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# Retrospective analysis of multiplex PCR results and their impact in current practice

Léopold Letouzé

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Faculté de Médecine

Université Nice Sophia-Antipolis

THÈSE D'EXERCICE DE MÉDECINE

Pour l'obtention du Diplôme d'État de Docteur en Médecine

Par

**Léopold LETOUZÉ**

Né le 27 Mars 1993 à Paris

# Analyse rétrospective des résultats de PCR multiplexe et de leur impact en pratique courante

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*à la Faculté de Médecine de Nice*

Spécialité Anesthésie-Réanimation et Médecine Péri-Opératoire

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## ABRÉVIATIONS DU MANUSCRIT

**CAP = Community-acquired pneumonia**  
**HAP = Hospital-acquired pneumonia**  
**VAP = Ventilator-associated pneumonia**  
**ICU = Intensive care unit**  
**AST = Antibiotic susceptibility testing**  
**Rm-PCR = rapid multiplexed-Polymerase Chain Reaction**  
**US = United-States**  
**ESICM = European Society of Intensive Care Medicine**  
**FDA = Food and Drug Administration**  
**EMA = European medicines agency**  
**EU = European Union**  
**MRB = Multiresistant bacteria**  
**MRSA = Methicillin resistant *Staphylococcus aureus***  
**ESBL = Extended-spectrum bêta-lactamase**  
**NDM = New-Delhi metallo bêta lactamase**  
**MREJ = mec right extremity junction**  
**KPC = *Klebsiella pneumoniae* carbapenemase**  
**VIM = Verona integron-encoded metallo bêta lactamase**  
**MERS-COV = Middle-east respiratory syndrome - coronavirus**  
**ETA = Endo tracheal aspirate**  
**DPA = Distal protected aspirate**  
**BAL = Broncho alveolar lavage**  
**SARS-CoV-2 = Severe acute respiratory syndrome – Coronavirus 2**  
**CASFM = Comité de l'antibiogramme de la société française de microbiologie**  
**BMI = Body mass index**  
**COPD = Chronic obstructive pulmonary disease**  
**MDR = Multidrug resistant**  
**MV = Mechanical ventilation**  
**ARDS = Acute respiratory distress syndrome**  
**COVID-19 = Coronavirus infectious disease – 2019**

## REMERCIEMENTS

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Vous me faites le privilège d'être présents dans cet amphithéâtre aujourd'hui. Je suis honoré que vous jugiez mon travail, j'espère qu'il revêtira à vos yeux la qualité et la détermination que j'ai tenté d'atteindre.

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Docteur en médecine, Anesthésie-Réanimation et Médecine Péri-Opératoire**

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## INTRODUCTION

Among intensive care patients, lower respiratory tract infections are a leading cause of infectious complications and one of the leading causes of in-ICU death.(1) (2) Depending on the acquisition context, it can be classified as community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) or as ventilator-associated pneumonia (VAP).(3) (4)

Therefore, VAP is the most common ICU-reported infection in mechanically ventilated patients and it is associated with significant increases in morbidity and ICU-length of stay.(5) (6) Accurate HAP & VAP diagnosis and treatment remain challenging since this condition presents with a wide variety of symptoms, severity and causative agents.(7) (8) Timely antibiotherapy, rapid bacterial identification followed by antibiotic susceptibility testing (AST) are crucial for outcome.(9) (10) (7)

Empirical broad spectrum antibiotherapy is, however responsible for half of the ICU antibiotic consumption.

Recent European and US. epidemiological data show that gram negative bacilli such as Enterobacteriaceae and Acinetobacter, Staphylococcus aureus and Pseudomonas aeruginosa account for the vast majority of both HAP and VAP microbial aetiologies. (11) (12)

Current gold standard in microbial diagnosis consists of respiratory tract sampling, quantitative bacterial culture, direct staining and antimicrobial susceptibility testing. The entire process takes from 48 hours up to 72 hours before being able to safely narrow activity spectrum according to identification and AST result. However, it suffers from a lack of sensitivity as no pathogen can be identified in up to 70% of pneumonia cases.(13)

Antibiotic stewardship programs urge the shortest use of antibiotics with the narrowest spectrum and any unnecessary antibiotic therapy avoidance.(14) (15)

Rm-PCR assays are an emergent and promising field for few years in laboratory microbial identification technologies, enabling rapid multiple identification of the micro organisms present in patient samples. (16) (17) (18) (19) This new molecular diagnostic technique is now available in routine laboratory practice and has been acquired by some hospitals in our department.

Rapid bacterial characterization in VAP-suspicious patients by means of accurate and robust rapid molecular diagnostic routine laboratory technology might lead to a shortening of empirical broad-spectrum antibiotics course.(20)

The BioFire® FilmArray® Pneumonia plus Panel (bioMérieux, France) is a rm-PCR panel allowing the simultaneous detection of several VAP & HAP-causative microorganisms and the corresponding antibiotic resistance genes in a short announced time.(21)

Some studies have evaluated this technique and its equivalents available to clinicians but they were either conducted in other clinical settings or they evaluated other rm-PCR kits. Therefore, the existing knowledge on this particular rm-PCR panel is not sufficient to evaluate the diagnostic performance and the clinical impact of this diagnostic panel on the therapeutic strategy of HAP & VAP.(22) (23) (24) (25) (26) (27) (28)

The aim of this study is to determine the diagnostic performance and to evaluate the clinical impact of the BioFire® FilmArray® Pneumonia Plus panel (bioMérieux, France) for the detection of HAP and VAP causative bacteria in ICU patients.

## **MATERIAL AND METHODS**

### **Setting**

We performed an observational retrospective study between March 20, 2020 and April 30, 2021, in three French medico-surgical ICUs (Nice-University Hospital, Cannes-General Hospital and Grasse-General Hospital).

### **Patients**

All rm-PCR performed on a respiratory sample were analyzed. Medical charts were analyzed in order to ensure that all patients were at least 18. Criteria of community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP) were searched. We used the clinical and radiological criteria for pneumonia according to the ESICM guidelines (3,7) : new lung infiltrate on a chest X-ray and evidence that the infiltrate was of an infectious origin, i.e., at least two of three clinical features (fever greater than 38°C, leukocytosis >12.000/mm<sup>3</sup> or leukopenia <4.000/mm<sup>3</sup>, and purulent secretions).

HAP was defined as a non-ventilated pneumonia occurring > 48h after hospital admission. VAP relates to pneumonia arising > 48h after endotracheal intubation. CAP was defined as pneumonia acquired outside of the hospital.

In accordance with definitions, HAP and VAP are neither present nor incubating at the time of hospital admission or at the onset of mechanical ventilation. (29)

Each laboratory rm-PCR performed on respiratory tract assays in critically ill adults was included. Unavailability of conventional microbiology on the same sample used for rm-PCR resulted in exclusion of the VAP, HAP or CAP episode-suspicion from analysis.

The choice to conduct a rm-PCR test was based on the decision of the attending physician. Regarding the lack of evidence upon this new test, it was conducted in a bundle with the gold standard, i.e. microbiologic direct smearing, staining and culture along with the rm-PCR side by side. We could hereby consider microbiologic standard examination as the control intervention against which the rm-PCR was evaluated.

Different methods of respiratory samples were used at the physician's discretion: sputum specimen, tracheal aspirates, distal protected aspirates, broncho alveolar lavage. Samples from other sites (aero & anaerobic blood cultures, urine cultures, catheter cultures), urinary pneumococcal and legionella antigens, MRB and MRSA screenings taken at the same moment were also examined as a comparison to rm-PCR results.

Biological samples were immediately taken to the laboratory according to the standard procedure and both standard microbiology and rm-PCR assay were conducted. The operational turnaround time is the time period between sample collection and final rm-PCR results validation in clinical conditions.

Results of both techniques were transmitted to the clinicians as soon as they were available. Medical data were retrospectively gathered by the investigating physician and included in the analysis. The clinical diagnosis stated in the medical report was reassessed retrospectively by the investigating physician in light of the collected medical data.

Results for rm-PCR are expressed as qualitative results (negative or positive) for resistance genes, for non typical bacteria and for viruses and as semi-quantitative results for typical bacteria ( $10^4$  to  $\geq 10^7$  DNA copies/mL after PCR amplification).

Announced manufacturer rm-PCR total turnaround time (time from sample collection to result validation) lies around an hour.(30) (31) Routine laboratory practice was maintained throughout the whole study period both for gold standard and for rm-PCR realization in order to stay in routine clinical practice conditions.



## Microbiology

BioFire® FilmArray® Pneumonia plus Panel (bioMérieux SA, Marcy-l'Étoile, France) is a Food and Drug Administration (FDA)-approved and EU-marked syndromic rapid multiplexed-Polymerase Chain Reaction (rm-PCR) that simultaneously identifies 33 targets: fifteen typical and three atypical bacterial pathogens, eight respiratory viruses and seven genetic markers of antimicrobial resistance.

Semi-quantitative results are given for the fifteen typical bacterial targets. Along with the microbiological identification and in order to further differentiate pathogens from colonisers, a semi-quantification of detected pathogens is provided among 15 typical bacterial targets. Antimicrobial resistance determinants include CTX-M (ESBL gene), OXA-48, IMP, NDM (Carbapenemase genes), *mecA/C* & MREJ (Methicillin resistance genes). (See Figure 1 for list of detected targets)

<b><u>Bacteria</u></b>	<b><u>Atypical bacteria</u></b>	<b><u>Antibiotic resistance genes</u></b>
<i>Acinetobacter baumannii</i> complex	<i>Chlamydia pneumoniae</i>	<u>Methicillin resistance</u>
<i>Enterobacter cloacae</i> complex	<i>Legionella pneumophila</i>	<i>mecA/C</i> & MREJ
<i>Escherichia coli</i>	<i>Mycoplasma pneumoniae</i>	
<i>Haemophilus influenzae</i>		<u>ESBL</u>
<i>Klebsiella aerogenes</i>	<b><u>Viruses</u></b>	CTX-M
<i>Klebsiella oxytoca</i>	Adenovirus	
<i>Klebsiella pneumoniae</i> group	Coronavirus	<u>Carbapenemases</u>
<i>Moraxella catarrhalis</i>	Enterovirus / Human rhinovirus	KPC
<i>Proteus</i> spp.	Human metapneumovirus	NDM
<i>Pseudomonas aeruginosa</i>	Influenza virus A / B	OXA48-like
<i>Serratia marcescens</i>	MERS-CoV	VIM
<i>Staphylococcus aureus</i>	Parainfluenza virus	IMP
<i>Streptococcus agalactiae</i>	Respiratory syncytial virus	
<i>Streptococcus pneumoniae</i>		
<i>Streptococcus pyogenes</i>		

**Figure 1.** List of FilmArray PneumoniaPlus-panel genetical targets

MERS-CoV: Middle-East Respiratory Syndrom Coronavirus

Respiratory samples were analyzed according to French recommendations (Rémic, 2018).

Upon sample arrival, Gram coloration was performed on sputum and endotracheal aspiration. These samples and serial dilution were seeded only if they matched Bartlett score. We did not realize smear examination on airway samples [sputum, endotracheal aspirate (ETA), broncho alveolar lavage (BAL) or distal protected aspirate (DPA)] to avoid SARS-CoV-2 aerosolization risk related to cytocentrifugation use.

Samples and serial dilutions depending on sample type were plated on Colombia agar + 5% horse blood, McConkey agar, Candida agar (bioMérieux SA, Marcy-l'Étoile, France) and incubated at 36±2°C

under aerobic conditions, on Chocolate agar PolyViteX incubated at  $36\pm 2^{\circ}\text{C}$  under 5%  $\text{CO}_2$  conditions and on Colombia agar + 5% horse blood at  $36\pm 2^{\circ}\text{C}$  under anaerobic conditions. Superficial respiratory samples were incubated up to 48 hours and lower respiratory samples were incubated up to five days under anaerobic conditions.

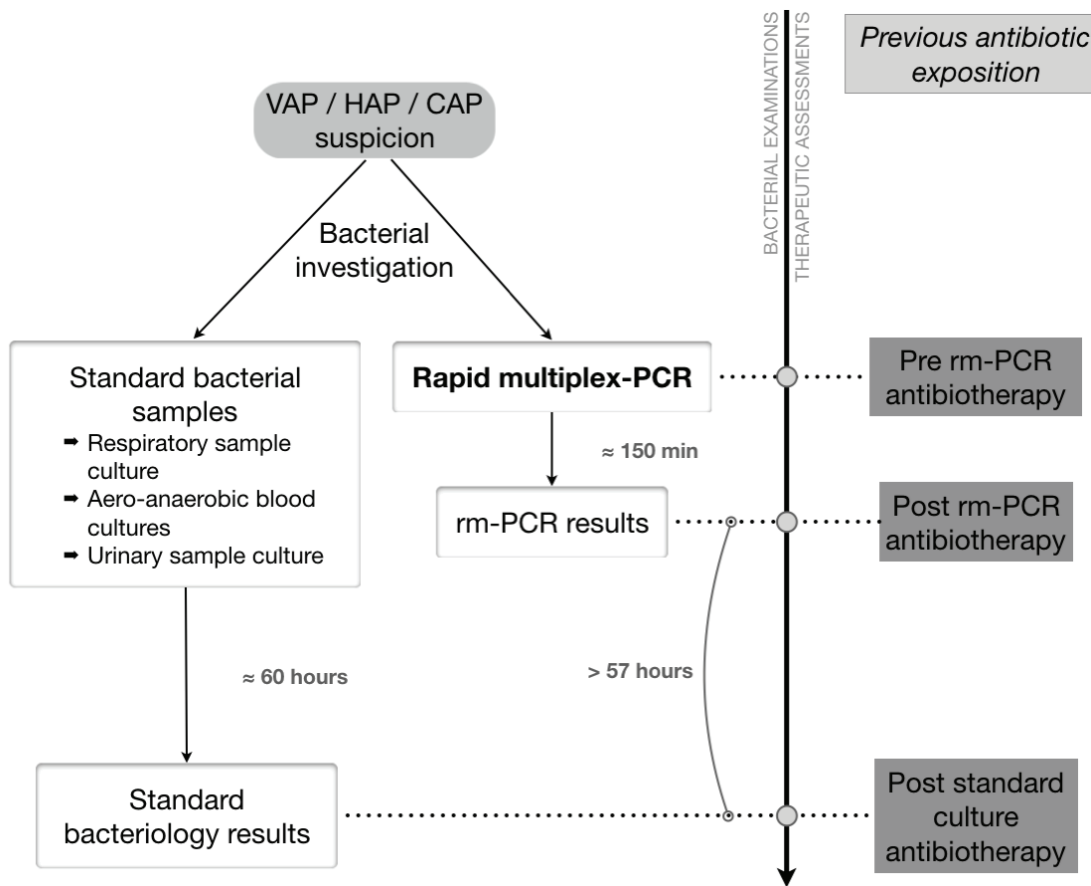
Original specimen bacteria count was estimated by colony counts and expressed as CFU/mL. Bacterial identification was performed using mass spectrometry (Biotyper, BrukerDaltonics, Germany). AST was performed using disc diffusion method on Mueller–Hinton media (i2a, Montpellier, France) from colonies isolated after primary culture, according to CASFM recommendations (Comité de l'Antibiogramme de la Société Française de Microbiologie). Enlarged Spectrum Beta Lactamase in Enterobacteriaceae and methicillin resistance in *Staphylococci* were phenotypically determined on AST. Carbapenemase genes were confirmed by Xpert® Carba-R (Cepheid, Sunnyvale, USA).

### **Potential antibiotic strategy-impact assessment**

We collected time-focused and clinical suspicion-focused data concerning bacterial targets selection and antibiotic spectrum adaptation in view of standard microbiologic data and rm-PCR in order to be able to assess any potential antibiotic strategy-impact originating in a rm-PCR result. In this purpose, any antibiotic change linked with a rm-PCR was classified into:

- “Escalation” if the antibiotic regimen adaptation purpose was to enlarge the antibiotic spectrum after rm-PCR result reception
- “De-escalation” if the antibiotic regimen adaptation purpose was to narrow the antibiotic spectrum after rm-PCR result reception
- “Unchanged” if no modification to the antibiotic regimen was made after rm-PCR result reception.

We listed antibiotic regimen evolution at the time of rm-PCR results and at the time of standard microbiology results and evaluated if the therapeutic decisions made in response to any result were 1) contributory and 2) hazardous regarding antibiotic spectrum choice.



**Figure 2** Data retrieval example flowchart of a pneumonia suspicion

### Statistical analysis and ethics

The data are described as their frequencies and percentages for categorical variables, and as their medians [Interquartile range] for quantitative variables. Descriptive statistical analyses and Pearson's Chi-squared two-sided tests for categorical variables distribution were conducted using the R software (3.3.2, R Foundation for Statistical Computing, Vienna, Austria) and the RStudio cloud service (RStudio, Boston). Each missing data was excluded from the statistical analysis and from percentages calculation to minimize its potential impact.

In conformity with French law, ethical board review was waived since this trial used readily available information, did not require any supplementary intervention and did not put patients at risk. All data were anonymously gathered and complied with the French Informatics and Liberties Commission (CNIL- MR N°3 – declaration n°2213943) recommendations on such information treatments to ensure patient data anonymity and safety.

## RESULTS

### Demographic description

Over the course of the study, medical data from 103 incident pneumonia episodes all originating from 48 patients hospitalized in participating ICUs were gathered and subsequently analyzed according to the study protocol (Table 1).

Our patients were mainly men, ages ranged between 44 and 84 with most of our patients over 50. The vast majority of our patients were overweight (36 patients, 75% of our population), top BMI reached 39,6 kg/m<sup>2</sup>, we found a 25% (12 patients) obesity prevalence.

Three out of four carried at least one cardiovascular risk factor. Underlying immune depression was quite frequent with a quarter of our patients concerned by this condition while respiratory conditions were quite rare.

Upon further examination, the most frequent risk factors in our population were hypertension (17 patients), ischaemic cardiopathy (14 patients), chronic renal failure (7 patients) and diabetes (7 patients).

*Table 1. Patient characteristics*

	<b>Number (%) (n=48)</b>
<b>Population</b>	
Age (years)	73 (64 – 78)
Male	40 (83%)
<b>Medical conditions</b>	
BMI (kg/m <sup>2</sup> )	26.8 (25.1 – 29.9)
Cardiovascular comorbidities	37 (77%)
Hypertension	17 (35%)
Respiratory failure	4 (8%)
Renal failure	2 (4%)
Smokers	4 (8%)
COPD	3 (6%)
Immune deficiency	13 (27%)
Corticosteroid treatment	3 (6%)
Transplant recipients	2 (4%)
Chemotherapy	4 (8%)
Hemopathy	7 (14%)
MDR-carrier risk factors	30 (62%)
<b>Severity upon admission</b>	
Oxygen supply > 6L/min	28 (59%)
Mechanical respiratory support	20 (41%)
IGS2 score	42.5 (34.8 – 49)
<b>Evolution</b>	
Invasive ventilatory support	39 (81%)
Intensive care length of stay (days)	13 (10 – 28)
Invasive ventilation duration (days)	9 (3.5 – 25.5)
Renal replacement therapy	14 (29%)
In-ICU death	25 (52%)

### **Clinical course and evolution**

Major reason for hospital and ICU-admission was acute respiratory distress secondary to a SARS-CoV-2 respiratory infection (100% of our patients), which resulted in the death of one in two patients (Table 1). Median time interval between first symptoms onset and ICU-admission was 7 days (IQR 4 – 10). Median ICU-stay was 13 days (IQR 10 – 28).

Upon ICU admission, all our patients needed oxygen support, be it passive support or mechanical support [16 patients (33%) required high flow nasal cannula oxygen support, 12 patients (25%) required bag-mask oxygen support, 8 patients (17%) required non-invasive ventilation whereas 12 patients (25%) were already under invasive ventilatory support]. Each patient was suspected with approximately 2 VAP or HAP suspicions during hospitalization. In total, 40 patients (83%) were treated with immunomodulators, being mainly corticosteroids (in 37).

### Samples and test result

Samples were taken on invasively ventilated patients in 85% of circumstances, at 7 days (IQR 2 – 17.5) of median ICU-stay (sample types detailed in table 2). Our specimens were realized after more than 4 days of invasive respiratory support in 49% (51 tests) or after more than 4 days of ICU-stay in 59% (61 tests), meaning 49% of our tests concerned late-onset VAP suspicions and 59% concerned late-onset HAP suspicions (Table 2).

Positive rm-PCR rate was 48% (50 tests), with molecular test retrieving more than one germ in 17% (18 tests), more than two germs in 6.8% (7 tests) and more than three germs in 1.9% (2 tests).

*Table 2. Rapid multiplexed-PCR results description*

	<b>Number (%) (n=103)</b>
Positive rm-PCR	50 (48%)
> 1 germ detection	18 (17%)
Turnaround-time (min)	150 (110 – 290)
Average MV duration (days)	6 (2 – 14)
Test realized ≥ 5 days in-ICU	61 (59%)
Test realized ≥ 5 days of invasive respiratory support	51 (49%)
VAP & HAP episodes	2 (1 – 3)
<b>Specimen type</b>	
Sputum	10 (9%)
Endotracheal aspirate	26 (25%)
Distal protected aspirates	59 (57%)
Bronchoalveolar lavage	8 (7%)
<b>Resistance detection</b>	
Bacterial resistance detection rate	4 (4%)
Pseudomonas aeruginosa detection rate	14 (13%)
Escherichia coli detection rate	13 (12%)



## Microbiology and statistical analysis

Agreement rate between rm-PCR and standard microbiology reached 60% (62 tests exactly concordant with the standard bacteriology).

Individual comparison of rm-PCR results and the corresponding standard microbiology results showed a statistically significant agreement rate with a  $\chi^2$  derived p-value < 0.001.

Analysis of rm-PCR results showed an overall 71.7% sensitivity, 84.2% specificity leading to an overall 78.6% positive predictive value and a 78.7% negative predictive value.

Most frequently undetected bacteria were Enterobacteriaceae (*Escherichia coli*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Citrobacter koseri*, *Hafnia alvei*) and also *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and *Acinetobacter baumannii* complex. It is worth noting that *Citrobacter koseri*, *Stenotrophomonas maltophilia*, *Hafnia alvei* and *Enterococcus faecalis* are not integrated in the detection panel. Rm-PCR allowed precise bacterial identification that could not have been achieved with standard microbiology in 9 cases (8%) (Table 3). It was unable to efficiently detect clinically relevant bacteria later diagnosed by standard microbiology in 27 cases (26%) mainly because of an absence of bacterial detection (24 cases) or a lack of resistance detection (3 cases).

**Table 3.** Rm-PCR results repartition among negative conventional bacteriology cases

	<b>Positive rm-PCR (n=50)</b>	<b>Negative rm-PCR (n=53)</b>
Negative blood culture	38 (76%)	46 (86%)
Negative respiratory culture	6 (12%)	40 (75%)
Total negative bacterial specimen	9 (18%)	39 (73%)

No *mecA/C*, *MREJ*, *KPC*, *VIM*, *IMP*, *NDM* or *Oxa-48*-like genes were detected by rm-PCR on our specimens. Three specimens showed arguments for viral co-infections (2 seasonal coronaviruses and 1 herpes simplex virus).

Positive rm-PCRs had been realized on invasively ventilated patients in 80% of the occurrences. Median rm-PCR turnaround time was 150 min (IQR 110 - 290). The average standard microbiology turnaround time to antibiotic susceptibility final result reached a median time of 60 hours (IQR 51 – 68). It seems that rm-PCR leads to approximately 57 hours of time gain compared to standard microbiology.

## Impact on therapeutic management

Table 4 shows an estimation of the rm-PCR results contributivity and hazard analysis.

In total, rm-PCR enabled a valuable therapeutic modification (appropriate escalation or appropriate de-escalation) in 39 cases (38%) prior to standard microbiology definitive results.

Upon analysis, we estimated rm-PCR results to be contributory in 52 cases (50%), however, we found that the patients were placed at risk for ineffective initial antibiotherapy in 22 cases (21%). These results could be considered non-contributory in 51 cases (50%) and in the end, rm-PCR results were non-hazardous in 81 cases (79%), they were contributory and safe in 43 cases (41% of all rm-PCR, 86% of all positive rm-PCR).

**Table 4.** Rm-PCR results impact on therapeutic strategy, results contributivity and hazard analysis

Antibiotic regimen		rm-PCR result qualification	
Pre vs post rm-PCR result	Pre vs post standard microbiology result	Contributivity	Hazardous impact
Unchanged	Unchanged	-	
29 (28%)			
Unchanged	Escalation	-	<b>Hazard</b>
13 (12%)			
Unchanged	De-escalation	-	
9 (8%)			
Escalation	Unchanged	+	
23 (22%)			
Escalation	Escalation	+	<b>Hazard</b>
8 (7%)			
Escalation	De-escalation	+	
3 (2%)			
De-escalation	Unchanged	+	
16 (15%)			
De-escalation	Escalation	+	<b>Hazard</b>
1 (1%)			
De-escalation	De-escalation	+	
1 (1%)			
<b>Total</b>		<b>52 (50%)</b>	<b>22 (21%)</b>

## DISCUSSION

This retrospective analysis of 103 VAP-suspicions arising in COVID-19 severe ARDS patients provided data from individuals hospitalized in three medico-surgical ICUs concerning the practical aspects of a rm-PCR technique in clinical setting. Our results show good clinical and diagnosis performance with high sensibility, high specificity and good overall agreement with the actual gold standard for microbiological diagnosis. We showed that the implementation of a rm-PCR assay in the standard care of VAP & HAP-suspicious patients could yield tangible and accurate microbiologic results in an importantly shorter time than standard microbiologic diagnosis methods (around two days and a half shorter). This technique could thus enable early adequate antibiotics administration and further promote wide-spectrum antibiotics spare.

Most importantly, rm-PCR result was contributory and led to a modification of the empiric antibiotic therapy in one case out of two, it resulted in a valuable & non-hazardous antibiotic scheme modification in 86% of all positive rm-PCR results.

Existing evidence on our rm-PCR panel reports similar diagnosis performance with negative predictive value and positive predictive value respectively ranging between 52% - 100% and 86% - 99.5% in similar ICU-patient groups. (22) (21) Another equivalent rm-PCR model was studied by Kunze and colleagues and was found to give concordant results in 45%, with turnaround times averaging 6.5 hours(24), Gadsby and colleagues found sensitivity / specificity reaching 56.9% / 58.5% for the same panel.(25)

We found a higher negative rm-PCR rate compared to current evidence; it could be the result of a great proportion of our samples being done with distal protected aspirates technique. FilmArray is actually validated on sputum, broncho-alveolar lavage and endo-tracheal aspirates but not on distal protected aspirates due to different bacterial significativity thresholds.

It might also come from a high frequency of Enterobacteriaceae not comprised in the rm-PCR assay in our specimens or from a high prevalence of patients already under antibiotics at the time of sampling. Indeed, 68% of negative rm-PCRs and 66% of positive rm-PCRs have been collected in patients under newly or earlier introduced antibiotics.

Compared to other studies conducted in controlled environments, our results show longer turnaround times with excessively high times in few cases (nearly reaching golden standard turnaround times). This might reflect the practical reality that these tests are not considered a

priority but an optional / additional assay in bacteriology laboratories. It shows the need for a clarification concerning the right position of these tests in the diagnosis strategy.

A large proportion of falsely negative results and therefore some avoidable hazard could have been prevented if our panel had included frequently encountered *Enterobacteriaceae* such as

*Stenotrophomonas maltophilia*, *Enterococcus faecalis*, *Citrobacter koseri* or *Hafnia alvei*. (32) (12)

That is why conventional microbiological diagnosis & antibiotic susceptibility testing are not likely to be superseded by rm-PCR. Novel molecular diagnosis and these two techniques are to be considered complementary to each other.

Further more, the presence of a resistance determinant in our samples was always followed by a phenotypical resistance on AST but the low multiresistant bacteria prevalence warrants us to make any conclusions regarding resistance determinants performance and asks for other large studies focusing on this aspect.

Nevertheless, whenever rm-PCR detected no resistance determinant, conventional bacteriology later confirmed multisensibility. In light of the high rate of wide spectrum antibiotic used, we can however reaffirm the necessity of antibiotic strategy reassessment through antibiotic stewardship programs in order to spare any unnecessary antibiotic.

Due to its retrospective observational design and its small sample size, our study lacks power and we couldn't conduct analyses among small subgroups. Our population consisted of severe SARS-CoV-2 infections (we didn't enrol any ARDS or respiratory function impairment secondary to polytraumatism, cardiac arrest, septic shock or neurologic impairment), thus projecting our results to other categories of ICU patients could be inaccurate. Moreover, we didn't use any standardized antibiotherapy protocol, antibiotic escalation and de-escalation comparison is thus uneasy and inaccurate.

We recruited more than one hundred pneumonia episodes, which to our knowledge is one of the largest series of rm-PCR results in VAP & HAP suspicions. Our patient sample is similar to other severe COVID-19 ARDS patients from other studies and representative of one of the most frequent evolutive complications of invasive respiratory support.

Our work is one of the first independent studies to produce a time-gain estimation comparing this rm-PCR technique with the microbiologic gold standard. Although FDA and EMA-approval studies (conducted by the producing laboratory) advocate for a much larger turnaround-time gain, they have been conducted in controlled environments and this time gain might have been artificially maximized.(31) (30) We showed in a clinical routine setting that the actual time gain of a syndromic

rm-PCR molecular diagnosis technique – though being shorter than manufacturer claims – is still relevant and could be an interesting way of enhancing critical patient care.

## **CONCLUSION**

In this study, we found evidence that this new rm-PCR assay requires short turnaround times to produce safe and accurate microbiologic molecular diagnosis results when compared to standard microbiology. It gives helpful bacterial information in numerous cases of nosocomial pneumonias and could enable clinicians to make earlier crucial therapeutic decisions as well as allowing bacterial identification in clinical situations that couldn't be elucidated by conventional bacteriology. However, more scientific evidence from well-designed studies using standardized antibiotherapy protocols is needed to put more trust in this diagnosis technique and in order to discuss its role for the management of VAP and HAP-suspicious patients.

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## **SERMENT D'HIPPOCRATE**

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

## **ABSTRACT**

### **Background**

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are among leading causes of in-hospital infectious complications. They are associated with a significant rise in morbidity and ICU length of stay. Early and adequate antibiotherapy is a cornerstone of their management. Empirical broad-spectrum antibiotherapy is mandatory until definitive bacterial identification and antibiotic susceptibility testing results.

During the last years, laboratory bacterial diagnosis saw the emergence of rapid multiplexed-PCR (rm-PCR) syndromic molecular diagnosis assays for pneumonia giving results with much shorter turnaround times compared to actual standard bacterial diagnosis methods. This innovative rm-PCR diagnosis technique could yield interesting bacteriologic results that could help clinicians to earlier introduce effective antibiotics and to reduce wide-spectrum antibiotics use by quick antibacterial spectrum adaptation. Information upon clinical performance and routine use of this novative method is still lacking. The main objective of this study was to evaluate the clinical performance of this panel versus standard bacteriological methods in a clinical setting.

### **Methods**

We retrospectively examined medical data of 103 VAP and HAP suspicions occurring between March 20, 2020 and April 30, 2021 in ICU-patients from 3 different teaching hospitals. We compared results from conventional bacteriology and from rm-PCR while examining the clinical evolution and treatment strategy modifications in response to bacteriologic results to analyze impact on antibiotherapy.

### **Results**

Data from 103 pneumonia episodes (48 patients) were analyzed. Results were obtained 2.4 days before conventional bacteriology. Sixty-two (60%) tests were exactly concordant with conventional bacteriology.

### **Conclusions**

Rm-PCR provides ICU clinicians with mostly safe and useful results in significantly quicker turnaround times. More clinical evidence is needed to gain trust in this technique.