Identification of bacterial co-detections in COVID-19 critically Ill patients by BioFire® FilmArray® pneumonia panel: a systematic review and meta-analysis

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ABSTRACT

Among critically ill COVID-19 patients, bacterial coinfections may occur, and timely appropriate therapy may be limited with culture-based microbiology due to turnaround time and diagnostic yield challenges (e.g. antibiotic pre-exposure). We performed a systematic review and meta-analysis of the impact of BioFire® FilmArray® Pneumonia Panel in detecting bacteria and clinical management among critically ill COVID-19 patients admitted to the ICU. Seven studies with 558 patients were included. Antibiotic use before respiratory sampling occurred in 28-79% of cases. The panel incidence of detections was 33% (95% CI 0.25 to 0.41, I^2=32%) while culture yielded 18% (95% CI 0.02 to 0.45; I^2=93%). The panel was associated with approximately a 1 and 2 day decrease in turnaround for identification and common resistance targets, respectively. The panel may be an important tool for clinicians to improve antimicrobial use in critically ill COVID-19 patients.

1. Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a worldwide pandemic beginning in 2020. A recent meta-analysis has reflected all-cause mortality is 10% for hospitalized patients with coronavirus disease 2019 (COVID-19) but 34% among patients admitted to the intensive care unit (ICU) (Potere et al., 2020). Guidelines for the management of critically ill patients on mechanical ventilation with COVID-19 have recommended the empiric use of antimicrobials (Alhazzani et al., 2020). Concerns over bacterial coinfections have led to significant antimicrobial use with an estimated up to 80% of critically ill COVID-19 patients receiving antimicrobial therapy (Langford et al., 2020).

A recent meta-analysis on bacterial coinfections among COVID-19 patients has reported incidence of up to 15% for coinfections among patients with secondary bacterial infections, almost universally from studies utilizing culture-based methods (Lansbury et al., 2020). These methods are known to be insensitive, often due to a variety of factors including antibiotic exposure before specimens are obtained, poor quality samples, variation in plate growth interpretation, and the challenges associated with cultivating fastidious organisms (Jain et al., 2015; Metlay et al., 2019). The role of culture-independent techniques in the management of severe COVID-19 patients has been suggested as a potential avenue towards improving judicious therapy decisions and antimicrobial stewardship (Spernovasilis and Kofteridis, 2020). The BioFire® FilmArray® Pneumonia/Pneumonia *plus* Panels (BioFire PN/PN*plus*; BioFire Diagnostics, LLC, Salt Lake City, UT) are molecular multiplex PCR tests that allow for increased sensitivity of detecting causative etiologies of pneumonia and related resistance gene determinates (Murphy et al., 2020). The panels include 15 common bacteria targets reported with semi-quantitative results (10^4, 10^5, 10^6, $\geq 10^7$), qualitative results for 3 atypical bacteria (*Mycoplasma pneumoniae*, *Chlaymdia pneumoniae*, and *Legionella pneumophila*), 7 genetic markers for antibiotic resistance (mecA/C and MREJ, bla_{CTX-M}, bla_{KPC}, bla_{VIM}, $bla_{OXA-48-like}$, bla_{IMP}, bla_{NDM}), and eight groups of viruses identified (adenovirus, coronaviruses [OC43, NL63, HKU-1, 229E], MERS-CoV [BioFire PNplus Panel], human metapneumovirus, human rhinovirus/enterovirus [HRV/EV], influenza A, influenza B, parainfluenza viruses (1,2,3,4), respiratory syncytial virus). SARS-CoV-2 is not on the current version of the panel and is not cross-reactive to the panel's other coronaviruses. We performed a systematic review and meta-analysis to determine the incidence of bacterial co-detections using the BioFire PN/PN*plus* among critically ill patients with COVID-19.

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2. Methods

We reviewed PubMed and Embase from January 1, 2020 to June 4, 2021 for studies in English evaluating the use of the BioFire PN/PNplus among COVID-19 patients. We searched using the query: (bioMérieux OR BioFire OR FilmArray) AND (pneumonia OR LRTI OR 'lower respiratory tract infection') AND (COVID OR COV OR SARS-COV-2 OR SARSCoV2 OR Coronavirus). We included clinical studies which reported the incidence of bacterial co-detections by the panel among COVID-19 patients admitted to the ICU. Additionally, we evaluated patient characteristics, epidemiology of bacterial and viral codetections, detections by culture, and antimicrobial use among these studies. Studies were excluded if data were insufficient to evaluate the contribution of PN/PNplus Panels on incidence of co-detections such as missing data or analyte only results given multiple bacterial results are common with the panels. References of selected articles were reviewed for identification of additional articles of relevance in addition to a forward citation search via Google Scholar. Eligibility assessment, data extraction, and quality assessments were completed by two investigators (T.T.T.) and (K.D.H.) with any discordance resolved by a third investigator (C.C.G.). Quality assessments were completed using JBI Checklist (Institute, 2021). All meta-analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and included using 'meta' package (Balduzzi et al., 2019). Pooled incidence and 95% confidence intervals (CIs) for incidence of molecular bacterial co-detection in addition to non-culture based approaches were assessed using random-effect model with weights as described by DerSimonian and Laird (DerSimonian and Laird, 1986). Random effects modeling was employed on the assumption of heterogeneity among study characteristics. Heterogeneity was evaluated using I^2 and Cochran's Q test. For heterogeneity testing, results were considered significant with a p<.10 as the Q test has low power. Egger test was used to evaluate publication bias. The systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1).

3. Results

The literature search resulted in 155 studies meeting our search criteria (Supplementary Figure 1). Excluded studies were comprised of 12 duplicates studies, 96 non-PN/PNplus Panel studies, 18 review articles or position statements, 17 non-clinical or non-human studies, two commentaries, three non-SARS-CoV-2 study, and one study due to insufficient data for evaluating incidence of co-detections related to PN Panel (Khurana et al., 2021). After removing duplicate and non-applicable studies, seven studies with 558 patients were included for the systematic review and meta-analyses (Table 1, Supplementary Table 2) (Camelena et al., 2021; Contou et al., 2020; Foschi et al., 2021; Kreitmann et al., 2020; Kolenda et al., 2020; Maataoui et al., 2021; Verroken et al., 2020). Studies included a study from Belgium, Italy, and five studies from France occurring from January to December, 2020 and all used the PNplus panel version. Two studies had overlap of less than 10 patients (personal communication from Dr. Dauwalder) and thus both were included (Kolenda et al., 2020; Kreitmann et al., 2020; Wood, 2007).

All studies were solely among patients admitted to ICUs and having inclusion of respiratory specimens obtained at varying times during their ICU stay (e.g. at ICU admit, upon intubation, within 48h of intubation, etc.). Four studies reported on timing of specimen collection including two studies noting an average collection 1 and 5 days after ICU admission, one study reporting an average of 3 hours after intubation, and one study with 33% of PN Panel testing within 48 hours of ICU admission (Contou et al., 2020; Kreitmann et al., 2020; Maataoui et al., 2021; Verroken et al., 2020). Antibiotic use

Table 1
Characteristics of studies included.

Author Year	Country	Study Type	Period	N participants	Specimen type	Inclusion	Median Age (IQR)	Antibiotic use before sampling
Camelena et al., 2020	France	Prospective single-center cohort	March 22 to April 15 2020	43	BAL	Upon MV, at ICU admission if on MV, or if concern for VAP	64 (56–70)	55%
Contou et al., 2020	France	Retrospective single-center cohort	March 13 to April 16 2020	92	Sputum, ETA, BAL	Within 48h of ICU admission	61 (55–70)	42%
Foschi et al., 2021	Italy	Retrospective multicenter cohort	March 10 to December 30 2020	178	BAL or BAL-like	Requiring MV	NR	NR
Kolenda et al., 2020	France	Prospective multicenter cohort	March 1 to April 15 2020	99	Sputum, ETA, BAL, mini-BAL	Non-MV or within 48h of MV	NR	73%
Kreitmann et al., 2020	France	Prospective single-center cohort	March 16 to April 6 2020	47	ETA, BAL	Within 24h of MV	68 (56–74) no coinfection, 61 (58–67) coinfection	57%
Maataoui et al., 2021	France	Retrospective single-center cohort	January 29 to April 30 2020	67	Sputum, ETA, BAL, mini-BAL	All patients with physician request for PN Panel testing	57 (46–65)	79% or more[*]
Verroken et al., 2020	Belgium	Prospective single-center cohort	NR	32	Sputum, ETA	NR	NR	28%

BAL = bronchoalveolar lavage; ETA = endotracheal aspirate; MV = mechanical ventilation; NR = not reported; VAP = ventilator-associated pneumonia.
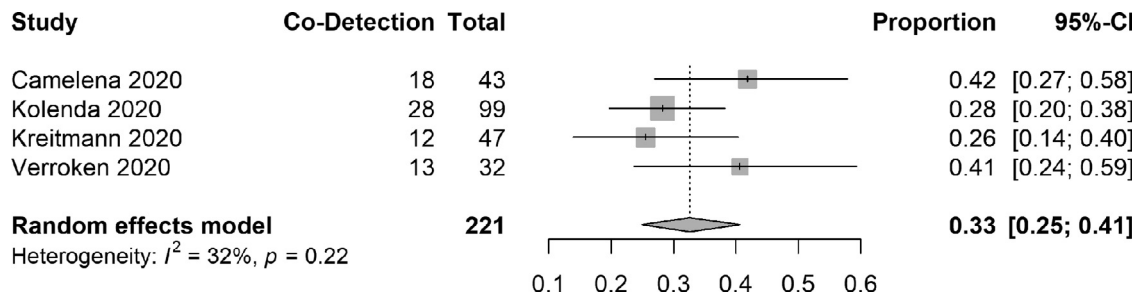[*] proportion of patients administered antibiotics before ICU admission.

Fig. 1. Forest plot of the pooled incidence of bacterial co-detections by BioFire PN detection.*Data not available for pooled per patient estimate from Contou et al. 2020, Foschi et al 2021, Maataoui et al 2021.

occurred in 28.1% to 79% of patients before respiratory specimens were obtained. One study reported on turnaround time (TAT) noting PN*plus* results having a significantly decreased median TAT compared to culture and antimicrobial susceptibility testing results, 5.5h vs 25.9h ($P < 0.001$) and 57h ($P < 0.001$), respectively (Camelena et al., 2021). Patients median age ranged from 57-68 years, and mortality was noted to range from 28% to 57% across studies.

The pooled incidence of co-detections by BioFire PN*plus* per patient was 33% (95% CI 0.25 to 0.41, I^2=32%, Cochran's Q P =0.22, Egger's test P = 0.34; Fig. 1) (Camelena et al., 2021; Kolenda et al., 2020; Kreitmann et al., 2020; Verroken et al., 2020). In contrast, culture-based detections yielded a pooled incidence of 18% (95% CI 0.02 to 0.45; I^2=93%, Cochran's Q P< 0.01, Egger's test P = 0.87; Supplementary Figure 2) (Camelena et al., 2021; Kolenda et al., 2020; Kreitmann et al., 2020). Two additional PN*plus* Panel studies only reported co-detections per specimen, indicating many patients had multiple specimens collected, and noted 33% and 40% bacterial co-detections, respectively (Foschi et al., 2021; Maataoui et al., 2021). Finally, one study did not report out bacterial co-detection attributed specifically to PN*plus* Panel per patient or per specimen, but noted overall 28% co-detections by either culture or PN*plus* Panel (Contou et al., 2020).

Bacteria detected by PN*plus* Panel among all evaluated specimens resulted in 302 positive organism results for non-atypical bacteria among 6 studies (Camelena et al., 2021; Contou et al., 2020; Foschi et al., 2021; Kolenda et al., 2020; Maataoui et al., 2021; Verroken et al., 2020). One study was excluded as individual organisms could not specifically be delineated to the PN*plus* Panel (Kreitmann et al., 2020). PN*plus* Panel detected typical bacteria including *Enterobacterales* (n = 83, 27.5%), *Staphylococcus aureus* (n = 69, 22.8%), *Pseudomonas aeruginosa* (n = 66, 21.9%), *Haemophilus influenzae* (n=36, 11.9%), *Acinetobacter calcoaceticus-baumannii* complex (n=20, 6.6%), *Streptococcus pneumoniae* (n = 15, 5.0%), *Moraxella catarrhalis* (n = 6, 2.0%), *Streptococcus agalactiae* (n = 4, 1.3%), and *Streptococcus pyogenes* (n=3, 1.0%). Atypical bacteria were detected in 2 studies reflecting *M. pneumoniae* and *L. pneumophila* (Foschi et al., 2021; Kolenda et al., 2020). Viral results were noted in two studies which reported a human rhinovirus/enterovirus and an adenovirus (Kolenda et al., 2020; Maataoui et al., 2021). Isolates with resistant gene detection were noted in 4 of 7 studies, including bla_{CTX-M} extended-spectrum β-lactamases (ESBLs), bla_{NDM} and bla_{VIM} carbapenemase, and *S. aureus* methicillin-resistance genes (Camelena et al., 2021; Foschi et al., 2021; Kolenda et al., 2020; Maataoui et al., 2021; Verroken et al., 2020).

Antibiotic therapy was reported in 6/7 (85.7%) of studies (Camelena et al., 2021; Contou et al., 2020; Foschi et al., 2021; Kolenda et al., 2020; Maataoui et al., 2021; Verroken et al., 2020). The majority of therapy us;ed included 3rd generation cephalosporin or narrower therapies. Two studies reported the clinical impact on antibiotic decision making (Maataoui et al., 2021; Verroken et al., 2020). In one study, the PN*plus* Panel was associated with early therapy changes in 34% (38of 112) episodes (Maataoui et al., 2021). For

negative results, 43% of cases allowed for antibiotic avoidance or discontinuation while the remainder of cases maintained therapy due to severe sepsis, infection from another site, continuation of previous treatment, or severely immunocompromised patients. The other study noted early antibiotic modifications occurred in 46.9% (14of 32) of patients, of which 35.7% (5 of 14) of patients on initial therapy had their antibiotics stopped due to a negative result (Verroken et al., 2020).

4. Discusssion

In this systematic review and meta-analysis of seven studies and 558 patients, the BioFire PN*plus* was associated with 33% co-detections among critically ill COVID-19 patients, nearly double the detections by culture and higher than previously reported in COVID-19 culture-focused meta-analyses (Langford et al., 2020; Rawson et al., 2020). Moreover, our review reflects a differing epidemiology of organisms that culture focused reviews with the molecular approach reporting predominantly *Enterobacterales, S. aureus*, and *P. aeruginosa*. A recent commentary by Rawson et al highlighted the disparities of current studies, including patient populations, disease severity and, importantly, diagnostic methods. This clearly highlights more systematic, comprehensive testing is needed to accurately define the composition, extent, and role of co-infections in COVID-19 disease (Rawson et al., 2021). Interestingly, our results corroborate findings in a comprehensive review of postmortem studies of bacterial superinfections among persons with COVID-19 reflecting 32% of potential bacterial superinfections based on histology (Clancy et al., 2021).

As diagnostic uncertainty is a known major driver of antibiotic use, the use of molecular diagnostics among critically ill COVID-19 patients has the potential to improve management (Livorsi et al., 2015). The relevance of this diagnostic approach is further highlighted from the included studies reflecting earlier antimicrobial streamlining in 34-47% of patients including 36-43% of antibiotics discontinued or avoided due to a negative result (Maataoui et al., 2021; Verroken et al., 2020). The importance of streamlining appropriate antimicrobial management is paramount with the high rates of antimicrobial use and mortality of up to 34% among these critically ill ICU admitted COVID-19 patients (Potere et al., 2020).

In addition to the importance of appropriate therapy at the patient level, there is significance for the overall state of increasing antimicrobial resistance globally. A recent review found despite only 8% of COVID-19 patients having a bacterial or fungal co-infection during hospitalization, up to 72% are reported to have received antimicrobial therapy overall and up to 100% when in the ICU (Clancy and Nguyen, 2020; Rawson et al., 2020). Similarly, the studies in our review reported antibiotic use in up to 79% of patients. The World Health Organization has emphasized the importance of antimicrobial stewardship in the pandemic response by identifying 5 key measures, among them rapid diagnostics that differentiate between bacterial and viral respiratory tract infections (Getahun et al., 2020). Diagnostic

platforms like the BioFire PN/PN*plus* can play an important role in reducing the antimicrobial prescribing behaviors that have developed during the COVID-19 pandemic and the potential subsequent lasting effects well into the future.

While the improved diagnostic yield of BioFire PN/PN*plus* among COVID-19 patients is recent in the literature, many studies have reflected this broadly among pneumonia patients. A recent study evaluating the diagnostic yield of the panel versus a pneumonia multi-test bundle determined the panel was twice as likely to yield determination of the bacterial etiology for community-acquired pneumonia (CAP) while costing $60 less per case for testing (Gilbert et al., 2020). Moreover, in a multinational evaluation among 52 laboratories, the BioFire PN*plus* was associated with a 20% increase in detections of one of more pathogens per specimen compared to standard of care testing (Ginocchio et al., 2021). The increase in diagnostic yield is likely multifactorial. For instance in one study, increased detections with the panel were shown to be likely related to previous antibiotic exposure and culture reporting process in 49% and 42% of cases, respectively (Buchan et al., 2020). The variation based on culture reporting process is further suggested by our data as the heterogeneity among BioFire PN*plus* detections was much lower than culture (I^2 32% vs 93%). In another study, the clinical relevance of increased detections was recently explored, reflecting strong positive correlations to level of WBC on gram stain thus indicating a correlation of inflammation with these detections (Rand et al., 2020). Finally, the increased sensitivity over culture has been demonstrated in a European multicenter study of the BioFire PN*plus*, the Curetis® Unyvero® Pneumonia Panel, and 16S metagenomic analysis which reflected consistency in detections among molecular platforms as being more sensitive than culture (Enne et al., 2020). Evidence reflecting the improved pathogen detection of molecular methods for pneumonia has previously been reported elsewhere (Gadsby et al., 2016).

As indicated in previous meta-analyses on COVID-19 coinfections, the present analysis is limited as some detections among the included studies may represent colonization (Langford et al., 2020). However, the Bio-Fire PN/PN*plus* may assist in this adjudication of infection vs colonization through semi-quantitative results. Several studies have examined the utility of using the panel's semi-quantitative values to assist in the differentiation of bacterial colonization versus infection (Buchan et al., 2020; Edin et al., 2020; Ginocchio et al., 2021; Lee et al., 2019; Yoo et al., 2020). Interpretation can be variable depending on several factors, including patient population, type of pneumonia (e.g. CAP versus ventilator associated pneumonia), sample type (sputum-like versus bronchoalveolar lavage-like), presence and amounts of other pathogens, WBC counts and adjunctive biomarkers. Although in general the panel's values tend to be one or more logs greater than conventional culture values, relative pathogen abundances can assist in determining pathogen significance similar to culture interpretation (Buchan et al., 2020; Edin et al., 2020; Ginocchio et al., 2021; Lee et al., 2019; Yoo et al., 2020). Thus, in conjunction with clinical judgment, the BioFire PN/PN*plus* can increase the diagnostic information available and rate of delivery to clinicians for earlier and more robust therapy decision making. While the panels detect common organisms and resistance targets, the results reported may be limited in generalizability depending on local organism and genotypic resistance epidemiology. Additionally, the results may be impacted by timing of specimen in the course of disease as noted in other reviews as classifying co-infection vs secondary infection is challenging (Langford et al., 2020). Moreover, the observed results on therapy impact may be different in varying patient populations, severity of illness, and illness history as indicated among one of the studies noting more severe illness or immunocompromised states may challenge streamlining of therapy on a case-by-case basis. The results of our study are limited by regional representativeness of the included studies all originating in Europe. Variations of bacterial coinfections may be possible, and thus, our estimate of prevalence may lack generalizability. Future studies should evaluate molecular co-detections of bacteria among critically ill COVID-19 patients in additional regions. We included two studies which

had overlap of less than 10 patients (*personal communication from Dr. Dauwalder*) which could add some bias to our estimates of prevalence but based on the proportion of overlap, overall increases available information for estimate (Kolenda et al., 2020; Kreitmann et al., 2020; Wood, 2007). Finally, studies had heterogeneity in the eligibility for inclusion and analysis which may have impacted the results.

In conclusion, our study reflects the increase of bacterial co-detections among critically ill COVID-19 ICU patients using the BioFire PN/PN*plus* Panels. Thus, overcoming the limitations of culture-based methods in terms of sensitivity and turnaround time, the BioFire PN/PN*plus* Panels may be an important tool to frontline clinicians for improving antimicrobial use in critically ill COVID-19 patients.

Author contributions statement

T.T.T., K.D.H., and C.C.G. all conceived and developed study design. T.T.T. and K.D.H. performed all reviews, data extractions, and quality assessments. T.T.T. performed the data analyses and graphics. T.T.T., K.D.H., and C.C.G. all developed and completed the manuscript.

Declaration of competing interest

T.T. Timbrook and K.D. Hueth are employees of BioFire Diagnostics; C.C. Ginocchio is an employee of bioMérieux and BioFire Diagnostics. Authors report no other conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diagmicrobio.2021.115476.

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