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1 ***Clostridium difficile* infection in an endemic setting in the**
2 **Netherlands**

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15 Key words: *Clostridium difficile* infection, risk factor, endemic, fluoroquinolones, mortality

16 40-word summary: Risk factors for *Clostridium difficile* infections (CDI) in an endemic

17 setting differ from those in outbreak situations. Some risk factors that have earlier been

18 ascribed to CDI were in this study not specific for CDI, but for diarrhoea in general.

19 Running title: Risk factors for endemic CDI

20

21 **Abstract**

22 Purpose: To study risk factors for *Clostridium difficile* infection (CDI) in an endemic
23 setting.

24 Methods: In a 34 month prospective case-control study, we compared risk factors and
25 clinical characteristics of all consecutively diagnosed hospitalized CDI patients (n=93)
26 with those of patients without diarrhoea (n=76) and patients with non-CDI diarrhoea
27 (n=64).

28 Results: The incidence of CDI was 17.5 per 10,000 hospital admissions. *C. difficile* PCR-
29 ribotype 014 was the most frequently found type (15.9%), followed by types 078 (12.7%)
30 and 015 (7.9%). Independent risk factors for endemic CDI were use of second
31 generation cephalosporins, previous hospital admission and previous stay at the
32 intensive care unit. Use of third generation cephalosporins was a risk factor for diarrhoea
33 in general. We found no association of CDI with the use of fluoroquinolones or proton
34 pump inhibitors. The overall 30-day mortality rates among CDI patients, patients without
35 diarrhoea and patients with non-CDI diarrhoea were 7.5%, 0% and 1.6% respectively.

36 Conclusions: In this endemic setting, risk factors for CDI differed from those in outbreak
37 situations. Some risk factors that have earlier been ascribed to CDI were in this study not
38 specific for CDI, but for diarrhoea in general. Thirty-day mortality among CDI patients
39 was relatively high.

40 **Introduction**

41 Since 2002, outbreaks caused by *Clostridium difficile* infection (CDI) have been
42 reported in Canada, the USA and Europe, associated with the emergence of a new
43 hypervirulent type. This type has been characterized as North American pulsed-field type
44 1, restriction-endonuclease analysis group type BI, toxinotype III and PCR-ribotype 027
45 (type 027) [1-5]. During outbreaks in the USA and Canada, the reported incidences of
46 CDI varied between 155 and 225 per 10,000 hospital admissions [3, 6]. Peak incidences
47 of CDI due to type 027 during outbreaks in the Netherlands were remarkably lower,
48 around 50 per 10,000 hospital admissions [7, 8].

49 Most recent studies on risk factors of CDI focussed on outbreaks, whereas less is
50 known about CDI in settings with a low incidence. Well described risk factors for CDI in
51 outbreak situations are prior use of antibiotics, increased disease severity, and, in case
52 of outbreaks caused by type 027, advanced age and prior use of fluoroquinolones [9-11].

53 The aim of our study was to identify risk factors for CDI in a true endemic setting.
54 A second aim was to establish risk factors specific for CDI, in comparison with factors for
55 diarrhoea in general. To answer these questions, we performed a prospective case-
56 control study at the Leiden University Medical Center during a period of 34 months.

57 **Methods**

58 **Patients.**

59 From July 2006 through April 2009, all hospitalized patients with CDI were
60 included in the study. Tests for CDI were performed daily upon request and on all
61 unformed faecal samples from patients admitted for two days or more, regardless the
62 physicians' request. For each hospitalized CDI patient, two controls were included,
63 matched for ward at which CDI was diagnosed and time of admission. The controls
64 included one control patient without diarrhoea (control patient) and one control patient
65 with diarrhoea and a negative *C. difficile* toxin test (non-CDI patient). Controls were
66 consecutive patients on the alphabetical ward list.

67 **Definitions.**

68 Definitions as proposed by the European and American Centres of Disease
69 Control were used [2, 12]. Diarrhoea was defined as ≥ 3 unformed stools per 24 hours.
70 CDI was defined as the presence of diarrhoea in combination with a positive toxin test
71 for *C. difficile*. A community association was defined as development of CDI outside the
72 hospital or within 48 hours after admission, without a history of admission in the previous
73 three months. We defined diarrhoea as severe, when it occurred with one or more of the
74 following: bloody stools, hypovolemia, fever ($T > 38.0^{\circ}\text{C}$) and leucocytosis ($> 12.0 \times 10^9/\text{l}$),
75 hypo-albuminemia ($< 20 \text{ g/l}$), pseudomembranous colitis. A complicated course of CDI
76 was defined as: admission to the intensive care unit (ICU), a surgical intervention in

77 association with CDI, or death within one month. Mortality was considered contributable
78 to CDI when a patient died during admission, partly due to the consequences of CDI.

79 **Isolation and characterization of *Clostridium difficile*.**

80 *C. difficile* toxins in stools were detected by VIDAS *C. Diff.* toxin A during the first
81 12 months of the study and VIDAS toxin A/B assay during the ensuing 22 months
82 (BioMérieux, France). Each positive sample was cultured. Available isolates were
83 identified as *C. difficile* using a PCR to detect the presence of *gluD* and were PCR-
84 ribotyped as previously described [8, 13].

85 **Data collection.**

86 Approval was obtained from the Medical Review Ethics Committee to collect
87 demographical and clinical patient data. Information was collected on patients' age, sex,
88 co-morbidity, ward of acquisition, disease severity, clinical course and mortality.
89 Furthermore, data were collected on surgery, invasive procedures, admissions, use of
90 antibiotics and other medications in the 3 months prior to CDI. We gathered this
91 information through consultation of the physician in charge, as well as by using patient
92 records and the hospital electronic medical information system. The period of 3 months
93 prior to CDI was determined by calculating backwards from a reference date. For CDI
94 and non-CDI patients, this reference date was defined as the day on which the diarrhoea
95 started. The reference date for control patients was determined by adding the
96 hospitalized period of the matched CDI patient (time between admission and start of
97 diarrhoea) to the admission date of the control patient. Co-morbidity was assessed by

98 both the Charlson co-morbidity index and the ICD-10 classification in ten disease
99 groups; mentioned in table 1 [14].

100 **Statistical analysis.**

101 Continuous data were compared between groups using the T-test. The
102 Pearson's-chi-square test and the Fisher's exact test were used for the analysis of
103 proportions. Factors that were associated in univariate analysis (UVA) with a p-value
104 <0.10, as well as putative risk factors from earlier studies, were analyzed in a
105 multivariable model. Here, associations were always adjusted for age, sex, ward and
106 Charlson co-morbidity index. To evaluate the effect of medications and interventions on
107 (CDI) diarrhoea, we performed additional adjustments for co-medication and other
108 interventions. When comparing non-CDI patients with control patients, we also corrected
109 for the time between admission and the reference date. Relative risks were estimated as
110 odds ratios (OR) and presented with a 95% confidence interval (95% CI). Statistical
111 significance was reached with a 2-sided p-value <0.05; trends were defined by a p-value
112 <0.10. All analyses were performed using the SPSS for Windows software package,
113 version 17.0.

114 **Results**

115 During the 34 month study period, 93 patients were diagnosed with CDI. The
116 incidence varied from 0 to 43 per 10,000 hospital admissions with an average of 17.5.
117 During this period, no outbreaks were observed. CDI was community associated in four
118 patients (4.3%). Most patients (n=30; 32.3%) were hospitalized at the department of
119 internal medicine, followed by the general surgery ward (n=15; 16.1%). Eighty-nine CDI
120 patients were positive on both toxin testing and culture (95.7%). Isolates from 63 (67.7%)
121 patients were available for PCR-ribotyping: type 014 was the most frequently found type
122 (n=10; 15.9%), followed by types 078 (n=8; 12.7%) and 015 (n=5; 7.9%). Type 027 was
123 not present. Three patients with CDI had a co-infection with an enterovirus, norovirus,
124 and *Cryptosporidium*, respectively.

125 The 93 CDI patients were compared to 76 control patients and 64 patients with
126 non-CDI diarrhoea. Of all patients, physicians responded and records were available,
127 however, in some cases (the exact number is depicted in the subscript of table 1) no
128 information about use of nasogastric intubation, surgery or endoscopy was noted.

129 In the group of non-CDI patients, two patients were diagnosed with a rotavirus
130 and *Giardia Lamblia*, respectively. Among the other 62 patients no causal agent was
131 found. CDI patients had a median age of 56 years; non-CDI diarrhoea and control
132 patients had a median age of 50 years. Of the CDI patients, 60% were male, compared
133 to 50% and 54% of the non-CDI and control patients, respectively. The time span

134 between admission and start of diarrhoea did not significantly differ between CDI and
135 non-CDI patients.

136 ***Characteristics and risk factors.***

137 We present baseline characteristics and risk factors for CDI and non-CDI
138 diarrhoea in tables 1 and 2. The use of antibiotics as a risk factor for CDI and non-CDI is
139 depicted in table 3. All following results reached statistical significance in multivariable
140 analysis (MVA), unless otherwise stated.

141 *Age.* Patients with CDI were older than control patients (age > 65 years in 35.5%
142 vs. 23.7%; trend in MVA).

143 *Comorbidity.* Both CDI and non-CDI diarrhoeal patients had a higher Charlson
144 co-morbidity index (index of 3-4 or >5) than control patients (not significant). CDI patients
145 were more likely to have haematological malignancies, diseases of the urogenital tract or
146 other diseases (all trends in MVA). The category 'other diseases' comprised organ
147 transplants in 69.7%.

148 *Use of medications.* Compared to control patients, patients with CDI more
149 frequently used antibiotics, specifically second and third generation cephalosporins. CDI
150 patients also more frequently used penicillin and vancomycin (all significant only in
151 UVA). Furthermore, CDI patients used proton pump inhibitors (PPIs) more frequently
152 (significant only in UVA). The use of antacids (17.2% vs. 18.4%; OR 0.68; 95% CI 0.26-
153 1.79) or the combined use of PPIs and antacids (74.2% vs. 59.2%; OR 0.75; 95% CI

154 0.29-1.95) was not significantly more frequent in patients with CDI in MVA (data not
155 shown in the table).

156 Compared to control patients, patients with non-CDI diarrhoea more frequently
157 used third generation cephalosporins but less frequently used first generation
158 cephalosporins.

159 *Interventions and admissions.* Patients with CDI, compared to control patients,
160 were more frequently admitted in the previous 3 months, either at the hospital or ICU
161 department. They also more frequently had a nasogastric intubation or an endoscopy
162 (significant only in UVA).

163 Patients with non-CDI diarrhoea more frequently had a nasogastric intubation
164 (significant only in UVA), and were more frequently admitted to the ICU in the previous 3
165 months (trend in MVA).

166 ***Clinical course.***

167 Severe diarrhoea was present among 51 hospitalized patients with CDI (58.6%)
168 and 25 patients with non-CDI diarrhoea (39.7%) (OR 2.22; 95% CI 1.14-4.30). No
169 significant differences between CDI and non-CDI diarrhoeal patients were found
170 regarding the frequency of fever (55.6% resp. 43.3%), bloody stools (12.2% resp.
171 12.9%) or abdominal pain (54.5% resp. 48.2%). CDI patients did however have a higher
172 white blood cell count ($\geq 15 \times 10^9/l$: 49.9% resp. 30.0%, OR 2.28; 95% CI 1.13-4.59).
173 Most patients with CDI were treated with metronidazole (n=57; 63.3%), two patients
174 (2.2%) were treated with vancomycin and in 27 patients (30.0%) no specific CDI

175 treatment was initiated. The 30-day and 60-day mortality rates are depicted in figure 1.
176 At one month follow-up, a complicated course was observed in 9 CDI patients (10.3%),
177 comprising two colectomies, four ICU admissions due to CDI and seven deaths (7.5%).
178 CDI contributed directly to three of these deaths, but was not the primary cause. One
179 non-CDI patient (1.6%) and none of the control patients died at one month follow-up. No
180 significant association were detected between the severity of the diarrhoea, treatment or
181 outcome.

182 **Discussion**

183 In this 34 months prospective case control study, risk factors for CDI were
184 studied in an endemic setting with a low incidence rate of CDI. The inclusion of a control
185 group of patients with diarrhoea, tested negative for CDI, enabled us to discriminate
186 between risk factors for CDI and for diarrhoea in general.

187 Common risk factors for CDI outbreaks, such as age above 65 years and a high
188 comorbidity index, were recognized as trends in our study. This may be due to the fact
189 that these risk factors are of less importance in endemic settings, resulting in a lack of
190 power to discern these risk factors. Other well known risk factors for CDI, such as the
191 use of second generation cephalosporins and previous (ICU) admission were also found
192 in this endemic situation [3, 10, 15]. Conversely, the use of fluoroquinolones or PPIs was
193 not a risk factor for CDI. Furthermore, the previous use of third generation
194 cephalosporins was a risk factor for diarrhoea in general.

195 The CDI incidence in our hospital was lower than that described in other studies
196 in endemic situations, but comparable to the incidence of 18 per 10,000 hospital
197 admissions found in other Dutch hospitals [16]. Recently, a retrospective study analyzing
198 risk factors for CDI in an endemic setting in USA reported an incidence rate of CDI of
199 106 per 10,000 hospital admissions, which is a factor 5 higher than what we found in this
200 study [10]. There seems to be a considerable difference, per hospital and per country, in
201 the application of the definition of endemic CDI. Therefore, reported rates of endemic
202 CDI may merely reflect a baseline incidence.

203 In outbreak situations, the previous use of fluoroquinolones has been recognized
204 as an important risk factor for CDI [9, 11, 17, 18]. This association may be due to
205 disruption of the gut flora by newer fluoroquinolones or the high fluoroquinolone
206 resistance found among hypervirulent type 027 strains [19]. Although fluoroquinolones
207 (mainly ciprofloxacin) were frequently prescribed in this study, we found no association
208 with CDI. An explanation could be that we did not encounter type 027 in our hospital.
209 The most frequently found PCR-ribotypes in our study (types 014, 078 and 015) are
210 commonly found in the Netherlands and Europe and are more susceptible to
211 fluoroquinolones than type 027 [11].

212 The use of vancomycin was previously recognized as a risk factor for endemic
213 CDI [10]. Instead, in this study, the association between vancomycin and CDI was
214 strongly confounded by concomitant use of second and especially third generation
215 cephalosporins (the combination is part of the in-house empirical sepsis therapy) and
216 was not a risk factor for CDI.

217 PPIs raise the gastric pH, which is associated with enhanced bacterial
218 colonization of first part of the GI-tract. Studies to the use of PPIs in association with CDI
219 revealed conflicting conclusions [20, 21]. In our study, we found no association of the
220 use of PPIs with CDI. It should be noted that half of the non-CDI and control patients
221 also used PPIs.

222 Earlier studies have found high contamination and colonization rates with *C.*
223 *difficile* spores in the hospital environment, among hospitalized patients and

224 asymptomatic carriers [22, 23]. A high colonization pressure on a ward (exposure in time
225 to multiple colonized or infected patients) is associated with an increased risk of CDI
226 [10]. To insure that CDI and control patients were exposed to a similar colonization
227 pressure, we selected control patients from the same ward as CDI patients using the
228 same time period between admission and reference date [24].

229 We observed contributable and overall mortality rates of 3.2% and 7.5% after 30-
230 days follow-up, respectively. These rates are in between the overall 30-day mortality rate
231 of 4.7%, found in an endemic setting in Canada, and a reported rate of 20% after 60
232 days in a U.S. study [25, 26]. These mortality rates are much lower than those reported
233 during outbreaks caused by the type 027 strain [3, 11, 26, 27]. In the Netherlands, a
234 complicated course due to type 027 was described in 12,5%, with an attributable
235 mortality rate of 6.3% [9].

236 Our study has several limitations. First, we used the presence of toxins in faeces
237 as a screening test for CDI which is in agreement with the European recommendations
238 [28]. An alternative standard for diagnosing CDI is the detection of *C. difficile* in faeces
239 by toxinogenic culture or PCR. Application of this definition could have resulted in a
240 different case and non-CDI control group. However, none of the patients with non-CDI
241 diarrhoea developed CDI at a later moment during admission, which was in accordance
242 with the high negative predictive value of our toxin test. Second, although the endemic
243 incidence found in our study is comparable to that in other Dutch hospitals, it is lower

244 than incidence rates reported in other studies in endemic situations, which can imply that
245 our findings may not be applicable to endemic situations in other countries [8, 26, 29].

246 In conclusion, in this endemic setting, some risk factors for CDI were similar to
247 those found in outbreak situations, but some risk factors that have earlier been ascribed
248 to CDI were in this study not specific for CDI, but for diarrhoea in general. Use of
249 fluoroquinolones and PPIs did not influence the risk of endemic CDI. CDI patients were
250 more severely ill than non-CDI diarrhoeal patients, as illustrated by a higher leukocyte
251 count and the relatively high 30- and 60-day mortality. Because CDI is the most
252 important cause of nosocomial diarrhoea, more studies are needed to determine the
253 long term outcome associated with *C. difficile* infections.

254

255 **Transparency declarations**

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347

Table 1: Baseline characteristics of patients with CDI, patients with non-CDI diarrhea and control patients.

Risk factors	CDI patients (N=93) [◦]		Non-CDI patients (N=64) ^{◦◦}		Control patients (N=76) ^{◦◦◦}	
	N	(%)	N	(%)	N	(%)
Age > 65 years	33	(35.5)	18	(28.1)	18	(23.7)
Male sex	56	(60.2)	32	(50.0)	41	(53.9)
Charlson co-morbidity index						
0	14	(15.1)	12	(18.8)	19	(25.0)
1-2	38	(40.9)	26	(40.6)	32	(42.1)
3-4	28	(30.1)	15	(23.4)	18	(23.7)
5+	13	(14.0)	11	(17.2)	7	(9.2)
Any underlying disease	90	(96.8)	61	(95.3)	70	(92.1)
Malignancy	24	(26.1)	18	(28.1)	21	(27.6)
Solid tumor	10	(10.9)	5	(7.8)	11	(14.5)
Hematologic malignancy	15	(16.1)	13	(20.3)	10	(13.2)
Endocrine diseases	26	(28.0)	16	(25.0)	20	(26.3)
Respiratory tract diseases	14	(15.1)	9	(14.1)	8	(10.5)
Gastro-intestinal tract diseases	36	(38.7)	16	(25.0)	21	(27.6)
Cardiovascular tract diseases	42	(45.2)	27	(42.2)	30	(39.5)
Urogenital tract diseases	42	(45.2)	21	(32.8)	24	(31.6)
Nervous system diseases	6	(6.5)	4	(6.2)	6	(7.9)
Infectious diseases	13	(14.3)	6	(9.4)	7	(9.2)
Muscular / conn. tissue diseases	10	(10.8)	4	(6.2)	7	(9.2)
Other diseases	36	(39.1)	24	(37.5)	22	(28.9)
Any antibiotic	87	(93.5)	48	(75.0)	51	(68.0)
Proton pump inhibitors	64	(68.8)	36	(56.2)	38	(50.0)
NSAIDs	11	(11.8)	3	(4.7)	7	(9.2)
Immunosuppressive agents	54	(58.8)	38	(59.4)	34	(44.7)
Cytostatic agents	21	(22.6)	13	(20.3)	11	(14.5)
Nasogastric tube	39	(44.3)	29	(45.3)	20	(28.2)
Abdominal surgery	35	(37.6)	24	(37.5)	20	(28.6)
Endoscopy	28	(31.5)	16	(25.0)	10	(13.2)
Previous admission	68	(74.7)	19	(30.2)	30	(41.7)
Previous admission to ICU	26	(28.0)	12	(18.8)	5	(6.6)

◦ N between 88 and 93

◦◦ N between 62 and 64

◦◦◦ N between 71 and 76

ICU: intensive care unit

NSAIDs: non-steroidal anti-inflammatory drugs

Table 2: Crude and adjusted odds ratios for development of CDI and non-CDI diarrhea.

Risk factors	CDI vs. Control		Non-CDI vs. Control	
	Crude odds ratio (95% C.I.)	Adjusted odds ratio (95% C.I.)	Crude odds ratio (95% C.I.)	Adjusted odds ratio (95% C.I.)
Age > 65 years	1.77 (0.90-3.49) ^	1.82 (0.92-3.62) ^	1.26 (0.59-2.69)	1.17 (0.54-2.55)
Male sex	1.29 (0.70-2.39)	1.30 (0.70-2.43)	0.85 (0.44-1.67)	0.88 (0.45-1.72)
Charlson co-morbidity index				
0	Reference	Reference	Reference	Reference
1-2	1.61 (0.70-3.72)	1.78 (0.73-4.37)	1.29 (0.53-3.13)	1.35 (0.50-3.66)
3-4	2.11 (0.85-5.24)	2.42 (0.87-6.73) ^	1.32 (0.49-3.57)	1.32 (0.41-4.30)
5+	2.52 (0.80-7.95)	2.57 (0.76-8.65)	2.49 (0.76-8.19)	3.10 (0.82-11.7) ^
Any underlying disease	2.57 (0.62-10.7)	2.45 (0.58-10.4)	1.74 (0.42-7.27)	2.10 (0.46-9.56)
Hematologic malignancy	1.27 (0.54-3.01)	2.33 (0.86-6.23) ^	1.68 (0.68-4.15)	2.19 (0.70-6.88)
Urogenital tract diseases	1.78 (0.95-3.36) ^	1.97 (0.97-4.02) ^	1.06 (0.52-2.16)	0.99 (0.42-2.34)
Other diseases	1.58 (0.83-3.02)	1.47 (0.72-3.00) ^	1.47 (0.73-2.99)	1.41 (0.65-3.07)
Any antibiotic	6.82 (2.62-17.8) ^^	5.41 (1.79-16.3) ^^	1.41 (0.67-2.98)	0.99 (0.40-2.42)
Proton pump inhibitors	2.21 (1.18-4.14) ^^	1.14 (0.51-2.58)	1.29 (0.66-2.51)	1.01 (0.46-2.22)
NSAIDs	1.32 (0.49-3.60)	0.86 (0.27-2.73)	0.49 (0.12-1.96)	0.34 (0.07-1.57)
Immunosuppressive agents	1.71 (0.93-3.15) ^	1.39 (0.64-3.06)	1.81 (0.92-3.54) ^	1.44 (0.64-3.22)
Cytostatic agents	1.72 (0.77-3.85)	1.61 (0.61-4.24)	1.51 (0.62-3.64)	1.64 (0.58-4.63)
Nasogastric tube	2.03 (1.04-3.95) ^^	1.50 (0.66-3.43)	2.11 (1.04-4.31) ^^	1.77 (0.70-4.50)
Abdominal surgery	1.51 (0.77-2.94)	1.17 (0.56-2.45)	1.50 (0.73-3.10)	1.28 (0.57-2.84)
Endoscopy	3.03 (1.36-6.75) ^^	2.64 (1.00-6.96) ^	2.20 (0.92-5.27) ^	2.63 (0.90-7.64) ^
Previous admission	4.14 (2.13-8.05) ^^	4.49 (2.23-9.01) ^^	0.61 (0.30-1.23)	0.55 (0.26-1.17)
Previous admission to ICU	5.51 (2.00-15.2) ^^	5.47 (1.95-15.3) ^^	3.28 (1.09-9.87) ^^	2.64 (0.83-8.37) ^

^ Trend detected (p<0.10)

^^ Significant difference (p<0.05)

ICU: intensive care unit

NSAIDs: non-steroidal anti-inflammatory drugs

Table 3: The use of antibiotics expressed in Defined Daily Doses (DDD) in patients with CDI and non-CDI diarrhea and control patients.

Antibiotics	CDI patients (N=93) °		Non-CDI patients (N=64) °		Control patients (N=76) °		CDI vs. Control		Non-CDI vs. Control	
	N	(%)	N	(%)	N	(%)	Crude odds ratio (95% C.I.)	Adjusted odds ratio (95% C.I.)	Crude odds ratio (95% C.I.)	Adjusted odds ratio (95% C.I.)
Cephalosporins										
1st generation	13	(14.0)	5	(7.8)	12	(16.0)	0.85 (0.36-2.00)	0.79 (0.21-3.02)	0.45 (0.15-1.34)	0.18 (0.04-0.84) ^^
2nd generation	46	(49.5)	20	(31.3)	14	(21.5)	4.26 (2.10-8.67) ^^	7.64 (2.42-24.2) ^^	1.98 (0.90-4.34)	0.97 (0.31-3.05)
3rd generation	29	(31.2)	12	(18.8)	2	(3.1)	16.5 (3.80-72.1) ^^	20.4 (3.50-119) ^^	8.42 (1.81-39.2) ^^	9.53 (1.66-54.7) ^^
Penicillins	51	(54.8)	22	(34.4)	23	(30.7)	2.75 (1.45-5.20) ^^	1.47 (0.58-3.72)	1.18 (0.58-2.41)	0.69 (0.27-1.74)
Fluoroquinolones	31	(33.3)	21	(32.8)	20	(26.7)	1.38 (0.70-2.69)	0.57 (0.20-1.62)	1.34 (0.65-2.79)	0.93 (0.32-2.70)
Clindamycin	5	(5.4)	2	(3.1)	1	(1.3)	4.21 (0.48-36.8)	0.75 (0.03-17.2)	2.39 (0.21-27.0)	2.68 (0.14-50.2)
Vancomycin	22	(23.7)	14	(21.9)	7	(9.3)	3.01 (1.21-7.50) ^^	0.51 (0.11-2.40)	2.72 (1.02-7.23) ^^	1.55 (0.43-5.62)

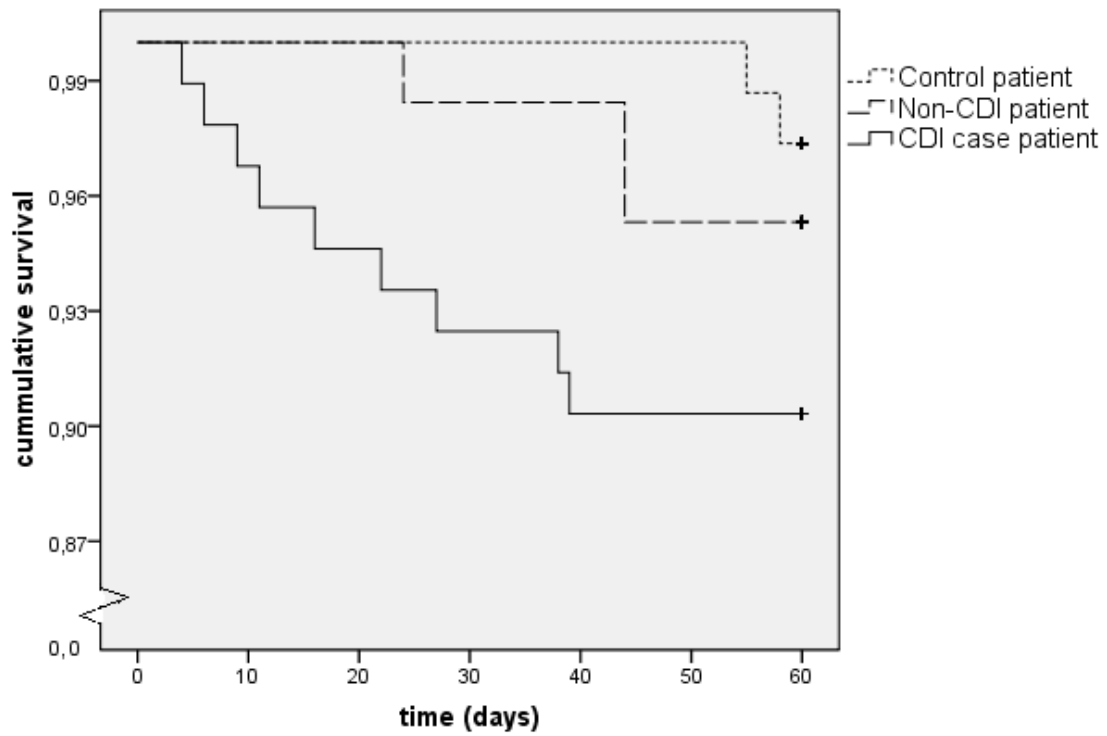
° This information was known for all patients, except one control patient

^ Trend (p<0.10) detected

^^ Significant difference (p<0.05) detected

351 **Figure 1: Survival curve of patients with CDI, non-CDI diarrhoea and control patients, in a**
352 **period of 60 days after the reference date.**

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