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1 **Can Real-Time PCR Allow a Faster Recovery of Hospital Activity in Cases of an**
2 **Incidental Discovery of Carbapenemase-Producing Enterobacteriaceae and**
3 **Vancomycin-Resistant Enterococci Carriers?**

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23
24 **Running title:** RT-PCR for Infection Control Management

25 **Summary**

26

27

28 **Background.** Detection of faecal carriers of carbapenemase-producing Enterobacteriaceae
29 (CPE) and vancomycin-resistant enterococci (VRE) has become a routine medical practice in
30 many countries. In an outbreak setting, several public health organizations recommend
31 threenweekly rectal screenings to rule-out acquisition in contact patients. This strategy,
32 associated with bed closures and reduction of medical activity for a relatively long time,
33 seems costly.

34 **Aim.** The objective of this study was to test the positive and negative predictive values of RT-
35 PCR(GeneXpert®) carried-out at Day-0, compared to conventional three weekly culture-
36 based rectal screenings, in identifying, among contact patients, those who acquired
37 CPE/VRE.

38 **Methods.** We conducted a multicentre retrospective study from January2015 to October2018.
39 We included all contact patients (CP) identified from index patients (IP) colonized or infected
40 with CPE/VRE, incidentally discovered. Each CP was investigated at Day-0 by PCR
41 (GeneXpert®), and by the recommended three weekly screenings.

42 **Findings.** Twenty-two IP and 159 CP were included. An average of 0.77 secondary case per
43 patient was noted, with a mean duration of contact of 10 days [range 1-64]. Among the 159
44 CP, 16 (10%) had a CPE/VRE-positive culture during the monitoring period. Rectal
45 screenings were positive at Day-0 (10 patients), Day-7 (2 patients), Day-14 (4 patients).
46 Thirteen out of 16 patients with positive culture had at Day-0 a positive PCR. Overall, a
47 concordance of 97.5% (155/159) was observed between the three-weekly screenings and
48 Day-0 PCR results. When performed on CP at Day-0 of the identification of an IP,
49 PCR(GeneXpert®) allowed to shorten turnaround time by 5 to 27days, compared to three
50 weekly screenings. PPV and NPV were respectively 100% and 98%.

51 **Conclusions.** RT-PCR (GeneXpert®) can avoid three weekly rectal samplings needed to
52 rule-out acquisition of CPE/VRE.

53 **Keywords.** Real-time PCR, Carbapenemase-Producing *Enterobacteriaceae*, Vancomycin-
54 Resistant *Enterococci*, infection control, outbreak, rectal screening.

55 **Text:**

56

57

58 **Introduction:**

59 Carbapenemase-producing Enterobacteriaceae (CPE) and vancomycin-resistant enterococci
60 (VRE) emerged globally over the last decade, resulting in antibiotic-resistant infections that
61 are difficult to treat and costly to healthcare facilities. ¹ The search and isolate policy is
62 considered the main infection prevention and control strategy. Rapid, accurate detection of
63 intestinal CPE and VRE colonization is critical to minimize transmission, and hence reduce
64 costly, difficult to treat infections caused by these emerging extensively drug-resistant (XDR)
65 bacteria. ²

66 The 2013 French National Guidelines recommend implementation of a strict isolation policy,
67 including cohorting patients with CPE in a dedicated ward with dedicated healthcare workers
68 (HCWs) and an extensive screening policy of contact patients. In case of identifying a non-
69 cohorted index patient, recommendations are to close the ward concerned and apply a
70 screening policy to all contact patients. Weekly rectal swabbing is recommended to
71 investigate possible acquisition among contact patients. Contact patients are considered non-
72 carriers if three consecutive weekly negative rectal swabs are obtained; they are then no
73 longer monitored. This strategy seems to be costly as it is associated with a reduction of
74 medical activity. Moreover, it could expose patients to higher risk of complications as they
75 will usually remain isolated until screening is complete. ³

76 The current process for detecting CPE in clinical samples is usually performed using
77 selective cultures and may require up to 72h for obtaining the results. ⁴

78 Different molecular assays have been developed and have shown their effectiveness in
79 identifying the resistance genes from bacterial colonies. Real-time PCR assays have been
80 reported to have lower limits of detection than conventional agar-based culture
81 methodologies. ⁴⁻⁷ When used directly on rectal samples, they offer laboratories the ability to
82 reduce turnaround times. However, there is no data on their effectiveness in this specific
83 situation. Moreover, no previous study has demonstrated if they have a potential added value
84 for infection control management in an epidemiological setting. Therefore, evaluating the

85 clinical utility of PCR-based assays as a screening tool, is needed.

86 The main objective of this study was to test in a multicentre retrospective survey the
87 effectiveness of real time PCR (GeneXpert®) carried out at Day 0 in identifying among
88 contact patients those who acquired XDR. An additional objective was to define the negative
89 predictive value (NPV) of this technique; a high NPV would support using this strategy in
90 place of the standard three week sampling and testing regimen.

91 Part of the results was presented at the 29th ECCMID Congress.

92

93 **Materials/methods:**

94 We conducted a multicentre retrospective study in three large French hospitals (Avicenne
95 Hospital AP-HP, Mignot Hospital- Hospital Center of Versailles, Grand Hospital Eastern Ile
96 Site de Marne-la-Vallée) from January 2015 to October 2018. In these hospitals, the 2013
97 French National Guidelines recommendations ⁸ for the prevention of spread of XDR are
98 systematically applied. Thus, in case of identifying an index patient, patients are cohorted and
99 an extensive screening policy for all isolated contact patients is applied. Contact patients are
100 only considered non-carriers, and isolation discontinued, if three consecutive weekly rectal
101 swabs screenings are negative by recommended culture techniques.

102 An index patient was defined as a non-cohorted patient colonized or infected with CPE or
103 VRE incidentally discovered post hospitalization. We defined contact patients as all the
104 adults (> 18 years old) staying in the same unit during the same period as an index patient,
105 sharing the same HCWs and for whom, at least three-weekly rectal screenings were
106 performed during the same hospitalization and after the end of their exposure using
107 conventional culture techniques, plus a real-time PCR (GeneXpert®) assay done on the first
108 screening sample. A secondary case patient was defined as a contact patient for whom CPE
109 or VRE was later identified by the weekly rectal screenings. A non-colonized patient was
110 defined as a contact patient who remained CPE- or VRE-negative during his stay in the
111 hospital. Exposure time was defined as the duration of contact between the index patient and
112 a secondary case patient before being identified as CPE or VRE positive or a control patient
113 throughout his stay in the same ward. ⁹

114 Data were collected retrospectively in case and control patients by reviewing medical and
115 microbiological records. Collected data included demographic characteristics, including age,
116 gender, ward of contact (medical, surgical, or intensive care unit), exposure time, duration of
117 hospitalization in the ward, and antibiotic administration during the exposure period.

118 CPE and VRE detections were performed using respectively Xpert® Carba-R and Xpert®
119 vanA/vanB (Cepheid, GeneXpert) following manufacturer recommendations, on the first
120 screening sample. CPE detection by culture consisted of direct plating of the rectal swab on
121 ChromID® CARBA SMART medium (BioMérieux, Marcy-l'Étoile, France) for 24h,
122 likewise, screening of VRE was carried out on ChromID® VRE medium (BioMérieux,
123 Marcy-l'Étoile, France). Antibiotic susceptibility testing according to Comité de

124 l'antibiogramme de la Société Française de Microbiologie - European Committee on
125 Antimicrobial Susceptibility Testing (CA-SFM - EUCAST) guidelines ¹⁰ was performed on
126 each type of suspected colony grown on selective media. Confirmation of resistance was
127 accomplished using Carba NP test and β -Carba test (Bio-Rad, Marnes-la-Coquette, France)
128 ^{11,12} and Xpert® Carba-R on suspected CPE isolates and Xpert® vanA/vanB on suspected
129 VRE isolates.

130 Statistical method:

131 The sensitivity, specificity, positive predictive value (PPV) and negative predictive value
132 (NPV) were calculated for all tested isolates. Statistical analysis was performed using 95%
133 confidence intervals (CIs) calculated using Student's *t*-test.

134 **Results:**

135 During the study period 22 non-cohorted patients, hospitalized in different wards, carrying or
136 infected with CPE (59%) or VRE (41%) were incidentally discovered post hospitalization.
137 The mean age of these index patients was 68 years-old and their average length of hospital
138 stay, 12 days (range between 1 and 50 days). 16 index patients over 22 (72.7%) were exposed
139 to antibiotics during their hospital stay. CPE accounted for 13 (59%) cases, with OXA-48
140 being the most prevalent mechanism of resistance (Table I).

141 Among the 159 contact patients (as defined previously) only 17 (10.7%) acquired an XDR. In
142 fact, 8 index patients of 22 generated at least one secondary case patient, the average being
143 0.77 secondary case per patient (range between 0 and 3). The mean duration of contact in the
144 whole population was 10 days (range between 1 and 64 days). Among the 159 patients 96
145 (60.4%) patients were receiving antibiotic therapy during the contact period (Table II).

146 According to French recommendations, all contact patients were followed-up weekly and
147 were screened by rectal swabbing. Furthermore, real-time PCR (GeneXpert®) carried out on
148 rectal swabs of the 159 contact patients at Day 0 and 14 patients were detected as CPE
149 carriers. Conventional agar-based methodology used for weekly rectal screenings, was
150 positive in 16 patients. Ten had a positive culture result at first day of screening (Day-0), 2 at
151 the second screening week and 4 at the third screening week. In one case, PCR was positive
152 at Day 0, whereas, conventional culture remained negative for the three-weekly rectal
153 screenings. In 3 other cases, all related to VRE acquisition, PCR was negative at Day 0, while
154 cultures were positive at the 2nd or 3rd round screening.

155 Overall, a concordance of 97.5% (155/159) was observed between the three weekly rectal
156 screens using culture techniques and Day 0 real-time PCR (GeneXpert®) results. When
157 performed on all contact patients at Day 0 after identifying of an index patient, real-time PCR
158 (GeneXpert®) allowed to shorten turnaround time by 5 to 27 days (6 days in average)
159 compared to the conventional three weekly culture-based rectal screening method. Among
160 the 4 discordances, one case had a positive PCR at Day 0 for CPE OXA-48, whereas,
161 conventional culture methodology stayed negative for the threenweekly rectal screens. In the
162 3 remaining discordant cases, all VRE acquisition, PCR was negative at Day 0, while cultures
163 were positive during the 2nd screening in one case, and the 3rd screening in the two other
164 cases (Table III).

165 We did not find any statistically significant differences in age, duration of contact and
166 antibiotic consumption between secondary case patients diagnosed during the 1st screening
167 and those found negative during the 1st screening but identified as carriers later at the 2nd or
168 3rd screening.

169

170 **Discussion and Conclusion:**

171 In our multicentre retrospective study a concordance of 97.5% (155/159) was observed
172 between the three-weekly rectal screenings using culture techniques and Day 0 real-time PCR
173 (GeneXpert®) results. All, secondary cases among contact patients were considered having
174 acquired the XDR bacteria within the first day of contact with the index patient and before
175 the identification of carriage. Indeed, after identification, all case index were systematically
176 cohorted according to the French recommendations and contact patients were not in contact
177 with any other index patient or known carrier during their hospital stay. Among the 4
178 discordances, one case had a positive PCR at Day 0, whereas, conventional culture
179 methodology stayed negative for the three-weekly rectal screenings. This may be explained
180 by the fact that the patient had been receiving antibiotics, affecting the expression of the
181 resistance genes in culture, or, since it was an OXA-48 gene detected, the possibility of a
182 transiently carriage of *Shewanella spp.* which naturally produce OXA-48 variants.⁵ It needs
183 to be considered also that molecular methods may be more sensitive than the culture method
184 that was the reference standard in our study. Knowing that, heavily colonized patients are
185 more likely to yield opportunities for horizontal transmission, it raises the issue of whether
186 the excellent sensitivity of PCR and detection of very low levels of colonization is
187 significant, regarding the consequent costly infection control measures.²

188 In the 3 remaining discordant cases, all VRE acquisition, PCR was negative at Day 0, while
189 cultures were positive during the 2nd screening in one case, and the 3rd screening in the two
190 other cases. The absence of detection in these 3 cases at Day 0 may be associated with low
191 undetectable bacterial load in the rectal swab specimens, becoming detectable at the 2nd or 3rd
192 screenings or even to sample techniques.¹³ However, looking closer to those cases, all 3 are
193 parts of complicated outbreaks generating several secondary cases. Therefore, we can also
194 suggest that those 3 patients were “true-negative” at Day 0 and have acquired the VRE later
195 during their hospital stay.

196 Detection of faecal carriers of XDR bacteria has become a routine clinical practice in many
197 parts of the world and is recommended by public health organizations for the containment of
198 their spread. Among different approaches used, more recently, molecular approaches have
199 been developed to increase detection sensitivity and decrease reporting time.¹⁴

200 When performed on all contact patients at Day 0 of the discovery of an index patient, real-
201 time PCR (GeneXpert®) allowed to shorten turnaround time by 5 to 27 days (6 days in

202 average) compared to the conventional three weekly culture-based rectal screenings method.
203 The result of a diagnostic assay has a clinical implication, and as a screening tool for XDR
204 bacteria, that implication is the implementation of infection control measures. The rapid
205 cohorting of carriers is crucial to prevent outbreaks and reduce the social impact and the cost
206 of infection control measures empirically implemented for high risk patients, who end up
207 being negative for XDR bacteria colonization.⁵ Moreover, the knowledge of the PPV and
208 NPV is essential for decision making by the infection control team in respect to the value of a
209 positive and a negative test result. Some authors have studied the performance of real time
210 PCR (GeneXpert®), but most have studied its effectiveness in detecting resistance
211 mechanisms on bacterial strains.¹⁵⁻¹⁹ In addition, the limited number of authors who have
212 been interested in evaluating the performance of GeneXpert® directly on rectal swabs,
213 compared to the routine culture techniques, have studied its effectiveness only at the
214 admission of patients considered as 'high-risk' for CPE carriage.^{2,4-7,14,20-22} Hence, there are
215 few data on the effectiveness of real-time PCR in this specific situation and no previous study
216 has demonstrated if they have a potential added value for infection control management in an
217 epidemiological setting. To our best knowledge, this is the first report evaluating the clinical
218 utility of PCR-based assays as a screening tool. Our study suggested that real time PCR
219 (GeneXpert®), carried out at Day 0 is efficient in identifying among contact patients those
220 who acquired XDR, with an NPV of 98%.

221 According to the 2013 French National Guidelines recommendations⁸ and the international
222 recommendations,²³ in cases of identifying an index patient, an extensive screening policy
223 for all isolated contact patients must be applied. Contact patients are only considered non-
224 carriers and no more isolated, if three weekly rectal swabs screenings came back with a
225 negative result, by recommended culture techniques. This strategy seems to be costly as it is
226 associated with bed closures and reduction of medical activity, for a relatively long duration
227 of time. In addition to that, it could expose the isolated patients to a higher risk of
228 complications as they are possibly receiving less optimal management for their medical
229 condition, compared to non-isolated patients with the same medical condition.

230 The major strength of our study is the finding that, in an outbreak context, if the screening
231 real-time PCR (GeneXpert®) test for a patient at Day 0 is negative, the risk that it will be
232 discovered later colonized remains weak. Thereby, contact patient's isolation will only be

233 limited to those who have their screening real-time PCR positive, means that they have
234 acquired the XDR bacteria.

235 We acknowledge that this study suffers from several limitations. First, its retrospective nature
236 and the lack of retrospective clinical data allowing for better targeting patients at risk of
237 acquisition of XDR bacteria, knowing that Hilliquin *et al* demonstrated recently in their large
238 multicentre case-control study, that at least three risk factors are associated with KP OXA- 48
239 acquisition in contact patients of a non-cohorted index patient: (i) geographical proximity (ii)
240 antibiotic therapy during exposure time and (iii) at least one invasive procedure.⁹ Second, the
241 sample size with the limited number of secondary cases. Third, we could not exclude that the
242 negative results on culture and/or on PCR were possibly the consequence of a poor quality of
243 sampling (no macroscopic staining was visualized), information not available retrospectively.

244 In conclusion, PCR (GeneXpert®) can provide valuable information for infection control
245 programs, and avoid three-weekly rectal samplings needed to rule out acquisition of CPE or
246 VRE. When included in a clinical algorithm, it can reduce the cost behind the infection
247 control measures implementation. Further studies need to be conducted comparing different
248 real-time PCR techniques to the three-weekly rectal screenings using culture techniques, on a
249 larger number of patients, taking into account different risk factors of XDR acquisition and
250 transmission.

251

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253 _____

254 _____

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257

258 **Conflicts of Interest**

259 _____

260 _____

261 None to report.

262 **References**

263

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343

344 **Tables**

345

346

347 Table I. Description of the characteristics of the index patients

Total Index Patients N=22 (%)	
Female sex	11 (50)
Age, mean	68
Hospitalization duration (days), mean	12
Ward of admission	
Medical	15 (68.2)
Surgical	4 (18.2)
Intensive Care Unit	3 (13.6)
Antibiotic therapy during hospitalization	16 (72.7)
Secondary cases generated	8 (36.4)
Mechanisms of resistance	
VRE¹ (vanA)	9 (40.9)
CPE² (OXA 48)	11 (50)
CPE² (NDM)	1 (4.5)
CPE² (KPC)	1 (4.5)

348

349 ¹ VRE: Vancomycin-resistant enterococci

350 ² CPE: Carbapenemase-producing Enterobacteriaceae

351

352

353 Table II. Description of the characteristics of the contact patients

354

	Total Contact Patients N=159 (%)	Secondary Cases N=17 (%)	Negative Cases N=142 (%)	p
Female sex	78 (49)	10 (58.8)	68 (47.9)	0.44
Age, median CI [min25%-75%,max]	70	80 [61-85]	72 [60,2-83,7]	0.54
Duration of contact with IP (days), median CI [25%-75%]	10.4 [1,64]	5 [3,7]	10 [4,15]	0.03
Ward of admission				
Medical	120 (75.5)	12 (70.6)	108 (76)	0.56
Surgical	27 (17)	5 (29.4)	22 (15.5)	0.17
Intensive Care Unit	12 (7.5)	0 (0)	12 (8.5)	0.36
Antibiotic therapy during hospitalization	96 ³ (60.4)	11 (64.7)	85 (59.9)	0.79
Mechanisms of resistance	17 (10.7)			
VRE¹ (vanA)	10 (6.3)	10 (58.8)	0	
CPE² (OXA 48)	6 (3.8)	6 (35.3)	0	
CPE² (NDM)	1 (0.6)	1 (5.9)	0	

355 ¹ VRE: Vancomycin-Resistant-Enterococci

356 ² CPE: Carbapenemase-Producing-Enterobacteriaceae

357 ³ Penicillin + β-lactamase inhibitor 26; cephalosporins 32; carbapenems 5; fluoroquinolones

358 13; aminoglycosides 7; metronidazole 13; other antibiotics 27

359 Table III. Description of the characteristics of discordant cases between the three weekly
 360 rectal screening using culture techniques and Day 0 real-time PCR (GeneXpert®)
 361

	Case 1	Case 2	Case 3	Case 4
Day 0 real-time PCR	Positive	Negative	Negative	Negative
1st week screening	Negative	Negative	Negative	Negative
2nd week screening	Negative	Positive	Negative	Negative
3rd week screening	Negative	Negative	Positive	Positive
Sex	M	M	M	F
Age	55	81	69	91
Duration of contact with index patient (days)	2	4	14	7
Ward of admission	Surgical	Medical	Medical	Medical
Antibiotic therapy during hospitalization	Yes	No	No	Yes
Mechanisms of resistance	CPE ¹ (OXA 48)	VRE ² (vanA)	VRE ² (vanA)	VRE ² (vanA)

362 ¹ CPE: Carbapenemase-producing Enterobacteriaceae

363 ² VRE: Vancomycin-resistant enterococci