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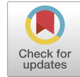
Rapid and accurate eXDR screening: use Xpert Carba-R® with FecalSwab®



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ABSTRACT

The FecalSwab® displays high performances for stool culture, but it was not assessed for carbapenemase-producing Enterobacterales (CPE) screening. We assess the performances of the Xpert Carba-R v2® with the FecalSwab®. Using a collection of 12 CPE strains, the limit of detection was assessed at 158 CFU/swab [interquartile range 93−589]. In 2019, 1540 swabs were included by 4 hospital laboratories, of which 39 (2.5%) yield an invalid result. Among the 1501 valid, 87 (5.8%) were positives by culture and PCR and 25 (1.7%) were discrepant: 7 PCR-negative culture-positive, and 18 PCR-positive culture-negative. Two PCR-positive culture-negative results involved non-Enterobacterales strains: a KPC-producing *Acinetobacter baumannii* and a KPC-producing *Aeromonas* spp. The overall percent agreement was 98.3% and the Kappa value was 0.88. FecalSwab® is an accurate sampling device for CPE screening. It allows performing all eXDR screening using a single swab, simplifying the sample collection, and improving the patient comfort. Regarding discrepant, we suggest combining a CPE screening by both culture and Xpert Carba-R v2® methods.

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1. Introduction

Accurate identification of eXDR (emerging extensively drug-resistant organisms) carriers, that is, carbapenemase-producing Enterobacterales (CPE) and vancomycin-resistant enterococcus (VRE) carriers, is needed in order to implement eXDR-specific infection prevention and control (IPC) measures and avoid cross-transmission (Banach et al. 2018; Lepelletier et al. 2015; Magiorakos et al. 2017a). As the culture on selective media needs at least 24 to 48 hours, a rapid and robust method is required. The Xpert Carba-R v2® is a fully-integrated molecular method that provides accurate results within less an hour (Saliba et al. 2020). However, as it detects about 95% of all known carbapenemase genes and antimicrobial susceptibility testing is required, a culture remains needed (Dortet et al. 2017). Thus, rapid eXDR screening requires both a fully-integrated molecular method and a conventional culture using selective media.

According to the manufacturer recommendations, Xpert Carba-R v2® should be performed on rectal or perirectal swabs sampled using the Transystem double swab (TDS) (Copan, Brescia, Italy). Consequently, at least 2 swabs are required in order to perform an eXDR (VRE plus CPE) screening. The FecalSwab® (Copan, Brescia, Italy) combines a flocked swab with 3 mL of Cary-Blair medium. It displays high performances for stool culture (Goneau et al. 2019). The accuracy of Xpert Carba-R v2® using FecalSwab® has never been assessed yet. In the present study, we aim to assess the limit of detection of the Xpert Carba-R v2® with the FecalSwab® and its performances in routine use.

2. Material and methods

2.1. Limit of detection

Twelve CPE strains expressing a bla_{OXA-48} ($n = 3$), $bla_{OXA-181}$ ($n = 1$), bla_{NDM-1} ($n = 2$), bla_{NDM-4} ($n = 1$), bla_{NDM-5} ($n = 1$), bla_{KPC-2} ($n = 1$), bla_{KPC-3} ($n = 1$), bla_{VIM-4} ($n = 1$), and bla_{IMP-1} ($n = 1$) genes were included. All the strains were identified using MALDI-TOF mass spectrometry as recommended by the manufacturers. The identification

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of carbapenemase gene was assessed using a polymerase chain reaction (PCR) -based assay as previously described (Dortet et al. 2014a).

The limit of detection (LoD) was assessed for each strain using a 10^4 CFU/mL calibrated suspension in sterile water. The suspension concentration was checked by plating Columbia agar plates in triplicate (BD; Franklin Lakes, NJ) with a 10-fold series dilution of the suspension. The plates were then incubated overnight at 35°C in ambient atmosphere, and the colonies numbered.

The FecalSwab® were inoculated using 100 μL of the calibrated suspension and vortexed for 10 seconds. The Xpert Carba-R v2® was performed using 100 μL of the Cary-Blair transport media. Depending on the first result, a second analysis was processed using either 50 or 200 μL of the Cary-Blair transport media if a positive or negative result was obtained respectively.

2.2. Assessment of the Xpert Carba-R v2® accuracy in routine use

The accuracy of the Xpert Carba-R v2® in routine use was assessed between January 1, 2019, and December 31, 2019. Four French clinical laboratories participated in the study: hospital Foch (Suresnes), hospital Henri Mondor (Créteil), hospital Bicêtre (le Kremlin-Bicêtre), Hospital Franco-Musulman Avicenne (Bobigny). According to the French guidelines, CPE screenings were performed on the admission of a patient hospitalized abroad within the past year, at the readmission of an eXDR carrier or in contacts of eXDR carriers (Lepelletier et al. 2015). The patients were sampled using the flocked swab which was then introduced in the Cary-Blair transport media. For all samples included, both the Xpert Carba-R v2® and a chromogenic selective culture were performed using 200 μL of Cary-Blair transport media.

For CPE cultures, the Cary-Blair transport media was plated on a selective chromogenic agar plate, the ChromID CARBA SMART® (BioMérieux, Marcy-l'Etoile, France), and incubated at 35°C in aerobic atmosphere for 18 to 24 hours. One center performed enrichment culture using a homemade selective broth. A 10 mL Brain Heart Infusion broth was supplemented with 5 μg of ertapenem and incubated at 35°C for 24 hours before plating. Enterobacterales colonies were identified using MALDI-TOF mass spectrometry as recommended by the manufacturer. Carbapenemase confirmation was performed using a phenotypic and a molecular-based approach as previously described (Boutal et al. 2018; Dortet et al. 2014a; Dortet et al. 2014b).

In order to assess invalid results provided by the GeneXpert device, all centers were invited to provide the number of overall, positive (including the gene detected) and invalids of the Xpert Carba-R v2®. If the test was repeated, the second result was recorded. The results of the Xpert Carba-R v2® and the selective cultures were then compared after excluding invalids. For each discrepant, the Cycle Threshold (Ct) of the positive target, and if available the number of colonies on selective agar were recorded. If a new sample was requested, the results of the screening was recorded.

Statistical analyses were performed using Excel software (Microsoft Corporation; Albuquerque, New-Mexico,). The results of the Xpert Carba-R v2® were compared with those of the selective culture using the overall, positive, and negative percent of agreement and the Kappa test.

3. Results

3.1. LoD

All carbapenemase genes were detected in all inoculated swabs. Overall, the median LoD was assessed at 158 CFU/swab [interquartile range 93–589] (Table 1). The LoD range from 55 to 593 CFU/swab in OXA-48-like-producing strains, 156 to 203 in KPC-producing strains, and from 75 to 160 in NDM-producing strains. The VIM-4 and the IMP-1-producing strains display a LoD of 1767 CFU/swab and >5000 CFU/swab respectively. No invalid results were obtained regardless of the volume of transport media used, and there was no unspecific amplification of a carbapenemase gene. Regarding these results, and in order to increase the sensitivity of the test, we selected a volume of 200 μL of FecalSwab® transport media for the assessment of the Xpert Carba-R v2® performances in routine use.

Table 1
Limit of detection of the Xpert Carba-R v2® performed on FecalSwab for 10 CPE.

Strain No.	Species	Carbapenemase type	Limit of detection (CFU/swab)
1	*E. coli*	OXA-48	587
2	*C. freundii*	OXA-48	593
3	*K. pneumoniae*	OXA-48	55
4	*E. coli*	OXA-181	96
5	*K. pneumoniae*	KPC-2	156
6	*K. pneumoniae*	KPC-3	203
7	*E. coli*	NDM-1	113
8	*E. coli*	NDM-5	160
9	*K. pneumoniae*	NDM-4	82
10	*K. pneumoniae*	NDM-1	75
11	*E. cloacae*	VIM-4	1,767
12	*K. pneumoniae*	IMP-1	> 5000

3.2. Invalid of the Xpert Carba-R v2®

Overall, 1540 rectal swabs were processed on the Xpert Carba-R v2®. Thirty-nine (2.5%) samples yield an invalid result, the rate of invalids was significantly different according to the participant center, ranging from 1.0% to 3.8% (*P = 0.03*). All-but-one samples were negative in culture, the only positive growth in culture was an OXA-48-like-producing *Escherichia coli*. The Xpert Carba-R v2® was not repeated for this sample. Twenty-eight (71.8%) invalids were repeated using the same sample: 19 (67.9%) were negatives while 9 (32.1%) were found invalids again.

3.3. Discrepant between the Xpert Carba-R v2® and the selective culture

Among 1501 valid Xpert Carba-R v2®, 105 (7.0%) and 94 (6.3%) samples were positive using the Xpert Carba-R v2® and the selective culture respectively. The genes detected using the Xpert Carba-R v2® were 65 (61.9%) $bla_{\text{OXA-48 like}}$, 28 (26.7%) bla_{NDM}, 9 (8.6%) bla_{KPC}, and 3 (2.8%) bla_{VIM}. Overall, 1476 results were concordant between the 2 methods, of which 1389 (92.5%) and 87 (5.8%) were negative and positive respectively (Table 2). Among the 25 (1.7%) discrepant results, 7 (29.2%) were PCR-negative culture-positive, and 18 (70.8%) were PCR-positive culture-negative.

All 7 PCR-negative culture-positive samples were considered as false-negative of the Xpert Carba-R v2®. The CPE recovered were as follows 2 OXA-48-producing *E. coli*, 1 OXA-181-producing *E. coli*, 2 OXA-48-producing *Klebsiella pneumoniae*, 1 NDM-1-producing *K. pneumoniae*, and 1 NDM-5-producing *E. coli*. The number of bacterial colonies on selective media was recorded for 5 samples. Four cultures were positive with less than 5 CFU/plate. One of them was positive after enrichment of the Cary-Blair transport media using a selective

Table 2
Xpert Carba-R v2® results in comparison to the selective culture.

	PCR+ Culture+	PCR+ Culture-	PCR- Culture+	PCR- Culture-	Rate of culture- among PCR+
$\textbf{\textit{bla}}_{\textbf{OXA-48 like}}$	54	11	5	1431	16.9%
$\textbf{\textit{bla}}_{\textbf{NDM}}$	24	4	2	1471	14.3%
$\textbf{\textit{bla}}_{\textbf{KPC}}$	8	1	0	1492	11.1%
$\textbf{\textit{bla}}_{\textbf{IMP}}$	0	0	0	1501	0.0%
$\textbf{\textit{bla}}_{\textbf{VIM}}$	1	2	0	1498	66.7%
Overall	87	18	7	1389	17.1%

broth but negative by direct plating of the Cary-Blair transport media. The remaining sample was positive for numerous colonies of OXA-48-like-producing *E. coli* after direct plating.

Over the 105 positives Xpert Carba-R v2®, 18 (17.1%) were negative in selective culture. Three of them yield the growth of carbapenemase-producing bacteria. Two were positive for an NDM-producing *Acinetobacter baumannii* and *Aeromonas spp.* For both strains the Xpert Carba-R v2® performed on bacterial colonies was positive. The third sample was found positive for a bla_{KPC} and a bla_{VIM} using the Xpert Carba-R v2® but, it yields the growth of a KPC-producing *K. pneumoniae*. It was therefore considered as a false-positive of the bla_{VIM} gene. The 15 remaining samples do not yield the growth of bacterial colonies on selective media. They display a median Ct of 34.0 [31.5–37.5]. The Ct was greater than 30.0 and 35.0 in 86.7% and 46.7% samples respectively. Of note, 4 cultures were performed without and with enrichment in selective broth. In 6 (40.0%) cases, a new sample was requested that was negative by both culture and Xpert Carba-R v2®. The rate of culture-negative among PCR-positive samples was not significantly different according to the gene detected using the Xpert Carba v2® ($P = 0.18$; Table 2).

The Xpert Carba-R v2® and the selective culture show an overall, negative and positive percent agreements of 98.3%, 92.5%, and 98.7% respectively. The Kappa value was 0.88.

4. Discussion

Our results suggest the FecalSwab® is a suitable sampling device for Xpert Carba-R v2® as it allows detecting carbapenemase genes with comparable LoD to the recommended TDS (Ko et al. 2019; Vasoo et al. 2019). As swabs with liquid transport media are also accurate for Xpert *vanA*/*vanB*®, the main advantage of this strategy is the use of a single swab for eXDR screening by both culture and fully-integrated PCR methods (Rasoanandrasana et al. 2017). Consequently, the sample collection is simplified and the patient comfort is improved. Furthermore, while a swab of the TDS is entirely consumed for the molecular assay, the Cary-Blair transport media of the FecalSwab is in excess allowing to repeat the test in case of invalid results.

When performing the Xpert Carba-R v2® directly on a bacterial suspension, the LoD was previously reported at 46 CFU/swab which is lower than here (Ko et al. 2019). However, this methodology does not reflect the condition of testing a rectal swab as it does not take into account the release of the CPE from a polymicrobial swab. But, using an inoculated TDS, the Xpert Carba-R v2® LoD was reported similar to the present study (Ko et al. 2019; Vasoo et al. 2019). Furthermore, the high variability of the LoD according to strains and enzyme type reported here as in the previous study could reflect strain variability (e.g., variation in the copy number of carbapenemase genes-carrying plasmids) or an important area of technical uncertainty that has not been assessed yet. Indeed, high LoD were previously reported in an OXA-181-producing *K. pneumoniae* (i.e., 1600 to > 4000 CFU/swab) and a VIM-producing *K. pneumoniae* (i.e., 2250 CFU/swab) (Ko et al. 2019; Vasoo et al. 2019). It is not known to date if patients displaying a low CPE load are at lower risk for cross-transmission or not.

Almost all the false-negative samples of the Xpert Carba-R v2® yields the growth of a few numbers of CPE colonies on selective chromogenic agar, suggesting a low CPE load in these patients. The ChromID CARBA SMART is a bi-plate agar displaying 2 media, "OXA-48" and "CARBA," respectively selective for OXA-48-like-producing Enterobacterales and others CPE. By direct plating a bacterial suspension, the LoD of ChomID CARBA SMART agar has been assessed below 10 CFU/plate (Girlich et al. 2013; Ko et al. 2019). In another report using inoculated swabs, the ChromID CARBA SMART LoD has been assessed at least 5-times below that of the Xpert Carba-R v2® depending on the strain (Vasoo et al. 2019). This probable lower LoD of selective culture might explain false-negative of the Xpert Carba-R v2®. It suggests PCR-positive culture-negative samples are false-positive of the Xpert Carba-R v2®. Considering this hypothesis, a nonspecific amplification could be attributed to an interference of the feces as the LoD assay does not reveal unspecific gene amplification. However, our results highlight false-positive could be due to carbapenemase-producing nonfermenting Gram-negative rods such *Acinetobacter baumannii*. Otherwise, they could be a result of OXA-244-producing Enterobacterales which are part of the OXA-48-like group. This gene is detected by the Xpert Carba-R v2® but due to the low level of resistance to carbapenem conferred, OXA-244-producing Enterobacterales culture on ChromID CARBA SMART® is usually fastidious (Emeraud et al. 2020; Hoyos-Mallecot et al. 2017a). Therefore, the samples positive for a $bla_{\text{OXA-48-like gene}}$ using the Xpert Carba-R v2® but negative in culture could be due to an OXA-244-producing Enterobacterales. However, the rate of culture-negative among PCR-positive samples was not significantly different according to enzyme type suggesting a few numbers of samples containing an OXA-244-producing Enterobacterales were included here. It is also possible that enzyme subtype with a similar singularity to OXA-244 exists for other carbapenemase genes. Finally, we could hypothesis a non-Enterobacterales carbapenemase-producing species that growth is not supported by ChromID CARBA SMART® generates a false-positive. Byun et al. founded a false-positive rate of 26.5% using the Xpert Carba-R v2®, mainly for non-KPC genes (Byun et al. 2020). The author concluded a positivity of a non-KPC gene should be investigated. In the present study, few samples were positive for a KPC-producing strain and we could not conclude to a difference in performances regarding the carbapenemase gene. Furthermore, Tato et al. reported a low rate of false-positive, with no differences between KPC- and non-KPC-producing strains (Tato et al. 2016). As a subsequent swab was negative by both PCR and culture in 6 cases, this suggests PCR-positive culture-negative patients are likely false-positive of the Xpert Carba-R v2® (Hoyos-Mallecot et al. 2017b). However, the number of samples included here is limited, and face to this result, a subsequent sample is probably required in order to conclude to an eXDR carriage or not (HCSP 2019).

The update of the French guidelines for the prevention of eXDR cross-transmission recommends not performing a selective culture in the case of a negative PCR (HCSP 2019). Recently, it was suggested the Xpert Carba-R v2® might replace up to five consecutive cultures for eXDR screening in contact patients (Fonville et al. 2017; Saliba et al. 2020). But, despite eXDR screening is performed in the patients at high risk of carriage, the relatively low prevalence of 6.5%, might explain the rate of 17.1% PCR-positive culture-negative. Indeed, the rate of false-positive is intrinsically linked to the prevalence of CPE carriage. In this context, combining both methods is probably more efficient at least in patients at high risk of colonization in order to avoid false-negative (Girlich et al. 2020). A major adverse-effect of a false-negative is to disregard an eXDR carrier and therefore not implement specific IPC measures. The overall percentage agreement of 98.3% suggests IPC measure could be stopped or maintained according to the Xpert Carba v2® result. The strategy could be adapted within 2 days if the result of the culture is discordant. Using this strategy would allow to implement rapidly an optimal organization and limit the risk of cross-transmission especially if the compliance to standard precaution is high and the pressure colonization is low (Legeay et al. 2018; Magiorakos et al. 2017b). In contrast, a false-positive result would conduce implementing non-justified eXDR-specific IPC measures, therefore, disrupting the organization of the hospitals, increasing hospitalization cost, and possibly conveying an unsuitable message to medical and paramedical staff. Furthermore, the result of an eXDR screening is related to several pre-analytical findings. Indeed, it should be performed on a swab soiled with feces (Lepelletier et al. 2015). However, due to the volume of transport media and the coloration of the transport media and the walls of the

tube, the quality of swabs with liquid transport media is uneasy to assess visually. A solution would be to plate a non-selective agar in order to check the growth of fecal flora. Consequently, it encourages performing screenings by both culture and PCR.

Finally, the rate of invalid results was significantly different according to the participant center suggesting it might be related to a batch of reagent or a mishandling. However, the study was conducted over a one-year period and several batches were used by each center. In contrast, mishandling was previously reported as a cause of invalid results for fully integrated molecular methods (Farfour et al. 2020; Trabattoni et al. 2018). This high rate of invalid could also be due to the use of liquid media. Indeed, the supplier suggests not to perform the Xpert Carba-R v2® in case of highly soiled swabs (Cepheid 2020). If the fecal amount is too high, its homogenization can be difficult, and in this case, the instrument may give "error" as a result, due to difficulties in loading the sample into the analytical system of the cartridge. In contrast to standards swabs, highly soiled swabs cannot be evaluated with the FecalSwab®.

Our study presents some limitations. No Enterobacterales strains carrying a bla_{VIM} or a bla_{IMP} genes were found in culture during the assessment of the Xpert Carba-R v2® assay in routine use. This finding is more likely related to the low prevalence of these genes in the Paris area rather than to the higher LoD of the Xpert Carba-R v2® assay. Indeed, no selective culture grew an IMP or a VIM-producing Enterobacterales. Furthermore, only one centre used to perform enrichment cultures before plating the Cary-Blair transport media on CPE selective media which increase the sensitivity of the culture. We estimated the LoD of the Xpert Carba-R v2® using inoculated FecalSwab with calibrated bacterial suspensions. The use of inoculated stool samples would better reflect a clinical sample and allow an assessment of possible stool interference.

In conclusion, FecalSwab® is an accurate sampling device for CPE screening using the Xpert Carba-R v2® assay. It allows performing all eXDR screening using a single swab, simplifying the sample collection, and improving patient comfort. As the Cary-Blair transport media is in excess, a test could be repeated in case of an analytical problem. However, the Xpert Carba-R v2® should be performed simultaneously to a CPE selective culture in order to avoid false-positive and false-negative results. All discrepant of the two methods require control using a subsequent sample.

Author statement

Eric Farfour: Conceptualization, Methodology, Investigation, Formal analysis, Writing - Original Draft; Alexandra Lomont: Investigation, Review & Editing; Vincent Fihman: Investigation, Review & Editing; Marion Lecuru: Investigation, Review & Editing; Sophie Hüssler: Investigation, Review & Editing; Souad Ouzani: Investigation, Review & Editing; Jean-Ralph Zahar: Investigation, Review & Editing; Laurent Dortet: Investigation, Review & Editing.

Declaration of competing interest

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