

CDI, *Clostridium difficile* infection.
[a] Not analysed by age due to small patient numbers.
[b] Patients may have received more than one antibiotic.
[c] Outcomes data not available for one patient in Madrid and four patients in Rome.
[d] Defined as a second episode of CDI occurring within 2–8 weeks of the index case within hospital stay.

Table 3
Hospital LOS for all CDI episodes, including first episode and first or second recurrence

	Institution							
	Madrid			Barcelona[b]	Rome			Naples
	All (n = 75)[a]	≤65 years (n = 26)	>65 years (n = 49)	All (n = 12)	All (n = 126)	≤65 years (n = 54)	>65 years (n = 72)	Paediatric (n = 19)
Mean LOS, days (range)								
Infected	20.6 (1–85)	23.3 (1–85)	19.2 (2–80)	42.1 (5–161)	36.0 (5–154)	39.1 (5–154)	33.7 (5–126)	7.4 (0–41)
Non-infected	11.0 (0–227)	13.8 (0–227)	8.5 (0–56)	7.9 (1–26)	18.0 (0–391)	17.0 (0–391)	19.7 (0–368)	0.3 (0–8)
Median LOS, days								
Infected	13.0	12.5	13.0	26.5	29.5	27.5	29.5	5.0
Non-infected	5.5	7.0	4.0	7.5	8.0	7.0	8.0	0
Mean ICU stay, days (range)								
Infected	3.4 (0–126)	1.2 (0–28)	4.5 (0–126)	7.9 (0–69)	2.1 (0–57)	2.9 (0–46)	1.4 (0–57)	0
Non-infected	0.5 (0–29)	0.8 (0–29)	0.3 (0–12)	1.3 (0–14)	0.6 (0–35)	0.3 (0–11)	1.2 (0–35)	0
Median ICU stay, days								
Infected	0	0	0	0	0	0	0	0
Non-infected	0	0	0	0	0	0	0	0
Increase in LOS attributable to CDI, days[c]	7.6	6.0	8.0	20.0	19.0	21.0	19.0	5.0
Mean length of isolation, days (range)	9.3 (0–53)	9.8 (0–41)	9.0 (0–53)	8.8 (0–16)	11.9 (0–52)	10.9 (0–39)	12.5 (0–52)	3.5 (0–30)
Median length of isolation, days	7.0	8.0	7.0	10.0	10	10	10	0

LOS, length of stay; CDI, *Clostridium difficile* infection; ICU, intensive care unit.
[a] Number of patients refers to the infected cohort; the uninfected cohort included twice as many patients as the infected cohort.
[b] Not analysed by age due to small patient numbers.
[c] Calculated using multivariate linear regression analysis with LOS as the continuous outcome variable and based on median values.

difference was much smaller (20 and 24 days, respectively) (Tables 4 and 5). However, it should be noted that patient numbers for these analyses were small.

3.5. Costs attributable to CDI

The costs associated with CDI differed between sites. In Madrid, the estimated average cost per day varied between €480.28 and €610.58 based on 5.2% and 23.4% of the total hospital stay being in the ICU for those patients aged ≤65 and >65 years, respectively. Therefore, the attributable hospitalization costs were €4265, €2882, and €4885 per patient for all patients and those aged ≤65 and >65 years, respectively. Drug costs add approximately €131 per patient (based on a total metronidazole dose of 12 958 mg and a total vancomycin dose of 3728 mg per patient). Assuming 7601 cases per year,[27] the annual cost of CDI would be €33 413 971.

In Rome, the total cost attributable to CDI was €14 023 per patient (19.0 days × €738.06) for all patients. The cost was €15 668 for those in the age group ≤65 years and €13 862 for those aged >65 years, with the difference in cost being due to differences in length of stay (21 vs. 19 days, respectively) and cost per day. For subgroups aged 18–64, 65–79, and >79 years the costs were €15 668, €16 487, and €11 112, respectively. For patients with recurrence, the total cost attributable to CDI was €17 714 per patient (attributable LOS 25 days), while for patients with a single episode of CDI, the cost was €14 936. Drug costs add approximately €51 per patient (based on a total metronidazole dose of 6504 mg and a total vancomycin dose of 9173 mg per patient). Based on the most recent epidemiological data for Rome,[18] this translates to an estimated cost of CDI of €32 371 per 10 000 patient-days.

For the paediatric patients in Naples, the total cost attributable to CDI was €3545 per patient (5.0 days × €709), with drug costs

Table 4
Hospital LOS for patients with a first episode of CDI

	Institution							
	Madrid			Barcelona[b]	Rome			Naples
	All (n = 71)[a]	≤65 years (n = 24)	>65 years (n = 47)	All (n = 10)	All (n = 101)	≤65 years (n = 61)	>65 years (n = 40)	Paediatric (n = 17)
Mean LOS, days (range)								
Infected	17.9 (1–80)	19.7 (1–65)	17 (2–80)	46.0 (5–161)	34.4 (5–126)	35.3 (5–141)	33.6 (5–126)	7.7 (0–41)
Non-infected	11.3 (0–227)	14.4 (0–227)	8.6 (0–56)	8.2 (1–26)	11.8 (1–59)	10.6 (1–59)	14.2 (0–62)	0.3 (0–8)
Median LOS, days								
Infected	13.0	11.5	13.0	26.5	28.0	26.5	30.0	5.0
Non-infected	6.0	7.0	4.0	7.5	8.0	7.0	11.0	0
Mean ICU stay, days (range)								
Infected	2.2 (0–57)	1.3 (0–28)	2.7 (0–57)	9.5 (0–69)	2.6 (0–46)	3.3 (0–46)	1.9 (0–57)	0
Non-infected	0.5 (0–29)	0.8 (0–29)	0.3 (0–12)	1.6 (0–14)	0.3 (0–8)	0.3 (0–9)	0.4 (0–8)	0
Median ICU stay, days								
Infected	0	0	0	0	0	0	0	0
Non-infected	0	0	0	0	0	0	0	0
Increase in LOS attributable to CDI, days[c]	6.4	5.0	8.0	20.0	20.0	20.0	19.0	5.0
Mean length of isolation, days (range)	8.0 (0–33)	8.8 (0–30)	7.6 (0–33)	8.9 (0–16)	10.1 (0–39)	10.0 (0–39)	10.2 (0–46)	3.8 (0–30)
Median length of isolation, days	7.0	8.0	7.0	10.0	10.0	10.0	10.0	0

LOS, length of stay; CDI, *Clostridium difficile* infection; ICU, intensive care unit.
[a] Number of patients refers to the infected cohort; the uninfected cohort included twice as many patients as the infected cohort.
[b] Not analysed by age due to small patient numbers.
[c] Calculated using multivariate linear regression analysis with LOS as the continuous outcome variable and based on median values.

Table 5
Hospital LOS for patients with one recurrent episode of CDI

	Institution				
	Madrid[a]	Barcelona[a]	Rome[a]	Naples	All patients
	All (n = 5)	All (n = 2)	All (n = 23)	Paediatric (n = 1)	All (n = 31)
Mean LOS, days (range)					
Infected	63.5 (50–77)	22.5 (15–30)	44.3 (5–154)	0.0 (0–0)	42.5 (0–154)
Non-infected	8.5 (0–23)	6.3 (2–9)	46.3 (1–391)	0.0 (0–0)	37.1 (0–391)
Median LOS, days					
Infected	63.5	22.5	34.0	0.0	34.0
Non-infected	5.0	7.0	9.5	0.0	8.0
Mean ICU stay, days (range)					
Infected	25.2 (0–126)	0.0 (0–0)	0.0 (0–1)	0	4.2 (0–126)
Non-infected	0.0 (0–0)	0.0 (0–0)	2.0 (0–35)	0	1.6 (0–35)
Median ICU stay, days					
Infected	0	0	0	0	0
Non-infected	0	0	0	0	0
Increase in LOS attributable to CDI, days[b]	45.0	NP	24.0	NP	26.0
Mean length of isolation, days (range)	19.8 (7–53)	8.5 (7–10)	17.5 (5–35)	0.0 (0–0)	16.7 (0–53)
Median length of isolation, days	11.0	8.5	18.0	0	15.0

LOS, length of stay; CDI, *Clostridium difficile* infection; ICU, intensive care unit; NP, not possible due to small sample size.
[a] Not analysed by age due to small patient numbers.
[b] Calculated using multivariate linear regression analysis with LOS as the continuous outcome variable and based on median values.

contributing <€100 per patient. Based on the most recent epidemiological data for Rome, this translates to an estimated cost of €8154 per 10 000 patient-days.

4. Discussion

This study shows that the burden of CDI in Spain and Italy in terms of the use of hospital resources and costs, and in particular CDI-attributable LOS, is considerable, with costs of up to €14 023 per patient. Based on data from Italy, costs appeared to be higher for adults with recurrent disease than for those with a first infection (€17 714 vs. €14 936; difference of €2778), with the majority of the cost difference likely being due to an increase in LOS with the first recurrence, highlighting the potential value of preventing recurrence. In both Spain and Italy, the majority of the CDI-associated costs in both adults and children were due to excess hospitalization. However, the attributable LOS for adults differed between the two countries, at 6–10 days in Spain compared to 19–21 days in Italy. This difference resulted in a difference in costs between the countries (€4396 per patient in Spain vs. €14 023 per patient in Italy). Drug-related costs were relatively low and resulted from vancomycin and metronidazole therapy. Despite being part of treatment protocols in both countries, fidaxomicin was not used, probably because it was approved only for third-line use in Spain, where few patients had a second recurrence, and was approved for use in Italy only after data had been collected (November 2013).

As in the present study, previous studies in adults have reported varying data for attributable LOS due to CDI. A study in Spain reported an attributable LOS of 4 days,[18] with other studies in Europe and the USA providing similar estimates.[29,30] In contrast, a literature review of European data provided estimates of up to 18 days depending on the country,[22] and attributable LOS of up to 16.09 days was reported in a study in four European countries, including Spain (13.56 days), although this study focused on patients at increased risk of CDI.[31] The reasons for these differences are likely to include differences in patient populations, patient history, underlying severity of disease, and comorbidities.[31] Data on some of these factors were collected in the present study for the adult patients, and for underlying severity of disease using the McCabe–Jackson disease classification and Charlson comorbidity index in particular. These data indicated that adult patients in Spain had more severe underlying disease than those in Italy and a similar level of comorbidity. These factors are therefore unlikely to explain the longer attributable LOS in Italy. Similarly, the CDI disease characteristics, although different, did not reveal any differences that might explain the differences in attributable LOS.

One factor that could influence LOS is prior antibiotic use: the duration of non-CDI-related antibiotic exposure has been shown to be related to adverse outcomes.[32] Unfortunately, while data on the type and dose of antibiotic used prior to CDI diagnosis, which appeared to differ in Spain and Italy, were collected in the present study, no data regarding the duration of use were collected, which would have provided greater insight. However, the use of isoniazid, ethambutol, and rifampicin (**Supplementary Material**, Online Resources 1 and 2) suggests that more patients in Italy than Spain had tuberculosis, which may in part explain the longer LOS in Italy. Furthermore, we did not collect information on the *C. difficile* serotypes implicated in CDI and it is therefore possible that patients in Italy were more likely to be infected with hypervirulent serotypes, which would also influence LOS.

In relation to LOS, it is also interesting to note that the median duration of isolation of adult patients was similar in Spain and Italy. Thus, while on average adult patients in Spain were isolated for most or all of the CDI-attributable LOS, those in Italy were isolated for only approximately half of their CDI-attributable LOS. The reason for and effect of this are difficult to assess, but could also be related to the suggestion that more patients in Italy than Spain had tuberculosis.

An additional observation in relation to LOS was that attributable LOS with a first recurrence was increased compared to the initial episode in both Madrid and Rome. This confirms the burden of recurrent disease for patients with CDI and for healthcare systems. Although the attributable LOS appeared to be considerably higher in Madrid than in Rome, small patient numbers mean that no conclusions should be drawn based on this.

Data on the burden of CDI in children are very limited. Furthermore, specific considerations relating to asymptomatic colonization and the use of diagnostic testing mean that estimates of the incidence of CDI in paediatric patients are uncertain.[33] In the present study, the majority of cases of CDI in children occurred in the community rather than the hospital setting. This contrasts with the situation in adults, where hospitalization is a risk factor for CDI, although the incidence of infections occurring in the community is increasing.[2,26,34] Furthermore, in the children included in this study, the median CDI-attributable LOS appeared to be less than

that in adults in Italy (5 vs. 19 days in Rome), as did isolation and ICU use. Therefore, although daily costs of care are higher for children than adults, the overall burden of CDI in the paediatric population in Italy is lower than that in adults.

As the costs of CDI in Spain and Italy are driven by the attributable LOS, it is important to note that the methodology for assessment in the present study differed from that used in other studies. To account for the excess stay attributable to CDI, comparisons of infected and non-infected patients must take into account the potential effect of confounding factors. Matching based on these potential confounding factors can be difficult to achieve, so it is more efficient to control for them through the analysis. In addition, the distribution of LOS was not normal. This precluded the use of multiple linear models. For this reason, an adjusted comparison of median LOS was performed. In line with the data for Spain obtained in this study, a recent retrospective cohort study found an adjusted median excess LOS attributable to CDI of 6 days.[35]

Various limitations of this study can be identified. First, there were differences in data collection and reporting between the different institutions. Thus, the observed differences in CDI severity between Spain and Italy could have been influenced by data collection in the different institutions. Furthermore, cure and recurrence were not recorded homogeneously in the available medical records, again potentially affecting the reported rates. This makes the assessment of factors potentially affecting cure and recurrence rates, such as severity, treatment, or other variables, difficult.

Another limitation is the retrospective matched-cohort methodology. Sources of error due to confounding and bias are more common in retrospective studies than in prospective studies. In addition, matching infected patients with non-infected patients by propensity scoring may have yielded different results. Furthermore, obtaining information from medical records could introduce bias around the assessment of outcomes, due to potential inaccuracy and a lack of information regarding the outcome criteria.

A further potential limitation relates to the severity of disease in the patients studied. The hospitals participating were all tertiary care institutions, which may have resulted in the inclusion of patients with more severe disease than if the study had involved other institutions. However, patient APACHE III scores (an estimate of disease severity) were in general relatively low (mean 9.3–34.7; maximum score of 73 on a 299-point scale). Similarly, mean scores based on the Charlson comorbidity index, used to estimate survival at 10 years, ranged from 2.8–6.3, with an individual maximum of 18 on a 45-point scale. These scores are indicative of patient populations with a moderate 10-year survival prognosis. The Charlson comorbidity index takes into account patient age; as the mean age of patients was >65 years in Madrid and in the infected patient cohort in Rome, the higher Charlson comorbidity index scores and thus moderate 10-year survival prognosis in these populations are perhaps not unexpected.

Finally, the duration of data collection ranged from 10 months–7 years in the different study centres, with some patients treated as early as 2006 being included. Therefore, it is possible that changes in patient management, as well as the recent trend towards shorter hospital stays in recent years, could have biased some of the estimates towards estimating a longer attributable stay.

In conclusion, these data add to the evidence that the burden of CDI, which is known to be increasing, remains considerable. The causes of the increasing burden are two-fold: first, the incidence and severity are increasing, and second, the population is ageing. As this study shows, the impact of CDI in older patients is considerable, even though differences in cure and recurrence rates between patient age groups were less pronounced in Spain than in Italy, and in those with recurrent CDI. In this context, treatments that can reduce LOS by reducing recurrence rates have the potential to reduce the burden of CDI. Other solutions include antibiotic stewardship, i.e., promoting the selection of the optimal antibiotic drug regimen, dose, duration of therapy, and route of administration, and infection control measures, including cleaning and barrier precautions. Jones et al. estimated the annual cost of CDI in Europe at €3 billion per year,[36] further emphasizing that approaches that can reduce CDI-associated resource use and costs should be of interest. Antibiotics are a key component of therapy for CDI, but currently represent a minimal cost in the overall budget for CDI management. The introduction of new antibiotics will increase drug costs; however, these agents are likely to shorten hospital stay, reduce CDI recurrence, and reduce the time to clinical response.[37–39] Therefore, the use of new antibiotics may be justified economically if reductions in the cost of CDI due to shorter hospital LOS and/or fewer recurrences are demonstrated. Furthermore, other strategies for the treatment of CDI are in development or available: toxin-targeted monoclonal antibodies are in development, and bacteriotherapy with probiotics and fecal microbiota transplantation are available for third-line use after failure of systemic drug therapy. However, the costs of these approaches differ considerably and they therefore need to be assessed from a pharmaco-economic perspective.

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Conflict of interest: AA, SDB, ALV, SG, BI, RS, and NP have declared no conflicts; WMH is an employee of EcoStat Consulting, contracted by Astellas Pharma EMEA, the manufacturer of fidaxomicin, to collect and analyse the data; MW and JN are employees of Astellas Pharma EMEA.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2015.05.013.

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