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1 Factors affecting reported *Clostridioides difficile* infection rates; the more you look the more
2 you find, but should you believe what you see?

3

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41

42 Abstract:

43

44 Background:

45 Reported rates of *C. difficile* infection (CDI) have increased in many settings; however, these
46 can be affected by factors including testing density (test-density) and diagnostic methods.

47 We aimed to describe the impact of multiple factors on CDI rates.

48

49 Methods:

50 Hospitals (n= 182) across five countries (France, Germany, Italy, Spain, and UK) provided
51 data on; size and type of institution, CDI testing methodology, number of tests / month and
52 patient-bed-days (pbds) / month over one year. Incidence rates were compared between
53 countries, different sized institutions, types of institutions and testing method.

54

55 Results:

56 After univariate analyses, the highest CDI rates were observed in Italy (average
57 11.8/10,000pbds/hospital/month), acute/primary hospitals
58 (12.3/10,000pbds/hospital/month), small hospitals (16.7/10,000pbds/hospital/month), and
59 hospitals using methods that do not detect toxin (NO-TOXIN) (e.g. GDH/NAAT or standalone
60 NAAT) (10.7/10,000pbds/hospital/month). After adjusting for test-density, highest
61 incidence rates were still in Italy, acute/primary hospitals and those using NO-TOXIN. The
62 relative rate in long-term healthcare facilities (LTHCFs) increased, but size of institution no
63 longer influenced the CDI rate. .

64

65 Conclusions:

66 Test-density appears to have the largest effect on reported CDI rates. NO-TOXIN testing still
67 influences CDI rates, even after adjusting for test-density, which is consistent with tests that
68 ‘overall’ true CDI. Low test-density can mask the true burden of CDI, e.g. in LTHCFs,
69 highlighting the importance of good quality surveillance.

70

71 Introduction:

72 The burden of *Clostridioides difficile* infection (CDI) in healthcare settings worldwide is
73 considerable; published articles on '*Clostridium difficile*' increased almost 3-fold in the last
74 decade [1]. *C. difficile* has been listed as one of the three most important antibiotic
75 resistant pathogens by the US centres for Disease Control and Prevention (CDC), and the
76 European Centre for Disease Prevention and Control (ECDC) recommends that all countries
77 undertake CDI surveillance [2-3].

78

79 Reported CDI rates have increased both within healthcare settings and in the community [4-
80 6], as documented in large multi-national European studies from 2008-2013 [4-5]. Whilst
81 surveillance is encouraged, there is little information on how to interpret CDI rate data,
82 especially considering the potential for ascertainment bias. Some factors can affect
83 surveillance data, but studies are usually based on univariate analyses. A recent pilot study
84 demonstrated that reported rates can be impacted by factors including testing frequency
85 and diagnostic methods [7]. In addition, US surveillance data had to be adjusted to take
86 account of the use of NAATs; sensitivity analyses showed that the rate was inflated by
87 approximately 2-2.5 times if all versus no laboratories used NAATs for CDI diagnosis [8].
88 Little attention has been given, however, to the potential relationship of such factors with
89 seasonal CDI variation. For example, if a country reports that they have no cases of CDI, is
90 this because they have not tested, they have used the wrong laboratory methods, or they
91 have not collected the right data?

92

93 Using a systematic, observational large scale sampling approach, which was first successfully
94 piloted in 2014-2015 [7], we aimed to describe the impact of multiple factors on CDI rates
95 using a multivariate model.

96

97 Methods:

98 National coordinators recruited 182 hospitals across five countries; France (n = 39),
99 Germany (n = 38), Italy (n = 38), Spain (n = 30), and UK (n = 37) to represent a wide
100 geographical area, in accordance with the selection criteria in a pilot study [7]. Hospitals
101 provided institutional data (size and type of institution), details of CDI laboratory diagnostic
102 methods, and policies in use for the period April 2014 to March 2015, and monthly data on
103 numbers of CDI tests and cases for the same time period via a dedicated on-line secure
104 study database. These data were collected prospectively for the 60 pilot study hospitals [7]
105 and retrospectively for an additional 112 hospitals added to the full study. Additional
106 demographic data were collected for each CDI case (as defined locally, dependant on local
107 testing strategy) and for selected CDI negative controls (all CDI negative patients with
108 samples collected on 3 specified days within each of July 2014 and January 2015).

109

110 Participating institutions were classified by size: small <100,000 patient bed days (pbd) per
111 annum; medium 100,000-500,000 pbds per annum; and large >500,000pbds per annum;
112 and by type; primary - district or first level referral hospital without teaching function;
113 secondary - provincial hospital with some specialisms with some teaching function; tertiary
114 - central or region referral hospital with highly specialised staff, often a university hospital or
115 associated with a university. CDI testing methods were classified according to European
116 guidelines [9]: recommended algorithm (two-stage test of GDH or NAAT followed by direct

117 toxin detection); non-recommended algorithm (two or three stage test not matching the
118 first criteria, e.g. culture followed by toxin detection); methods only detecting toxin 'Toxin-
119 only' (e.g. standalone toxin enzyme immunoassay (EIA); and methods not detecting toxin
120 'NO TOXIN' (e.g. GDH/NAAT or standalone NAAT). All data were analysed at the European
121 coordinating centre.

122 This surveillance study was granted ethical approvals as follows: University of Leeds
123 (SoMREC13032) for UK data collection and European wide analysis; the national Institute for
124 Infectious Diseases 'Spallanzani', Rome, for Italian data collection. Ethical approval was not
125 required in France, Germany or Spain.

126

127 Data analysis

128 Monthly testing and incidence CDI rates (primary and recurrent) were calculated per 10,000
129 pbds for each hospital, and were compared between countries/institutions, according to
130 size, type and testing method. Patient demographics were compared for the same
131 variables. CDI rates were also compared between summer (June-August) and winter
132 (December-February). Outlier hospitals (n = 11) with an average of
133 >200cases/10,000pbds/month were removed from the analysis to prevent bias; there were
134 no outlier hospitals with low case rates. For univariate analyses, rates and age distributions
135 were compared by Kruskal-Wallis, and proportions were compared by Chi-squared.
136 Analyses were performed on SPSS 21 (IBM).

137

138 Results:

139 There were 182 participating hospitals across five countries. There were no acute/primary
140 hospitals recruited in Spain, but there were similar proportions of secondary hospitals in all
141 five countries (Supplementary materials). France and Spain had no speciality hospitals, and
142 only Italy and Spain had long-term care facilities (LTCF). There were also larger proportions
143 of small hospitals in Italy and Spain than the other three countries (Supplementary
144 materials).

145

146 National testing guidelines

147 Although 116/182 hospitals reported that they had national guidelines, only 107/116
148 (92.2%) confirmed that they followed these (Supplementary materials); compliance was
149 100% in France and the UK, but only 50% in Germany, although only 32% of the latter
150 hospitals reported that they had knowledge of existing national guidelines. There was
151 higher awareness of national guidelines in large hospitals (100%), compared with smaller
152 institutions (57.7%). Secondary and tertiary facilities also had higher levels of awareness of
153 national guidelines (69.1% and 68.1%, respectively), with equally high levels of compliance
154 (89.4% and 98.9%, respectively) (Supplementary materials).

155

156 Testing methodology

157 UK hospitals had the highest proportion following the recommended algorithm (89.2%).
158 Italy had the highest number of hospitals using Toxin-only methods (13.2%), primarily in
159 Specialist institutions. German hospitals favoured NO-toxin methods (78.9%). The UK had
160 the least variation in testing methodology across the different hospital types (Figure 1). In
161 France, 100% of Acute/Primary level hospitals used recommended methods, but use of NO-
162 toxin increased from primary to secondary to tertiary centres. In Spain, approximately 30%

163 of testing within hospitals was via a recommended algorithm; however, only non-
164 recommended algorithms were used in LTHCFs.
165
166 Testing and case density univariate analyses
167 The highest reported testing rates were observed in UK hospitals, Secondary and Tertiary
168 hospitals, small hospitals and those using non-recommended testing methods (all
169 comparisons $P < 0.001$ by Kruskal Wallis) (Figure 2). The highest reported CDI rates were
170 observed in Italian hospitals (average of 11.8/10,000pbds/hospital/month) acute/primary
171 hospitals (12.3/10,000pbds/hospital/month), small hospitals (16.7 /10,000pbds/
172 hospital/month) and those institutions using methods that do not detect toxin
173 (10.7/10,000pbds/hospital/month) (all comparisons $P < 0.001$, except testing method which
174 is non-significant) (Figure 3a). After adjusting for testing density, the highest incidence rates
175 were still seen in Italian hospitals and in those institutions that using NO-toxin methods.
176 There was a large variance in rates according to institution type; LTHCFs had a similar CDI
177 rate as the acute/primary hospitals after adjusting for testing density (13.9 and 12.5CDI
178 cases/10,000pbds per tests/10,000pbds/hospital/month, respectively). Additionally, the
179 size of the hospital no longer influenced the CDI rate (Figure 3b).
180
181 When reported CDI rates were compared between summer and winter months, Italian
182 hospitals and those using Toxin-only or NO-toxin methods had significant differences (Italy
183 12.6 versus 9.7 cases/10,000pbds winter vs summer, respectively, $p = 0.017$, toxin-only 18.3
184 vs 5.5 cases/10,000pbds winter vs summer, respectively $p = 0.039$, NO-toxin 13.8 vs 9.3
185 cases/10,000pbds winter vs summer, respectively $p = 0.044$) (Figure 4a). Once testing rate
186 was taken into consideration, only Italian hospitals and those using toxin-only had

187 significantly more CDI cases in winter than in summer (Italy 0.20 vs 0.15 cases/10,000 per
188 tests/10,000pbds winter vs summer, respectively $p = 0.02$, toxin-only 0.11 vs 0.04
189 cases/10,000 per tests/10,000pbds winter vs summer respectively $p = 0.05$) (Figure 4b).

190

191

192 Patient demographic data

193 Of patients tested for CDI, the median age of patients with a CDI positive test was
194 significantly higher than those with a negative test result (76 vs 70 years, Mann Whitney $p =$
195 <0.001) (Table 1). Tested patients in Italy were significantly older than subjects in other
196 countries (Kruskall-wallis $p = <0.001$) (Table 1). The median age of all patients tested for CDI
197 (regardless of country) was significantly higher for hospitals using toxin-only (80 years) or
198 no-toxin methods (76 years) compared with those using the recommended algorithm (74
199 years) (both $P <0.001$).

200

201 In the UK, patients were tested for CDI significantly earlier than those in other countries
202 (mean 3 days between admission and testing both for those with and without reported CDI
203 (Kruskall-wallis $p \leq 0.001$) (Table 1). The definition of 'diarrhoea' in the UK was less strict (any
204 loose stool) compared with in other countries (at least 3 loose stools).

205

206 Discussion:

207 Our large European, multi-centre study highlighted the impact of several key factors on
208 reported CDI rates. Testing rate has a large impact on reported CDI incidence even when
209 other factors are considered. Our previously published findings based on pilot data across
210 three countries have been confirmed here after extension to include more hospitals and a

211 further two countries [8]. As before, the highest CDI reported rate was in Italy, with an
212 average of 11.8 /10,000pbds/hospital/month. Germany and Spain had similar CDI rates (6.1
213 and 5.9/10,000pbds, respectively), which were higher than incidences in France and UK (3.2
214 and 2.5/10,000pbds, respectively). This may be related to the method of testing, especially
215 in Germany where a large number of hospitals used no-toxin methods (and may therefore
216 over-report true CDI cases) [10]. Italy was also the only country in which an increase in case
217 density was seen over the winter months (average of 12.6/10,000pbds/hospital/month in
218 winter versus an average of 9.7 in summer) (Figure 4). Since this was also the country with
219 the highest CDI case density, this may reflect outbreaks, as countries with low CDI rates
220 (France and UK) do not see such seasonal variation. Importantly, Italy still had the highest
221 CDI incidence even after adjustment for testing rate (Figure 3b), suggesting that high
222 endemic rates are truly present in Italy.

223

224 In comparison with two previous studies, France has had consistently reported levels of
225 testing since 2008 (45/10,000 pbds [4] and 38.2/10,000pbds [5]). Conversely, levels of
226 testing in Germany appear to have decreased to an average of 52.8/10,000pbds (72 and
227 70/10,000pbds previously [4,5]).The reasons for this decrease are not clear, although it
228 could be related to financial pressures. It is also possible that a perceived decrease in case
229 numbers leads to a decrease in testing rates. Italy had a similar level of testing to that
230 reported in 2011/2012 (67.6/10,000pbds), but an increase from that in 2008
231 (39/10,000pbds). In Spain, however, the testing rate has been steadily increasing since 2008
232 (45/10,000pbds, to 57.3/10,000pbds in 2011/2012 and 83.3/10,000pbds in this study (2014)
233 [4,5]. Although the UK has consistently had the highest testing levels throughout the last
234 decade, these rates have decreased from 115/10,000pbds and 132.5/10,000pbds seen in

235 2008 and 2011/2012 to 96/10,000pbds in this study (2014) [4,5]. This may represent some
236 complacency within the UK healthcare system where CDI rates have fallen markedly from
237 their peaks around 2007/08 [11].

238

239 Primary hospitals had the highest CDI rates and showed the most intra-year variation in case
240 density, with an increase in late winter; summer vs winter 9.6 vs 11.3; tertiary hospitals had
241 a small increase between summer vs winter (6.9 vs 8.5 cases/10,000pbds/ hospital/month).
242 The effect of testing density was clearly apparent when examining the CDI rates in LTHCFs,
243 which had very low levels of testing, therefore likely masking their true CDI rate (Figures 3a
244 and b); variation of CDI rates was also marked in this hospital type, presumably driven by
245 the low testing density and the possibility of missing cases. Previously we have shown that
246 small hospitals appear to have high CDI rates in comparison with larger facilities [8].

247 However, we have now been able to show that once testing density is taken into
248 consideration, this difference is no longer significant; the high reported CDI rate in small
249 hospitals appears to be largely driven by high testing rates (Figure 3a and b). The reasons
250 behind this high testing rate are unclear, and do not appear to be driven by guidelines, as
251 smaller hospitals had lower levels of awareness of national guidelines than larger hospitals
252 (57.7% vs 100%). This is perhaps unsurprising given that larger hospitals often have
253 dedicated microbiology laboratories and staff, compared with less specialised staff at
254 smaller hospitals.

255

256 The method of testing clearly has an impact on the reported rates of CDI, with previous
257 studies highlighting both under- and over-diagnosis of cases [4,10,12]. Importantly
258 however, for the first time we have been able to show that this is still true, even after

259 figures have been adjusted to take account of the testing rate (Figures 3a and b). In
260 addition, there is marked seasonal variation in case density in those hospitals using toxin-
261 only methods, with an average over the year of 10.1/10,000pbds, but a mean of
262 5.5/10,000pbds in summer vs 18.3/10,000pbds in winter (Figure 4a and b). The reason for
263 this increase in winter months is unclear; however it is possible that toxin viability is
264 affected during the summer months. It is also clear that those hospitals using NO-toxin
265 methods have a consistently higher positivity rate, in keeping with a test that 'overcalls' true
266 CDI (Figure 4a and b) [10,12].

267

268 The median age and age distribution of tested patients in Italy was significantly higher than
269 elsewhere (Table 1), potentially reflecting targeted testing. This is comparable with the data
270 from our pilot study, where Italian cases were older than those in France and the UK [8]. The
271 addition of data regarding the age of patients without CDI, however, has enabled us to show
272 that the median age of patients tested for CDI in Italy was older than in other countries,
273 reflecting different targeting of testing. The median age of tested patients was also
274 significantly higher in hospitals using toxin-only or NO-toxin methods, than those using
275 other testing methodologies. Again, this confirms the pilot study data (for positive patients
276 only) that showed that CDI cases were significantly older in hospitals using these two testing
277 methodologies [8]. Previous evidence shows that CDI patients with a missed diagnosis of CDI
278 are significantly younger than those who were diagnosed [4]. In our study it would appear
279 that those hospitals that are not using the latest recommended testing methods also target
280 who they test for CDI, preferentially targeting the elderly, and potentially showing a lack of
281 awareness of current testing guidelines [9].

282

283 There are some limitations to our study, the most important of which is the low number of
284 LTHCFs included. It is particularly difficult to study these facilities, but the low testing rates
285 highlighted here demonstrate a clear need to engage with these institutions. In addition,
286 whilst this is a large study with 182 hospitals, they only represented facilities in five
287 countries; there is a need to expand this data collection across Europe given the country
288 specific issues we have identified. Whilst participating sites were selected to cover as wide
289 a geographical area as possible, the non-random nature of this process may have introduced
290 some bias. There is the possibility of co-linearity between the variables described, this could
291 be addressed by multivariate analysis, such as time series analysis, however such analyses
292 were outside the scope of this project. As this study expanded from a prospective pilot
293 study, this required the new hospitals to collect the data retrospectively. Whilst it is possible
294 that this may have introduced some bias, the data collected was extracted from electronic
295 laboratory management systems, thereby removing any recall bias. Finally, we did not
296 determine the appropriateness of testing on a per patient basis, as this was outside of the
297 scope of this project.

298

299 Low testing density has a large effect on reported CDI rates and can mask the true burden of
300 CDI, such as in long-term healthcare facilities, highlighting the importance of good quality
301 surveillance. Use of standalone NAAT testing still results in higher CDI rates even when
302 testing density is taken into account; this is consistent with a test that 'overcalls' true CDI. It
303 is therefore important to follow the ESCMID guidelines and use optimal testing
304 methodology. . It is therefore imperative that these factors are taken into account when
305 reviewing and comparing CDI incidence data.

306

307 Author contributions:

308 The LUCID study was designed by KD, GD, FB, NP, CD and MHW, with contribution from
309 Sanofi Pasteur. GD was responsible for project management and logistics. KD was principal
310 scientific European Coordinator. KD, FB, NP, RP, GB, FKB, ERR and EB were national
311 coordinators for each country. KD analysed the data and wrote the manuscript in
312 conjunction with MHW. All authors reviewed and approved the manuscript.

313 Parts of this work were previously presented at ASM Microbe 2016, Boston, USA, and
314 European Congress on Clinical Microbiology and Infectious Disease 2017, Vienna, Austria.

315 This manuscript is original and has not been published elsewhere.

316

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322 April 2017.

323

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326

327 **Conflicts of interest**

328 KD has received honoraria from Astellas Pharma Europe, Cepheid Inc and Summit, and grant
329 support from Astellas Pharma Europe, bioMerieux, Pfizer and Sanofi-Pasteur. GD has

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345 CD is an employee of Sanofi Pasteur. All other authors have no conflicts to declare.

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