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► To cite this version:

François Caméléna, Anne-Clotilde Moy, Emmanuel Dudoignon, Thibaut Poncin, Benjamin Deniau, et al.. Performance of a multiplex polymerase chain reaction panel for identifying bacterial pathogens causing pneumonia in critically ill patients with COVID-19. *Diagnostic Microbiology and Infectious Disease*, 2021, 99, pp.115183 -. 10.1016/j.diagmicrobio.2020.115183 . hal-03493840

HAL Id: hal-03493840

<https://hal.science/hal-03493840v1>

Submitted on 17 Oct 2022

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1 **Performance of a multiplex polymerase chain reaction panel for identifying**
2 **bacterial pathogens causing pneumonia in critically ill patients with COVID-**
3 **19**

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24 **ABSTRACT**

25
26 The FilmArray® Pneumonia Plus (FA-PP) panel can provide rapid identifications and semi-quantitative
27 results for many pathogens. We performed a prospective single-center study in 43 critically ill patients
28 with COVID-19, in which we performed 96 FA-PP tests and cultures of blind bronchoalveolar lavage
29 (BBAL). FA-PP detected one or more pathogens in 32% (31/96 of samples), whereas culture methods
30 detected at least one pathogen in 35% (34/96 of samples). The most prevalent bacteria detected were
31 *Pseudomonas aeruginosa* (n=14) and *Staphylococcus aureus* (n=11) on both FA-PP and culture. The FA-
32 PP results from BBAL in critically ill patients with COVID-19 were consistent with bacterial culture
33 findings for bacteria present in the FA-PP panel; showing sensitivity, specificity, positive and negative
34 predictive value of 95%, 99%, 82% and 100%, respectively. Median turnaround time for FA-PP was 5.5
35 hours, which was significantly shorter than for standard culture (26 hours) and AST results (57 hours).

36

37 **Keywords:** FilmArray Pneumonia plus, SARS-CoV-2, Bacterial pneumonia, Rapid diagnostics,

38

39 **1. Introduction**

40 Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes coronavirus disease 2019
41 (COVID-19), has rapidly spread worldwide. Several studies have reported complications of COVID-19,
42 such as bacterial pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ failure
43 syndromes [1–3]. Recent guidelines for the management of adults critically ill with COVID-19 have
44 suggested the empiric use of antimicrobial agents in patients with respiratory failure [4]. The accurate and
45 timely diagnosis of bacterial pneumonia, particularly in cases of hospital-acquired pneumonia (HAP) and
46 ventilator-associated pneumonia (VAP), is particularly challenging, and this condition remains a major
47 cause of morbidity and mortality [5,6]. Molecular tests provide a rapid turnaround time (TAT), together
48 with identifications and semi-quantitative results for many pathogens responsive to antimicrobial therapy.
49 Multiplex testing may provide additional information concerning the presence of antibiotic resistance
50 genes, thereby improving antibiotic management [7,8]. We performed a prospective single-center study on
51 critically ill patients with COVID-19, in which we conducted parallel tests of blind bronchoalveolar
52 lavage (BBAL) by conventional culture and FilmArray® Pneumonia Plus (FA-PP) panel (BioFire, Salt
53 Lake City, US). The aim of this study was to evaluate the performance of FA-PP and to compare its TAT
54 with that of conventional cultures.

55

56 **2. Materials and Methods**

57 *2.1. Study population*

58 We conducted a prospective single-center study of consecutive patients admitted to the ICU at the Saint-
59 Louis Hospital (Assistance Publique - Hôpitaux de Paris, Paris, France) between March 22, 2020 and
60 April 15, 2020, for COVID-19 complicated by respiratory failure. We included all patients on invasive
61 mechanical ventilation for whom BBAL was performed. The diagnosis of COVID-19 was based on the
62 detection of SARS-CoV-2 from nasopharyngeal samples. This detection relies on viral RNA amplification
63 by using RT-PCR (RealStar Altona®) to amplify SARSCoV2 E gene. Patients with the following criteria

64 were excluded from the analysis: aged under 18 years, pregnant or dying within 48 hours of admission.
65 For each patient, BBAL was performed immediately after intubation (or on admission to the ICU if the
66 patient was already intubated) and in cases in which VAP was suspected. We recorded clinical, laboratory
67 and antimicrobial therapy data. The study was approved by the local ethics committee (the ethics
68 committee of *Société Française d'Anesthésie Réanimation* IRB 00010254-2019-203).

69

70 2.2. Conventional microbiological analysis

71 BBAL was performed with a sterile catheter and a specimen trap kit. The suction tube was introduced
72 blindly through the endotracheal tube and wedged into the tracheobronchial tree before suction; 50 mL of
73 saline were successively injected and aspirated twice, and the contents of the second aspiration were
74 analyzed, the contents of the first being discarded [9]. Samples were transported immediately to the
75 laboratory. Samples received from 6 pm to 8 am were conserved at +4°C and tested the following
76 morning. We tested the BBAL samples in parallel by FA-PP and conventional culture, and the results
77 were released as soon as they become available. The decision to use FA-PP results for the management of
78 antimicrobial therapy was left to the discretion of the treating physician.

79

80 We plated 10 µL of BBAL on agar media (BioMérieux, Marcy l'Etoile, France) including blood, colistin-
81 nalidixic acid blood and chocolate agars, and incubated the plates in ambient air or under an atmosphere
82 enriched with 5% CO₂ at 35°C. No Gram staining was performed on the BBAL, to protect laboratory
83 staff, as this procedure requires centrifugation, which may generate aerosols. Bacteria were semi-
84 quantified by calculating colony-forming units (CFU) per ml (CFU/ml). Culture results were interpreted
85 according to the recommendations of the European Society for Clinical Microbiology and Infectious
86 Diseases [10], after observation at 18-24 hours, and negative plates were incubated for a further two days,
87 to ensure an absence of bacterial growth, before being classified definitively as negative. A cut-off of 10⁴
88 CFU/ml for significant growth of potential pathogens for BBAL was used. Bacteria were identified by

89 using MALDI-TOF MS (VITEK-MS, BioMérieux, Marcy-l'Étoile, France), according to the
90 manufacturer's instructions. Antimicrobial susceptibility testing (AST) was performed by the disk
91 diffusion method or with the VITEK 2 (BioMérieux, Marcy-l'Étoile, France), in accordance with the
92 recommendations of the European Committee on Antimicrobial Susceptibility Testing.

93

94 *2.3. Molecular investigation*

95 As recommended by the manufacturer, a dry swab was dipped into the BBAL and then immersed in
96 dilution buffer before injection of the fluid into the FA-PP cartridge. The analysis was carried out in 67
97 minutes on the Filmarray® apparatus (version 2.1.336.0), with the Pneumoplus v2.0 pouch system
98 (version 2.1.0.5).

99

100 *2.4. Statistical analysis*

101 Sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV and NPV), likelihood ratio
102 and κ index were calculated by comparing the results for conventional culture with those of FA-PP only
103 for bacterial pathogens present in the FA-PP panel. Performance was measured only for bacterial analysis,
104 with bacterial culture used as the gold standard reference method. Two-tailed Mann-Whitney tests were
105 used to compare TAT between the two methods.

106

107 **3. Results**

108 In total, 96 samples from 43 patients were tested in parallel by FA-PP and conventional BBAL culture.
109 The median age of the patients was 64 years, 86% were male, 27% were obese and 72% had hypertension
110 (Table 1). On admission to the ICU, 37 (86%) patients were already on invasive mechanical ventilation.
111 BBAL were performed under antibiotic treatment in 55% (53/96) of samples.

112 FA-PP detected one or more pathogens in 32% (31/96) of samples (corresponding to 18 patients), whereas
113 culture methods detected at least one pathogen in 35% (34/96) of samples (corresponding to 20 patients).

114 At first BBAL, 25% (10/43) of FA-PP tests and 21% (9/43) of cultures gave positive results. The most
115 prevalent bacteria detected were *Staphylococcus aureus* ($n=5$ on both FA-PP and culture) followed by
116 *Haemophilus influenzae* ($n=4$ and $n=2$ on FA-PP and culture, respectively) (Table 2). In cases in which
117 others BBAL were performed, 40% (21/53) of samples tested positive by FA-PP whereas 47% (25/53)
118 tested positive on culture. The most prevalent bacteria detected was *Pseudomonas aeruginosa* ($n=11$ on
119 both FA-PP and culture), followed by *S. aureus* ($n=6$ on both FA-PP and culture) (Table 2). The
120 performance of FA-PP for each pathogen is shown in Table 2. Of the 43 patients, 11/43 (25.5%) had only
121 one sampling, and in each case, a negative result was found for both FA-PP tests and cultures. For the
122 remaining 32/43 (74.5%) patients, iterative sampling was performed; all FA-PP test and culture results for
123 these patients are presented in Supplementary Table S1. Neither atypical bacteria nor viruses were
124 detected by FA-PP. The pathogen most frequently detected by FA-PP in the absence of positive cultures
125 was *H. influenzae* ($n=3$). Positive cultures were obtained for eight samples that tested negative by FA-PP.
126 In six of these eight samples, the pathogens present were not included in the FA-PP panel (*Citrobacter*
127 *koseri* in 4 cases, *Stenotrophomonas maltophilia* in one case and *Enterococcus faecium* in one case). *S.*
128 *aureus* and *Klebsiella aerogenes* were recovered from single culture from two samples that tested also
129 negative by FA-PP. Bacterial load was 10^3 colony-forming units (CFU)/mL of culture for both these
130 pathogens, corresponding to a low organism burden. We found that 28 of the bacteria of the FA-PP panel
131 grew to significant levels (*i.e.* $\geq 10^4$ CFU/mL) in culture, with 100% (28/28) presenting $\geq 10^4$ copies of
132 bacterial nucleic acid/mL on FA-PP. Another 10 bacteria grew to non-significant levels (*i.e.* $< 10^4$
133 CFU/mL), and 80% (8/10) of these bacteria were found to be present at a level $\geq 10^4$ copies/mL by FA-
134 PP. FA-PP detected two *bla*_{CTX-M} extended spectrum β -lactamase (ESBL), one *bla*_{VIM} carbapenemase and
135 two *S. aureus* methicillin resistance genes. AST detected the presence of an ESBL encoded by a *bla*_{CTX-M}
136 gene in *Escherichia coli* and methicillin-resistant *S. aureus* (MRSA) in two isolates corresponding to two
137 cases of *mecA/C* detection by FA-PP. The detection of the other resistance genes, one *bla*_{CTX-M} and one
138 *bla*_{VIM}, remained unexplained because no other viable bacteria with a phenotype corresponding to the
139 presence of these genes were obtained in culture.

140 Median TAT was significantly shorter for FA-PP tests than for standard culture and AST results (5.5
141 hours [IQR: 3.4-12.4] vs. 25.9 hours [IQR: 22.5-35.7] and 57 hours [IQR: 47.7-70.8], $p<0.001$ and
142 $p<0.001$, respectively).

143

144 **4. Discussion**

145 We studied 43 critically ill patients with COVID-19 who underwent BBAL at least once for suspected
146 bacterial pneumonia. A few cases of bacterial pneumonia have been reported in critically ill patients with
147 COVID-19. The diagnosis of bacterial pneumonia in such patients remains challenging, as obtaining distal
148 respiratory samples by bronchoscopy exposes intensivists to a high risk of contamination [1,2,11]. We,
149 therefore, performed BBAL, which is simple, suitable for bacterial culture and does not require
150 bronchoscopy [9]. Multiplex syndromic panels for the detection of bacterial pathogens responsible for
151 pneumonia have recently been developed and shown to yield more sensitive results more rapidly than
152 conventional culture, particularly in cases in which antibiotics were administered before sampling [6–8].
153 However, there are currently no recommendations for routine molecular testing and multiplex PCR is
154 rarely used for detection of the bacteria typically responsible for pneumonia. Questions about the clinical
155 usefulness of this approach remain, particularly in the context of critically ill patients with COVID-19.

156 This is, to our knowledge, the first study to evaluate, in real-time, FA-PP relative to culture, using
157 exclusively distal respiratory samples for the diagnosis of bacterial pneumonia in critically ill patients. It
158 shows that the results of FA-PP are consistent (Se 95%, Sp 99%, PPV 82% and NPV 100%) with those of
159 conventional culture for the bacterial pathogens present in the FA-PP panel. FA-PP significantly
160 decreased TAT and increased the number of bacterial detections in critically ill patients with COVID-19.
161 However, attention must be paid to bacteria not present in the FA-PP panel (*e.g. Citrobacter spp.*) that
162 might affect antibiotic therapy and to calculations of FA-PP performance that were performed
163 independently of the consideration of bacterial thresholds and antibiotic administration prior to sampling.

164 Bacterial cultures of BBAL grew with significant amount of bacteria (ie, $\geq 10^4$ CFU/mL) in 37% (n =16)
165 of patients. Among the 16 bacterial pneumonia, 4 (25%) were classified as community-acquired
166 pneumonia, 1 (6%) as HAP, and 11 (69%) as VAP. In our study, 6% (6/96) of the samples were found to
167 contain a bacterium not present in the FA-PP panel, and this bacterium was present at a high abundance
168 (*i.e.* $\geq 10^4$ CFU/mL) in four of these samples. These bacteria were involved in 1 HAP and 3 VAP.

169 Furthermore, FA-PP may provide a major argument for very early de-escalation and narrowing of
170 antimicrobial therapy in specific situations (such as to withdraw anti-MRSA), if negative FA-PP results
171 are obtained, or for the faster initiation of appropriate antimicrobial therapy, if positive FA-PP results are
172 obtained. We also found that most of the positive FA-PP results from culture-negative samples
173 corresponded to *H. influenzae*; the presence of this bacterium may reflect contamination by the
174 oropharyngeal flora. Antimicrobial therapy is also known to impact bacterial growth, as 88% (7/8) of the
175 false positive FA-PP results were obtained from BBAL performed under antibiotic treatment. Similarly,
176 63% (5/8) of bacteria, present at a level $\geq 10^4$ copies/mL by FA-PP and grew at non-significant level in
177 culture, were from BBAL performed under antimicrobial therapy. Furthermore, others studies have
178 described that the bacterial burden could be overestimate by FA-PP compared to culture [7,8]. In addition,
179 resistance genes detected by FA-PP were not confirmed by AST results in 2 samples suggesting
180 limitations to predict phenotypic susceptibility from molecular tests. These results raise important point
181 that PCR can detect both dead and viable bacteria [7,8,12]. It remains unclear for how long bacterial loads
182 remain detectable after the initiation of appropriate antibiotic treatment in critically ill patients with
183 COVID-19 and whether the monitoring of bacterial load by FA-PP would be useful in these patients and,
184 more broadly, in all patients with suspected VAP. Further studies are required to investigate this issue.
185 Additionally, FA-PP has a cost per test much greater than the costs of routine culture; future studies
186 should focus on how best to use this test in a cost-effective manner.

187 Finally, the strengths of this study are the well-characterized population of patients (COVID-19 in ICU),
188 the use of a single type of specimen (BBAL) and prospective testing by FA-PP and culture in parallel. Its

189 limitations are that it was a single-center study and that the COVID-19 population may not be
190 representative of the ventilated patients generally treated in the ICU

191 **5. Conclusion**

192 In conclusion, in this prospective study of critically ill patient with COVID-19, FA-PP results were in
193 agreement with standard culture for identifying bacterial pathogens in BBAL specimens, with a significant
194 decrease of TAT. The use of FA-PP may enable a more complete and faster approach for the diagnosis of
195 bacterial pneumonia in patient hospitalized in ICU. Further studies are required to address the clinical
196 impact of FA-PP on the management of VAP in critically ill patients.

197

198 **Acknowledgments**

199 The authors thank the intensive care teams and the clinical microbiology staff of Saint-Louis Hospital for
200 their contributions. They also thank Samuel Amar for his help with the collection of microbiological data.

201

202 **Declarations**

203 **Funding:** This work was supported by internal funding.

204 **Competing Interests:** F.C. received conference invitations from BioMérieux.

205 **Ethical Approval:** The study was approved by the local ethics committee (the ethics committee
206 of Société Française d'Anesthésie Réanimation IRB 00010254-2019-203).

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243

244 **TABLE AND FIGURE**

245 Table 1. Main characteristics of patients on admission to the ICU.

| Characteristics | Patients (n=43) |
|---|------------------------|
| Median age, years (IQR) | 64 [56-70] |
| Sex, male, no. (%) | 37 (86) |
| Median BMI, kg per m ² (IQR) | 27 [26-30] |
| Comorbidities, no. (%) | |
| Hypertension | 31 (72) |
| Heart failure | 1 (2.3) |
| ARBS | 17 (39.5) |
| Coronary disease | 5 (11.6) |
| Diabetes mellitus | 16 (37.0) |
| Pulmonary disease | 7 (16.0) |
| Immunosuppression | 3 (7.0) |
| Severity of illness | |
| Duration from onset of symptoms to ICU admission, days (IQR) | 8.5 [5.3-11.6] |
| SAPS II (IQR) | 37 [28-49] |
| SOFA score on day 1 (IQR) | 5 [4-7] |
| Acute kidney injury, no. (%) | 28 (65.1) |
| KDIGO 1 | 6 (13.9) |
| KDIGO 2 | 6 (13.9) |
| KDIGO 3 | 16 (34.9) |
| Renal replacement therapy, no. (%) | 8 (18.6) |
| Mechanical ventilation on ICU admission, no. (%) | 37 (86) |
| ARDS, no. (%) | 43 (100) |
| Ratio of PaO ₂ to FiO ₂ , mmHg (PaO ₂ /FiO ₂) at admission (IQR) | 136 [82.5-174.5] |
| Ratio of PaO ₂ to FiO ₂ nadir, mmHg (IQR) | 82 [70-103] |
| Median number of prone position ventilation sessions (IQR) | 1 [0-2] |
| Duration of mechanical ventilation, days (IQR) | 10 [7-12] |
| Use of noradrenaline during the first 48 hours, no. (%) | 36 (83.7) |
| Length of stay in ICU, days (IQR) | 11 [8-13] |
| Death, no. (%) | 12 (27.9) |
| Admission biological data | |
| WBC count, x 10 ⁹ cells per L (IQR) | 9.52 [5.2-12.4] |
| Lymphocyte count, x 10 ⁹ cells per L (IQR) | 0.79 [0.5-1.1] |
| Serum creatinine concentration, μmol per L (IQR) | 75 [57-100.5] |

| | |
|--|------------------|
| D-dimers, ng per mL (IQR) | 2610 [1490-4820] |
| Radiological data | |
| X-ray, number of dials affected at admission | 4 [2-4] |
| CT during hospitalization, no. (%) | 29 (67.4) |
| (10-25]* | 2 (6.9) |
| (25-50]* | 9 (31.0) |
| (50-75]* | 10 (34.5) |
| >75* | 8 (27.6) |
| Antimicrobial treatment, no. (%) | |
| Antibiotic therapy before admission | 29 (67.4) |
| 3 rd generation cephalosporin | 22 (51.1) |
| Macrolide | 21 (48.3) |
| Other antibiotics | 11 (25.6) |

246 **BMI:** Body mass index; **ICU:** Intensive care unit; **SAPS II:** Simplified Acute Physiology Score II;
247 **SOFA:** Sepsis-Related Organ Failure Assessment; **KDIGO:** Kidney Disease Improving Global
248 Outcomes; **ARDS:** Acute respiratory distress syndrome; **ARBs:** Angiotensin-renin-aldosterone
249 blocker system; **WBC.** White blood cells; **CT:** computerized tomography; *Specific COVID-19
250 pulmonary lesions

251

252 Table 2 Performance of FA-PP relative to conventional culture

| Bacterial pathogen | FA-PP+ & Culture+ | FA-PP+ & Culture- | FA-PP- & Culture+ | FA-PP- & Culture- | Se (95% CI) | Sp (95% CI) | PPV (95% CI) | NPV (95% CI) | LR+ (95% CI) |
|---------------------------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|--------------------|-------------------|---------------|
| <i>Acinetobacter baumannii</i> | 0 | 0 | 0 | 96 | - | 1.00 (-) | - | 1.00 (-) | - |
| <i>Staphylococcus aureus</i> | 10 | 1 | 1 | 84 | 0.91 (0.58-1.0) | 0.99 (0.94 - 1.0) | 0.91 (0.59 - 0.98) | 0.99 (0.93 - 1.0) | 77 (11 - 54) |
| <i>Streptococcus pneumoniae</i> | 3 | 1 | 0 | 92 | 1.00 (0.29 - 1.0) | 0.99 (0.94 - 1.0) | 0.75 (0.30-0.95) | 1.00 (-) | 93 (13 - 65) |
| <i>Escherichia coli</i> | 3 | 0 | 0 | 93 | 1.00 (0.29 - 1.0) | 1.00 (0.96 - 1.0) | 1.00 (-) | 1.00 (-) | - |
| <i>Enterobacter cloacae</i> | 0 | 1 | 0 | 95 | - | 0.99 (0.97 - 1.0) | 0.00 (-) | 1.00 (-) | - |
| <i>Klebsiella aerogenes</i> | 3 | 0 | 1 | 92 | 0.75 (0.19 - 0.99) | 1.00 (0.96 - 1.0) | 1.00 (-) | 0.99 (0.94 - 1.0) | - |
| <i>Klebsiella pneumoniae</i> | 0 | 1 | 0 | 95 | - | 0.99 (0.97 - 1.0) | 0.00 (-) | 1.00 (-) | - |
| <i>Klebsiella oxytoca</i> | 0 | 0 | 0 | 96 | - | 1.00 (-) | - | 1.00 (-) | - |
| <i>Pseudomonas aeruginosa</i> | 14 | 0 | 0 | 82 | 1.00 (0.77 - 1.0) | 1.00 (0.96 - 1.0) | 1.00 (-) | 1.00 (-) | - |
| <i>Haemophilus influenzae</i> | 2 | 3 | 0 | 91 | 1.00 (0.16 - 1.0) | 0.97 (0.91 - 0.99) | 0.40 (0.18 - 0.67) | 1.00 (-) | 31 (10 - 95) |
| <i>Streptococcus agalactiae</i> | 1 | 0 | 0 | 95 | 1.00 (0.03 - 1.0) | 1.00 (0.96 - 1.0) | 1.00 (-) | 1.00 (-) | - |
| <i>Streptococcus pyogenes</i> | 0 | 0 | 0 | 96 | - | 1.00 (-) | - | 1.00 (-) | - |
| <i>Serratia marcescens</i> | 0 | 0 | 0 | 96 | - | 1.00 (-) | - | 1.00 (-) | - |
| <i>Proteus spp.</i> | 0 | 1 | 0 | 95 | - | 0.99 (0.97 - 1.0) | 0.00 (-) | 1.00 (-) | - |
| <i>Moraxella catarrhalis</i> | 0 | 0 | 0 | 96 | - | 1.00 (-) | - | 1.00 (-) | - |
| Total (per analysis) | 36 | 8 | 2 | 1394 | 0.95 (0.82 - 0.99) | 0.99 (0.99 - 1.0) | 0.82 (0.69 - 0.90) | 1.00 (0.99 - 1.0) | 166 (83 - 33) |

253 FA-PP: FilmArray Pneumonia Plus; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV:
 254 Negative predictive value; LR: Likelihood ratio

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