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# Can real-time polymerase chain reaction allow a faster recovery of hospital activity in cases of an incidental discovery of carbapenemase-producing *Enterobacteriaceae* and vancomycin-resistant *Enterococci* carriers?

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## ► To cite this version:

R. Saliba, C. Neulier, D. Seytre, A. Fiacre, F. Faibis, et al.. Can real-time polymerase chain reaction allow a faster recovery of hospital activity in cases of an incidental discovery of carbapenemase-producing *Enterobacteriaceae* and vancomycin-resistant *Enterococci* carriers?. *Journal of Hospital Infection*, 2019, 103, pp.115 - 120. 10.1016/j.jhin.2019.07.004 . hal-03487531

**HAL Id: hal-03487531**

**<https://hal.science/hal-03487531>**

Submitted on 20 Jul 2022

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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:**

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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. <sup>1</sup> 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. <sup>2</sup>

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. <sup>3</sup>

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. <sup>4</sup>

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. <sup>4-7</sup> 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 29<sup>th</sup> 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 <sup>8</sup> 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. <sup>9</sup>

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 <sup>10</sup> was performed on  
126 each type of suspected colony grown on selective media. Confirmation of resistance was  
127 accomplished using Carba NP test and  $\beta$ -Carba test (Bio-Rad, Marnes-la-Coquette, France)  
128 <sup>11,12</sup> 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 2<sup>nd</sup> screening in one case, and the 3<sup>rd</sup> 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 1<sup>st</sup> screening  
167 and those found negative during the 1<sup>st</sup> screening but identified as carriers later at the 2<sup>nd</sup> or  
168 3<sup>rd</sup> 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.<sup>5</sup> 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.<sup>2</sup>

188 In the 3 remaining discordant cases, all VRE acquisition, PCR was negative at Day 0, while  
189 cultures were positive during the 2<sup>nd</sup> screening in one case, and the 3<sup>rd</sup> 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 2<sup>nd</sup> or 3<sup>rd</sup>  
192 screenings or even to sample techniques.<sup>13</sup> 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.<sup>14</sup>

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.<sup>5</sup> 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.<sup>15-19</sup> 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.<sup>2,4-7,14,20-22</sup> 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 recommendations<sup>8</sup> and the international  
222 recommendations,<sup>23</sup> 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.<sup>9</sup> 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

252 **Funding**

253 \_\_\_\_\_

254 \_\_\_\_\_

255 This research did not receive any specific grant from funding agencies in the public,  
256 commercial, or not-for-profit sectors.

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 (%)	
<b>Female sex</b>	11 (50)
<b>Age, mean</b>	68
<b>Hospitalization duration (days), mean</b>	12
<b>Ward of admission</b>	
<b>Medical</b>	15 (68.2)
<b>Surgical</b>	4 (18.2)
<b>Intensive Care Unit</b>	3 (13.6)
<b>Antibiotic therapy during hospitalization</b>	16 (72.7)
<b>Secondary cases generated</b>	8 (36.4)
<b>Mechanisms of resistance</b>	
<b>VRE<sup>1</sup> (vanA)</b>	9 (40.9)
<b>CPE<sup>2</sup> (OXA 48)</b>	11 (50)
<b>CPE<sup>2</sup> (NDM)</b>	1 (4.5)
<b>CPE<sup>2</sup> (KPC)</b>	1 (4.5)

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349 <sup>1</sup> VRE: Vancomycin-resistant enterococci

350 <sup>2</sup> CPE: Carbapenemase-producing Enterobacteriaceae

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

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

355 <sup>1</sup> VRE: Vancomycin-Resistant-Enterococci

356 <sup>2</sup> CPE: Carbapenemase-Producing-Enterobacteriaceae

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

362 <sup>1</sup> CPE: Carbapenemase-producing Enterobacteriaceae

363 <sup>2</sup> VRE: Vancomycin-resistant enterococci