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

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Abstract:

Background:

Reported rates of *C. difficile* infection (CDI) have increased in many settings; however, these can be affected by factors including testing density (test-density) and diagnostic methods. We aimed to describe the impact of multiple factors on CDI rates.

Methods:

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

Results:

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

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 'overcall' 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

Introduction:

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

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

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

Methods:

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

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

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

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

Data analysis

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

Results:

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

National testing guidelines

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

Testing methodology

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

of testing within hospitals was via a recommended algorithm; however, only non-recommended algorithms were used in LTHCFs.

Testing and case density univariate analyses

The highest reported testing rates were observed in UK hospitals, Secondary and Tertiary hospitals, small hospitals and those using non-recommended testing methods (all comparisons P< 0.001 by Kruskall Wallis) (Figure 2). The highest reported CDI rates were observed in Italian hospitals (average of 11.8/10,000pbds/hospital/month) acute/primary hospitals (12.3/10,000pbds/hospital/month), small hospitals (16.7 /10,000pbds/ hospital/month) and those institutions using methods that do not detect toxin (10.7/10,000pbds/hospital/month) (all comparisons P <0.001, except testing method which is non-significant) (Figure 3a). After adjusting for testing density, the highest incidence rates were still seen in Italian hospitals and in those institutions that using NO-toxin methods. There was a large variance in rates according to institution type; LTHCFs had a similar CDI rate as the acute/primary hospitals after adjusting for testing density (13.9 and 12.5CDI cases/10,000pbds per tests/10,000pbds/hospital/month, respectively). Additionally, the size of the hospital no longer influenced the CDI rate (Figure 3b).

When reported CDI rates were compared between summer and winter months, Italian hospitals and those using Toxin-only or NO-toxin methods had significant differences (Italy 12.6 versus 9.7 cases/10,000pbds winter vs summer, respectively, p = 0.017, toxin-only 18.3 vs 5.5 cases/10,000pbds winter vs summer, respectively p = 0.039, NO-toxin 13.8 vs 9.3 cases/10,000pbds winter vs summer, respectively p = 0.044) (Figure 4a). Once testing rate 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≤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

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

Primary hospitals had the highest CDI rates and showed the most intra-year variation in case density, with an increase in late winter; summer vs winter 9.6 vs 11.3; tertiary hospitals had a small increase between summer vs winter (6.9 vs 8.5 cases/10,000pbds/ hospital/month). The effect of testing density was clearly apparent when examining the CDI rates in LTHCFs, which had very low levels of testing, therefore likely masking their true CDI rate (Figures 3a and b); variation of CDI rates was also marked in this hospital type, presumably driven by the low testing density and the possibility of missing cases. Previously we have shown that small hospitals appear to have high CDI rates in comparison with larger facilities [8]. However, we have now been able to show that once testing density is taken into consideration, this difference is no longer significant; the high reported CDI rate in small hospitals appears to be largely driven by high testing rates (Figure 3a and b). The reasons behind this high testing rate are unclear, and do not appear to be driven by guidelines, as smaller hospitals had lower levels of awareness of national guidelines than larger hospitals (57.7% vs 100%). This is perhaps unsurprising given that larger hospitals often have dedicated microbiology laboratories and staff, compared with less specialised staff at smaller hospitals.

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

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

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

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

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

Author contributions:

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

Parts of this work were previously presented at ASM Microbe 2016, Boston, USA, and European Congress on Clinical Microbiology and Infectious Disease 2017, Vienna, Austria. This manuscript is original and has not been published elsewhere.

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Conflicts of interest

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

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	Hospital Clínico San Carlos Complejo Hospitalario	Paloma Merino
	Hospital Clinico Universitario Lozano Blesa	Cristina Seral
	Hospital de Galdakao	Ana Patricia Martinez
	Hospital Doctor Moliner	Salvador Giner
	Hospital General de Mostoles	María Teresa Pérez Pomata
	Hospital General La Mancha Centro	Rafael Carranza González
	Hospital General Virgen de la Luz de Cuenca	María José Rodríguez
	Hospital Gregorio Universitario Maranon	Elena Reigadas
	Hospital Nicolas Pena	Lucía Martínez-Lamas
	HOSPITAL NTRA. SRA. DE SONSOLES (COMPLEJO HOSPITALARIO DE ÁVILA)	Rafael Sánchez Arroyo
	Hospital Regional Universitario Carlos Haya	María Concepción Mediavilla
	Hospital San Augustin	Beatriz Iglesias
	Hospital son Espases	Ana Mena
	Hospital Universitario 12 de Octubre	María Angeles Orellana
	Hospital Universitario Central de Asturias	Jonathan Fernandez Suarez
	Hospital Universitario de Burgos	Eva Ojeda Fernández
	Hospital Universitario de Canarias	Laura Sante
	Hospital Universitario de Cruces	Ildefonso Perales Palacios
	Hospital Universitario de Salamanca	Olaia Cores
	Hospital Universitario Augusti (Hula)	Julia Pita Carretero
	Hospital Universitario Marques de Valdecilla	Marina Fernandez
	Hospital Universitario Virgen del Rocio	Angel Rodríguez
	Hospital Virgen de la Concha Area 11	Miriam Albert
	Policlinico Vigo Sa-Povisa	Irene Rodriguez Conde
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