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1 **Establishment of a French surveillance system of *Clostridioides difficile* infection:**
2 **comparison of patient's characteristics with other national and European data**
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25 **ABSTRACT**

26 **Introduction:** The magnitude and scope of *Clostridioides difficile* infection (CDI) has changed with an
27 increase in incidence and severity. The epidemiology of CDI is not well known in France due to
28 difficulties to conduct large continuous surveillance. The objectives were to compare the
29 characteristics of patients with CDI collected through repeated point prevalence survey via DIFTEC™,
30 a free electronic tool, with those from previous French or European studies.

31 **Methods:** DIFTEC™ was developed to evaluate epidemiological burden, diagnostic strategies and
32 management of CDI in France. National and European guidelines were used for definitions.

33 A literature review of studies conducted in Western Europe on CDI and published between January,
34 2008 and May, 2018 was done to compare their data with those included in the DIFTEC™ database.

35 **Results:** From January 2016, to December 2017, 455 CDI episodes from 22 French hospitals were
36 included. Most of CDI cases were health-care associated (HCA) (78%).

37 The comparison between included patients and French literature data showed that the rates of
38 previous antibiotics exposure, crude mortality and recurrence were not statistically different. However
39 HCA-CDI was significantly more frequent in the DIFTEC™ study.

40 Gender distribution, recurrence and crude mortality rates were not statistically different compared to
41 European data. HCA-CDI was more frequent in the DIFTEC™ study whereas previous treatment with
42 proton pump inhibitors and antibiotics were significantly higher in European studies.

43 **Discussion:** These results illustrated the added value of a new tool for increasing the reliable
44 knowledge of CDI in France based on epidemiological surveillance implemented in health-care
45 settings.

46 **Key words:** *Clostridioides difficile* infection, *Clostridium difficile* infection, France, Prevalence,
47 Surveillance

48 **INTRODUCTION**

49 *Clostridioides (Clostridium) difficile* infection (CDI) is the most frequent infectious cause of nosocomial
50 diarrhea with potential severe complications and major financial burden for health-care systems [1, 2].
51 In France, the extra cost of CDI in public acute-care hospitals was estimated to €163.1 million per year
52 [3]. The epidemiology of CDI has changed since the emergence of the 027/NAP1/BI strain, which was
53 implicated in large outbreaks [4, 5]. In Europe, the mean incidence of CDI in 2008 increased from 4.1
54 to 7.0 CDI cases per 10,000 patient bed-days in 2012 [6]. In France, after the emergence of the 027
55 strain, the French Institute for Public Health Surveillance published recommendations for the
56 surveillance and prevention of CDI with mandatory notifications of severe CDI and/or outbreaks [7].
57 Until 2018, there has been no systematic, annual surveillance for CDI in France. A recent descriptive
58 study of retrospective surveillance and alert data based on five different data sources was done to
59 estimate CDI incidence in acute health-care facilities [8]. However, this epidemiological surveillance of
60 CDI remains challenging and might benefit from various epidemiological tools [9, 10]. Prospective
61 surveillance study can provide key information regarding CDI burden, but ideally, such data need to be
62 obtained continuously over time. This approach is time-consuming and not easily feasible in practice.
63 Repeated point prevalence survey (PPS) addresses this limitation by providing standardized, validated
64 and long-standing monitoring to inform decision-making regarding this infection [11]. In addition, this
65 kind of study is widely accepted, particularly when it can be repeated at regular intervals in a large
66 hospitals sample and the results are easily shared with non-expert individuals [12]. In 2016, a simple
67 surveillance tool, DIFTEC™ (<https://www.diftec.net/>) was developed to evaluate diagnostic and
68 management of CDI in France. The tool is managed and coordinated by a national scientific
69 committee of microbiologists, infectious diseases specialists and epidemiologists. Data collected on a
70 secure website allow each participating center to monitor its local epidemiology of CDI.
71 The objectives of this study were to compare the characteristics of patients with CDI collected through
72 repeated point prevalence survey (PPS) via the DIFTEC™ project with those from previous French or
73 European studies.

74 **METHODS**

75 ***DIFTEC™***

76 DIFTEC™ has received the support of the following societies: the French Society of Microbiology
77 (SFM), the French Society of Infectious Diseases (SPILF) and the French Society of Hospital Hygiene
78 (SF2H). DIFTEC™ is an electronic tool available for free for all French hospitals. It is a web based
79 page which can be easily accessed by any computer, tablet or smartphone browser. Users can enter
80 and export data in Excel tables and graphic presentations.

81 DIFTEC™ offers the opportunity to centers to be part of a national observatory. For this, participating
82 centers should report their CDI prevalent cases diagnosed during one month twice yearly. The period
83 of reporting is acted by the centers. According to French law, a patient consent is not mandatory for
84 anonymous surveillance data. The study protocol was approved by the CNIL (*Comission Nationale de*
85 *l'Informatique et des Libertés* DE-2015-081/N° 1844884).

86 ***Collected data***

87 For each included patient, a standardized questionnaire was completed with the following variables:
88 age, gender, co-morbidities as defined by International Classification of Diseases-10 codes,
89 information on hospital stay, origin of acquisition of infection, results of microbiological tests, specific
90 CDI therapy, and infection outcome. Exposures to risk factors associated with CDI were also recorded
91 including previous treatment with antibiotics, proton pump inhibitors [PPI], and immunosuppressed
92 drugs. Biological data concerning: leukocytes and neutrophil counts, serum creatinine concentrations,
93 lactate dehydrogenase, and albumin were collected at diagnosis to evaluate the severity of CDI. No
94 additional testing was requested for the purpose of this study. A CDI case was defined as a patient
95 with diarrheal stools and a positive stool test result (detection of free toxins A (TcdA) and/or B (TcdB);
96 positive toxigenic culture or detection of toxin genes for TcdA or TcdB by PCR). CDI was assumed to
97 be health care-associated if diarrhea started 48 hours after hospital admission or if symptoms
98 occurred within 4 weeks of hospital discharge. Cases were defined as community-acquired if CDI
99 signs presented in the absence of previous hospitalization within the last 12 weeks in out-patients, or
100 in in-patients within the first 48 h of admission. Cases that did not fit any of these criteria were
101 classified as undetermined origin [13]. Recurrence was defined if symptoms reappeared at least 10
102 days after, but no more than 2 months after, the resolution of the first episode, and was associated
103 with a *C. difficile*-positive test result. Included patients were followed 90 days after CDI diagnosis.

104 Readmission during this period permits to record data on crude and attributable mortality and rates of
105 recurrence by day-30 and day-90.

106 ***Comparison of patients' characteristics included in DIFTEC™ vs French and/or European***
107 ***published data***

108 *Search criteria*

109 A literature search of of prospective, retrospective or cross-sectional studies conducted in Western
110 Europe (including United Kingdom) on CDI was done in PubMed. with the following combination of
111 Medical Subject Heading terms: **((Clostridium difficile AND "last 10 years"[PDat] AND**
112 **Humans[Mesh])) AND (((((((((((france) OR germany) OR italy) OR spain) OR portugal) OR**
113 **belgium) OR denmark) OR sweden) OR norway) OR ireland) OR great britain) OR finland) OR**
114 **switzerland) AND "last 10 years"[PDat] AND Humans[Mesh]).** All English- and French-language
115 articles published between between January, 2008 and May, 2018 (last update May, 31 2018) were
116 included.

117 *Search results, included and excluded papers*

118 The search yielded 1,351 potentially-relevant articles and 40 were included in the final analysis (Figure
119 1). Conference abstracts, reports of outbreaks, as well as review articles were excluded. Studies
120 conducted in community, in patients less than 18 years old, and those with a sample size <30 were
121 also excluded.

122 *Screening, quality assessment and data extraction*

123 Two reviewers (AH and NK) screened the articles titles and abstracts in the initial search to identify
124 those appropriate for inclusion. Subsequently, the full text of articles was read by each reviewer. The
125 results of both reviewers were compared and, in case of disagreements, were resolved through
126 discussion.

127 *Statistical analysis*

128 The *meta* package (R® statistical software) was used to compare means, median, and percentages.
129 The means of the different variables of the comparative studies were calculated according the study
130 design and the values of the "random effects model" were considered. Collected data were compared
131 using the Chi-square test after Bonferroni correction if needed. Statistical analyses were performed
132 with the R® statistical software (R Foundation for Statistical Computing, Vienna, Austria. URL:
133 <http://www.R-project.org/>).

134 **RESULTS**

135 ***Descriptive analysis***

136 From January 2016, to December 2017, 455 episodes of *C. difficile* infection in 414 patients from 22
137 French hospitals were reported through the DIFTEC™ database. Included patients had a mean of age
138 of 71.0 years and there were more men than women (P=0.04; Table 1).

139 CDI was confirmed by the detection of free toxins in 105 episodes (23.1%), toxigenic strain in 258
140 episodes (56.7%) and free toxins and toxigenic strain in 89 episodes (19.6%). Diagnosed CDI were
141 classified as health-care associated in 355 episodes (78.0%), 79 (17.4%) were community-acquired,
142 and 20 episodes (4.4%) were from undetermined origin.

143 Of the 455 episodes, previous antibiotics were received in 336 (73.8%) cases within the 60 days
144 preceding the onset of diarrhea. Exposure to proton pump inhibitors (PPI), chemotherapy,
145 immunosuppressive medication or steroids were observed in 208 (45.7%), 94 (20.7%), 35 (7.7%) and
146 20 (4.4%) episodes respectively.

147 ***Comparison of patients characteristics included in DIFTEC™ vs published data***

148 The characteristics of included patients were compared to those of 2,248 French CDI patients and
149 28,887 CDI cases from elsewhere in Europe (Table 1).

150 The comparison between included patients and French literature data showed that the rates of
151 previous antibiotics exposure (p=0.11), crude mortality by day 30 after diagnosis (p=0.99) and
152 recurrence (p=0.87) were not statistically different. The proportion of males (42.3% vs 50.3%) and
153 previous use of PPI (45.7% vs 53.5%) were more frequent in French published papers compared to
154 patients included in DIFTEC™ database. However health-care associated CDI were significantly more
155 frequent in DIFTEC™ study (78.0 % vs 65.6 % in French studies).

156 Gender distribution, recurrence and crude mortality rate were not statistically different between
157 patients included through DIFTEC™ and European data. Health-care associated CDI was more
158 frequent in the DIFTEC™ study (78.0 % vs 73.2 %) whereas previous treatment with PPI (45.7% vs
159 68.8%) and antibiotics (73.8 vs 82.6%) were significantly higher in European studies (Table 1).

160 **DISCUSSION**

161 The objective of this study was to evaluate the representativeness of a new epidemiological tool used
162 for multicentric surveillance of CDI in France. The data came from repeated reporting of prevalent
163 cases in France through the DIFTEC™ project and were compared to patient characteristics published
164 previously from surveillance, case-control and cohort studies (mono or multicentric) in France or other
165 Western European countries.

166 The results for the 22 hospitals that reported at least one month of data showed no major differences
167 regarding demographic characteristics but reported higher health-care associated CDI cases in this
168 study in comparison with French and European studies. This result could be arguably explained by an
169 increase of CDI incidence in France as reported in a recent study which showed a statistically
170 significant increase in CDI incidence between 2010 and 2016 (+ 14% annually) [8]. Nevertheless, this
171 rate is similar to some local data from France [10, 14]. However, a bias related to the recruitment of
172 included patients and/or the design of comparative studies cannot be excluded. A bias regarding a
173 specific interest for hospital acquired cases might not be eliminated. The recurrence rate in this study
174 fits well with French and European data despite the different clinical definitions used in those studies
175 [15]. In addition, the crude mortality rates were similar between the epidemiological sources which
176 underscore the lack of major differences regarding the clinical severity of the CDI cases by
177 epidemiological design. This can be explained by the size of our sample.

178 Previous exposure to antibiotics was significantly lower than reported in European studies. These
179 discrepancies can be related to several factors (as. Type, number and period of exposure to antibiotics
180 and other drugs associated with a risk of CDI), and a standardized definition of exposure is needed to
181 evaluate the real impact of antibiotics on CDI acquisition [16-19]. PPIs have also been described as a
182 potential risk factor for CDI [20, 21]. However, the influence of acid suppression in CDI remains
183 uncertain and controversial. In our study, previous exposure to PPI was significantly lower than to the
184 two groups of comparison. This may be related to the way that exposure was defined [22, 23]. In
185 published papers, the period of risk ranges one to 6 months prior to CDI, but the manner of exposure
186 is usually not defined.

187 Epidemiological surveillance is the appropriate tool for trends analysis, outbreak detection and
188 evaluation of intervention regarding CDI. However, such designs need many resources and might be
189 difficult to implement on large geographical areas, especially at a national level [24]. Then, repeated

190 prevalence studies, as national prevalence survey, might be an alternative with data collection around
191 the same time through the country but need an important preparation [25]. In addition, aggregate
192 analyses for prevalent cases from local sources, such as included in the DIFTEC™ database, can
193 provide insight into the changing epidemiology of CDI at national level. A restriction of DIFTEC™ is the
194 need to monitor regularly the representativeness of the centers prior extrapolation to a national level.
195 However both sources of prevalent data might be complementary with different objectives. DIFTEC™
196 developed at a local level can maintain a proximity awareness regarding CDI, encouraging a regular
197 commitment/motivation of the clinicians.

198 The limitations of the comparison between results from DIFTEC™ and published studies can be
199 related to differences in data definitions or diagnostic tools. This point needs to be taken into account
200 for discussion but is regularly a topic of concern regarding comparison between studies. Another limit
201 should be mentioned concerning the modality of participation in this project. In fact, volunteer centers
202 decided the time of their participation which can be associated with a potential selection biases.

203 However, the majority of cases included in this study came from hospitals with one time participation
204 and then it was not possible to check if there was a difference related to the participation's month.
205 Moreover, ongoing statistical analyzes did not shown any significant differences in hospital which
206 participated in 2016 and 2017.

207 Overall, this study illustrated the added value of a new tool for increasing our knowledge of CDI based
208 on epidemiological surveillance in France implemented in health-care settings. The tool is relatively
209 easily broadened to include the surveillance of CDI into a daily monitoring at national level. A regular
210 checking of data quality, an increase the number of participating hospitals from different French
211 regions, participation longer than one month, and a demonstration of plausibility of collected data in
212 the DIFTEC™ project would generate a reliable epidemiological data which might be shared at
213 national and international level.

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219 (Saint-Lô), Centre Hospitalier Nevers (Nevers), Centre Hospitalier Universitaire Nantes (Nantes),
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235 **Authors' contribution**

236 Study concept and design: AH, NK and PV. Acquisition of data: AH and NK. Data analysis: AH & NK.
237 Interpretation of data: NK, AH, and PV. Drafting of manuscript: NK, AH, and PV. Critical revision of the
238 manuscript and important intellectual input: all authors. All authors read and approved the final
239 manuscript.

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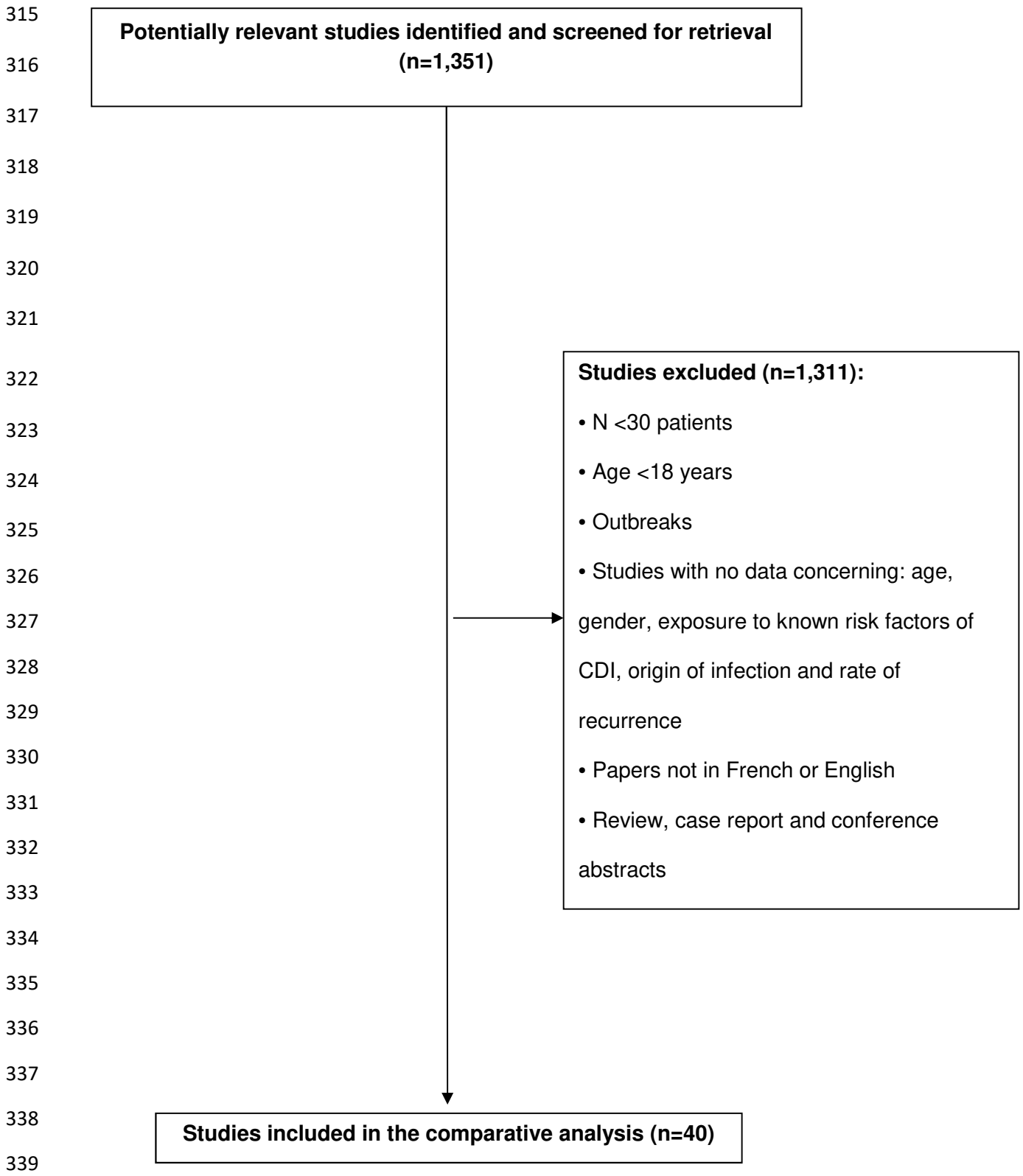
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312 nationale-de-prevalence-des-infections-nosocomiales-et-des-traitements-anti-infectieux-en-
313 etablissements-de-sante-france-mai-juin-2012.-r)

314 **Figure 1: Flow chart of studies screened and included in this study**



340 **Table 1: Comparison of characteristics between patients included in DIFTEC™ project and those included in French or European studies**

	DIFTEC™ project, France, n=414	Literature data from France, n=2,248	Literature data from Europe, n=28,887	<i>P</i> DIFTEC™ vs France	<i>P</i> DIFTEC™ vs Europe
<u>Type of study, n:</u>		9	31		
Prevalence		0	3		
Surveillance		2	8		
Observational		7	20		
Age, mean (min-max) in years	71.0 (18-100)	61.8 (58-74.7)	73.8 (62-86.1)	<10 ⁻³	<10 ⁻³
Male gender: % (CI 95%)	42.3 (37.5-47.1)	50.3 (48.2-52.4)	44.5 (43.9-45.1)	0.003	0.37
Healthcare associated disease: % (CI 95%)	78.0 (74.2-81.8)	65.6 (63.6-67.6)	73.2 (72.7-73.7)	<10 ⁻³	0.024
Recurrence: % (CI 95%)	11.9 (8.8-15.0)	10.6 (9.3-11.9)	14.6 (14.2-15.0)	0.87	0.17
Previous antibiotics: % (CI 95%)	73.8 (69.8-77.8)	77.5 (75.8-79.2)	82.6 (82.2-83.0)	0.11	<10 ⁻³
Previous PPI: % (CI 95%)	45.7 (41.1-50.3)	53.5 (51.4-55.6)	68.8 (68.3-69.3)	<10 ⁻³	<10 ⁻³
Mortality rate (≤ 1 month): % (CI 95%)	16.9 (13.3-20.5)	17.1 (15.5-18.7)	18.6 (18.1-19.1)	0.99	0.41

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Patients with CDI included in a repeated point prevalence survey via a free electronic tool called DIFTEC™



Comparison of their characteristics with CDI patients included in studies conducted in:



Western Europe

France



Gender distribution, recurrence and crude mortality rates were not statistically different

- HCA-CDI was more frequent in the DIFTEC™
- Previous treatment with PPI and ATB were significantly higher in European studies



Rates of previous ATB exposure, crude mortality and recurrence were not statistically different

HCA-CDI was significantly more frequent in the DIFTEC™