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RESEARCH ARTICLE

BioFire Film Array Blood Culture Identification Panel for Rapid Detection of Pathogens from Sterile Sites - A Diagnostic Accuracy Study

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Abstract:

Background:

Rapid diagnosis of the causative organism of invasive infections is critical to the improved care of patients. A new platform, FilmArray (BioFire Diagnostics, LLC, Salt Lake City, UT) allows for rapid PCR to be performed in less than two hours on positive blood cultures

Objective:

The aim was to perform a retrospective diagnostic accuracy study in a paediatric tertiary referral hospital comparing results from culture, our gold standard, against those obtained when the samples were tested directly using the FilmArray Blood Culture Identification (BCID) Panel (BioFire Diagnostics, LLC, Salt Lake City, UT).

Method:

Samples from sterile site infections were tested using traditional culture based methods as well as PCR testing, and these results were then compared to testing which was done directly on the FilmArray BC-ID panel.

Results:

Ninety-four samples were tested in total and concordant results were observed in 71 samples (76%). Correlation between detection of pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes* by PCR and culture result was high (94% and 88% respectively). Discordant results could be explained by the cultured organism not having a target on the panel (n=8) or PCR detection of potentially non-viable bacteria in the sample (n=8); the remaining samples (n=9) were negative by PCR despite culturing an organism with a target present on the panel for that organism. We have demonstrated an overall correlation of 76% and that in some instances the PCR detected non-viable yet clinically significant bacteria.

Conclusion:

Use of the FilmArray BCID panel directly for samples from sterile sites should be considered when there is a high index of suspicion of a single-organism infection at that site prior to sampling.

Keywords: Filmarray, Group A Streptococcus,Kingella, Osteomyelitis, PCR, Sterile site infection.

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1. INTRODUCTION

The availability of rapid diagnostic platforms for positive blood cultures has changed the speed at which the clinical microbiology laboratory can identify the causative organism. The shortened time to diagnosis and identification of pathogens has improved patient outcome, shortened inpatient stays, and reduced inappropriate antimicrobial prescribing previously in the paediatric setting [1, 2].

The FilmArray blood culture identification panel identifies 27 targets – 8 Gram positive targets, 10 Gram negative targets, five *Candida* species and three genes associated with antimicrobial resistance. It has been validated for the rapid detection of pathogens from blood cultures and shown to be highly sensitive and specific in multiple studies [3 - 6]. Previously there have been small studies that have investigated whether this panel could be used for the rapid identification of pathogens from sites other than blood – either through inoculation of blood culture bottles with specimens from a sterile site first or directly from the clinical specimen [7 - 9].

We undertook a retrospective diagnostic accuracy study using previously collected samples to evaluate the use of the FilmArray BCID panel directly from clinical specimens for diagnosis of infection, using culture as the gold standard. We envisaged that this would be of greatest benefit when sterile site samples were tested and thus we chose to process joint aspirates, pus collected from the operating theatre, pleural fluid and pus from deep tissue samples. We excluded CSF collected from ventriculoperitoneal shunts, peritoneal fluid with a normal white count from patients on continuous ambulatory peritoneal dialysis, and samples sent for culture without clinical evidence of infection.

Ethics statement: This study was approved by the Ethics Research Committee of the Children's University Hospital, Temple Street, Dublin, protocol number 16-018. Informed consent was waived because the study was blinded and all patient personal information was de-identified prior to analysis. Physicians were not informed of FilmArray result.

2. MATERIAL AND METHODS

All samples for this study were processed using the FilmArray BCID panel. The tests were performed as per manufacturer's instructions as indicated for blood cultures, using 200µl of sample. In cases where there was insufficient sample or the sample was too viscous, sterile saline was added and the sample was well mixed. The FilmArray BCID panel contains all the required reagents for sample preparation, reverse transcription-PCR, PCR and detection in a freeze-dried, room temperature stable format. The samples and hydration solution were injected into the pouch prior to the run. The panel was then introduced into the device and results were obtained in one hour. The results obtained from the FilmArray BCID panel were then compared to the original culture result.

For the conventional culture-based laboratory methods, samples were processed using standard procedures: Gram stain, culture and identification of isolates (VITEK-2 and/or MALDI-TOF (bioMérieux)) by medical laboratory scientists. If traditional culture methods had not detected a pathogen and there had been a high index of suspicion for infection at that site, samples were referred for molecular identification by in-house real time PCR at the Irish Meningitis and Sepsis Reference Laboratory [10 - 12]. The decision to refer samples for PCR was made at the time the patient was being managed clinically and not for the purposes of this study. Antimicrobial testing was performed as per European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [13].

3. RESULT

This retrospective study was performed in the Microbiology Laboratory of Temple Street Children's University Hospital, Dublin. Stored samples (stored at temperatures of -20°C or -80°C) which had been prospectively collected between January and December 2016, in addition to a limited number of samples from sterile sites which were processed in real time in conjunction with culture, were tested. These samples had been collected from several sites, both sterile and non-sterile, from patients admitted under all clinical specialties. Testing of all samples took place between January and May 2017. Additional reports were not issued based on Film Array results from stored samples nor samples processed in real time.

In total, 156 clinical specimens from several sites had been collected, frozen and stored in the laboratory prior to commencing testing. Samples were categorised as - bone, fluid, joint fluid, pleural fluid, peritoneal dialysis fluid (PDFL), pus, intracranial sterile site fluid (excluding CSF) and tissue. Results of conventional culture, in addition to any external tests such as real time PCR were recorded. Exclusion criteria allowed us to eliminate 62 of the samples. The remaining 94 samples were processed on the Film Array BCID panel.

Of the 94 samples, 50 (53%) were culture positive and 44 (47%) culture negative. The FilmArray BCID panel detected at least one bacterial target from 42 (45%) samples, did not detect a target from 51 (54%) and produced an invalid result from 1 sample. Five samples had multiple targets detected. The sample types tested and the results obtained are summarized in Fig. (**1**).

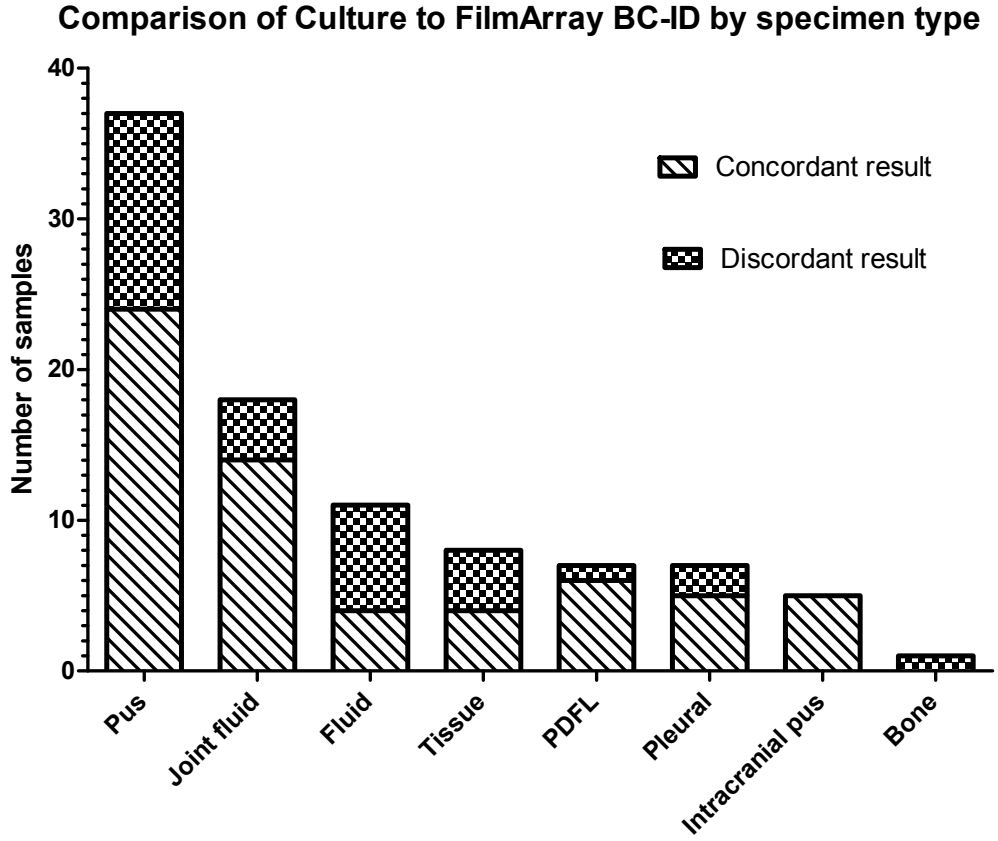

Fig. (1). Comparison of blood culture results to identification by the FilmArray BC-ID test panel.

The summary of FilmArray results against the result obtained from culture is shown in Table **1**. Seventy-one (76%) of the samples tested demonstrated a concordant culture and FilmArray result. Staphylococci were cultured from 28 samples, and the FilmArray BCID panel correctly identified this in 21 samples, a correlation of 75%. FilmArray correctly detected *S. aureus* in 16 samples and 15 (94%) of those were culture positive for *S. aureus*. The *mecA* gene, which confers resistance to methicillin in Staphylococci, was detected in ten samples – three of which were associated with the detection of *S. aureus* from the clinical specimen. Methicillin resistance was confirmed on all isolates when antimicrobial susceptibility testing was performed using the EUCAST method, and all samples which had *S. aureus* detected, and were *mecA* negative, were confirmed to be methicillin susceptible *S. aureus*. The rapid detection of methicillin sensitive or resistant strains of *S. aureus* directly from clinical specimens would be expected to provide benefit to patients as it allows earlier diagnosis, targeted antimicrobial therapy and promotes antimicrobial stewardship. *Streptococcus pyogenes* was isolated on culture from 8 specimens and the FilmArray correctly detected its presence from 7 (88%) of those samples. *S. pyogenes* was also detected on FilmArray from a further three culture-negative samples. There were no detections of the *vanA/B* nor bla_{KPC} genes in the samples we tested, but this was unsurprising as the prevalence of VRE and KPC-producing Enterobacteriaceae are both low in our patient population.

Table 1. Comparison of FilmArray BC-ID results to culture by organism type.

FilmArray BCID Panel Result	Number	Concordant Culture Result Number (%)	Discordant Culture Result Number (%)
No target detected	51	31 (61)	20 (39)
Staphylococcus species (total)	21	20 (95)	1 (5)
- *S. aureus*	16	15 (94)	1(6)

(Table 1) contd.....

FilmArray BCID Panel Result	Number	Concordant Culture Result Number (%)	Discordant Culture Result Number (%)
Streptococcus species (total)	18	12 (67)	6(33)
- *S. pyogenes*	10	7 (70)	3 (30)
- *S. agalactiae*	1	0(0)	1(100)
- *S. pneumoniae*	2	2(100)	0(0)
- *Enterococcus* species	2	1(50)	1(50)
Enterobacteriaceae species (total)	2	2(100)	0(0)
- *E. coli*	1	1(100)	0(0)
H. influenzae	4	1 (25)	3 (75)
P. aeruginosa	2	1 (50)	1 (50)

(The total number of results exceeds 94 as 5 samples had multiple targets detected)

Thirty-two (34%) of the ninety-four samples analyzed in this study gave a conflicting result Table **2**. There was poor concordance between culture and FilmArray for *H. influenzae*, *S. agalactiae, P. aeruginosa* and *Enterococcus* species, although it should be noted that numbers tested were small. There was a 46% correlation in samples that had a mixed culture and a mixed FilmArray result. In some cases, this can be explained by the fact that the mixture of organisms identified by conventional culture included species that do not have targets on the BCID panel. However, there were instances in which an organism, which has a target on the panel, was cultured but not detected on FilmArray. This may be explained by low levels of bacterial DNA being present in the sample such that they were below the lower limit of detection of the PCR.

Table 2. Summary of Discordant results between the FilmArray BC-ID and culture method.

	Sample number	Sample site	FA result	Culture result	Interpretation
FA target detected, but not confirmed on culture (n=7)	11	Pus (finger)	***S. aureus,*** ***S. agalactiae,*** *E. coli*	*E. coli,* Anaerobic Gram negative cocci	*E. coli* detected on FA and culture Anaerobic GNC not on panel **Potentially non-viable *S. aureus* and *S. agalactiae* therefore not cultured**
	21	Joint fluid	*Streptococcus* species	No growth	Potentially non-viable Streptococcal species in sample or may represent presence at low levels in sample, not consistent with infection
	30	Pleural fluid	*S. pyogenes*	No growth	Potentially non-viable *S. pyogenes* DNA in cultured sample
	52	Pus (neck)	*S. pyogenes*	No growth	Potentially non-viable *S. pyogenes* DNA in cultured sample
	56	Pus (submental abscess)	*S. pyogenes* ***H. influenzae***	S. pyogenes	True positive *S. pyogenes* **Potentially missed *H. influenzae* on culture**
	139	Tissue (hand)	*Pseudomonas aeruginosa*	No growth	Potentially non-viable bacteria in sample or present in low levels without causing infection due to site of collection (hand)
	146	Pus (sinus)	***S. pyogenes***	*S. epidermidis*	**Non-viable *S. pyogenes* DNA in cultured sample** Question significance of *S. epidermidis* on cultured specimen, possible contaminant
Missed organisms (n=9)	7	PDFL	No target detected	***E. coli*** *Moraxella* species	**Missed *E. coli*** *Moraxella* not on FA panel
	12	Pus (perinasal)	*H. influenzae*	***C. albicans*** ***S. dysgalactiae*** *Aggegatibacter* species *Bacteroides fragilis*	False positive *H. influenzae* detection (potential misidentification as *Aggregatibacter)* **Missed *C. albicans* and Streptococcal species** *Aggregatibacter* and *Bacteroides* not on panel
	20	Joint fluid	No target detected	*S. pyogenes*	Missed organism
	59	Joint fluid	No target detected	*S. aureus*	Missed organism
	65	Fluid (intra-abdominal)	No target detected	***S. anginosus*** *B. fragilis*	**Missed Streptococcal species** *B. fragilis* not on panel

(Table 2) contd.....

	Sample number	Sample site	FA result	Culture result	Interpretation
	70	Fluid (intra-abdominal)	No target detected	***S. anginosus*** *B. fragilis*	**Missed Streptococcal species** *B. fragilis* not on panel
	103	Fluid (Pseudomeningocoele)	No target detected	*E. coli* *S. constellatus*	Missed organisms
	115	Fluid (intra-abdominal)	No target detected	*E. coli* *S. constellatus*	Missed organisms
	136	Fluid (pump device)	No target detected	S. aureus	Missed organism
Organisms cultured which did not have targets on FA panel (n=8)	7	PDFL	No target detected	***E. coli*** *Moraxella* species	**Missed *E. coli*** *Moraxella* not on FA panel
	11	Pus (finger)	*S. aureus* *S. agalactiae* *E. coli*	*E. coli* **Anaerobic Gram negative cocci**	*E. coli* detected on FA and culture **Anaerobic GNC not on panel** Potentially non-viable *S. aureus* and *S. agalactiae* therefore not cultured
	12	Pus (perinasal)	*H. influenzae*	*C. albicans* *S. dysgalactiae* ***Aggegatibacter* species** ***Bacteroides fragilis***	False positive *H. influenzae* detection Missed *C. albicans* and Streptococcal species ***Aggregatibacter* and *Bacteroides* not on panel**
	29	Fluid (occipital aspirate)	No target detected	*Aspergillus fumigatus*	Organism not on FA panel
	65	Fluid (intra-abdominal)	No target detected	*S. anginosus* ***B. fragilis***	Missed Streptococcal species ***B. fragilis* not on panel**
	70	Fluid (intra-abdominal)	No target detected	*S. anginosus* ***B. fragilis***	Missed Streptococcal species ***B. fragilis* not on panel**
	123	Pus (abdominal fluid)	Streptococcal species detected	*S. intermedius* ***Eikenella corrodens***	Correct identification of Streptococcal species ***E. corrodens*** not on FA panel
	144	Pus (mastoid abscess)	Streptococcal species	*S. constellatus* ***Moraxella* catarrhalis**	Correct identification of Streptococcal species ***M. catarrhalis* not on FA panel**

4. DISCUSSION

The purpose of this study was to determine if the FilmArray BCID was an accurate diagnostic tool when used on samples collected from sterile sites and, if added to our procedures for processing samples collected from such sites could it be of clinical benefit, that is, shorten duration to diagnosis and allow for early appropriate tailoring of antimicrobial therapy for our patients. This study has shown that there is 74% concordance between FilmArray BC-ID panel and culture for sterile site samples.

A review of the results obtained from this study reveals that, as expected, some sample types will have a better recovery of microorganisms than others. Pus, tissue and pleural fluid were the sample types most likely to have the greatest recovery of bacteria. Most of our samples that had a positive culture and FilmArray result were positive for *S. aureus* (17%) or *Streptococcus pyogenes* (11%).

Samples such as intracranial pus and sterile site fluids tended to be both culture negative and FilmArray negative in our study. Joint fluids may be sent routinely for culture as part of the work up for non-infectious inflammatory arthropathies, and intra-operative joint aspirates may be sent to rule out infection as opposed to suspecting its presence in the first instance. By narrowing the availability of the test to those cases in which there is a high pre-test probability of infection we would hope to obviate the processing of joint fluids on the FilmArray routinely.

Samples which were culture positive did not necessarily yield a positive result on the FilmArray – in some instances this was due to fact that the organism isolated from conventional culture was not on the BCID panel of organisms (*e.g. Aspergillus fumigatus*, *Bacteroides fragilis etc*.). With the limited number of targets on the blood culture identification panel, only certain species can be detected using this method. If another species is suspected (*e.g.Kingella kingae*) in the clinical scenario of septic arthritis in children less than 5 years of age, pathogen-specific real time PCR may be more beneficial to aid pathogen identification.

It should also be noted that the BCID panel is designed to detect organisms in positive blood cultures and if bacterial DNA present in the sample was below the lower limit of detection then samples from sterile sites may yield a negative FilmArray result, despite having growth on conventional culture. Enrichment of the sample in a blood culture bottle and incubation on the BacTAlert system with processing only of positive samples on the FilmArray BCID panel

has been investigated in a previous study, but as we undertook this study to assess the performance of the FilmArray directly on samples to aid rapid diagnosis we did not include this step [8]. The impact of freezing and thawing on samples is unknown and future prospective real-time studies could exclude this issue. Original culture results were used instead of repeat culture of the frozen aliquots as certain fastidious organisms may not have survived the freezing.

Of the 94 specimens processed, discordant results Table **2** were obtained from 23 samples (24%). In 8 instances, this was due to the presence of organisms which are not present on the FilmArray BCID panel. *S. pyogenes* was detected on FilmArray, but not on culture, from three samples - two of pus, and one pleural fluid. *S. aureus*, *S. agalactiae* and *E. coli* were detected on FilmArray from one sample (the sample cultured *E. coli* and an anaerobic Gram positive coccus). It is possible these samples contained non-viable bacterial DNA and thus their presence was not detected using conventional culture based methods. The detection of these pathogens from sterile sites remains significant however and it is reasonable that such results would guide antimicrobial therapy for these patients in the future. Nine samples tested failed to identify organisms with targets present on the FilmArray BCID panel that were isolated on culture. It is possible that specimen processing, storage (including freezing and thawing) may have resulted in degradation of bacterial DNA and this may account for the discordant results. A prospective study involving the dual processing of samples using traditional culture based methods and the FilmArray BCID panel in real time would elucidate this further. A sample of pus and a sample of chest drain fluid which both cultured coagulase negative Staphylococci had discordant results when processed on the Film Array – the fluid sample did not detect any target and the pus sample detected *S. pyogenes*. Coagulase negative Staphylococci would most frequently be considered contaminants on culture and it is reasonable to infer that the FilmArray result represents the true result.

An interesting observation that arose during the review of discordant results was the detection of *H. influenzae* on the FilmArray. Four samples tested yielded a positive result yet just one of these samples cultured *H. influenzae* (25% correlation). Of the others, one (a sample of submental pus) isolated *S. pyogenes* in culture and one sample grew an *Aggregatibacter* species - this sample was referred for in house *H. influenzae* Real Time PCR but no *H. influenzae* DNA was detected; the remaining sample was culture negative, but had been referred for 16s rDNA PCR which detected *Aggregatibacter segnis*. It remains an interesting anomaly and one to be conscious of should *H. influenzae* be detected on the FilmArray when used on samples from sterile sites in future.

We had some limitations as to samples we processed in terms of volume as they were from a pediatric cohort of patients and were processed after routine tests (including any external tests). Additional limitations of the study would be that it was performed on mostly stored samples which had been frozen for a period of up to 12 months and it is possible there was degradation of bacterial DNA in samples which may have affected our results. We were also limited in terms of the samples we tested, while we did have exclusion criteria to remove samples such as peritoneal fluid with a normal white cell which was sent for routine culture we did not have information available regarding joint fluids or other fluids so samples were likely to have been tested in which there was no suspicion of infection. A prospective study involving the dual processing of samples for culture and FilmArray in cases of suspected infection involving sterile sites could address this.

We foresee the use of the FilmArray BCID panel on sterile site specimens in situations where there is a high index of suspicion for infection at that site prior to sampling. We hypothesize that this test would be of greatest clinical benefit, and most cost effective, in cases of suspected septic arthritis in a child who is systemically unwell, empyema, mastoiditis, deep skin and soft tissue infection with abscess formation. In these instances, in which monomicrobial infection would be expected, the rapid detection of a pathogen and markers of resistance such as the *mec*A, *van*A or bla_{KPC} gene would allow for early tailored antimicrobial therapy and aid infection control within the hospital should antibiotic resistance genes be detected.

We would not support testing from sites where polymicrobial infection is suspected, *e.g.* peritoneal pus, where multiple organisms, which may not have a target on the FilmArray BCID panel, may be present. This is because antimicrobial therapy is unlikely to be rationalized based on the FilmArray result. Further research is needed to determine if the early detection of a pathogen using the BCID panel can facilitate early directed antimicrobial therapy, aid antimicrobial stewardship initiatives, improve infection control and ultimately improve patient outcomes.

CONCLUSION

To our knowledge, this is the largest study on the use of the Film Array BCID panel directly on sterile specimens. We have demonstrated an overall concordance with results from culture of 76% but when our results were analysed

further in relation to specific pathogens, it correctly detected organisms such as *S. aureus*, the predominant cause of complicated skin and soft tissue infections in our patient population, in 94% of cases, and *S. pyogenes* in 88% of cases, when compared to culture. Upon review of our discordant results, we found that the FilmArray detected the presence of likely pathogens in 4 instances where culture had been negative. We would advocate the FilmArray BCID panel for use on samples of pus from sterile sites and on joint fluid where there is a high index of suspicion for septic arthritis, but recommend larger, prospective studies in the future to assess its full potential in this area.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Temple Street Hospital.

HUMAN AND ANIMAL RIGHTS

The study was carried out according to the Declaration of Helsinki principles.

CONSENT FOR PUBLICATION

Consent was not sought from patients as no additional samples were taken, the study was retrospective and also non-interventional.

CONFLICT OF INTEREST

This work was supported by the Temple Street Foundation (ID# RPAC-16-04).

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All authors contributed to the design, analysis and reporting of the results including approval of the final draft. AC, JC and MN performed the testing and sample analysis, including data collection. The authors would like to thank the Irish Meningitis and Sepsis Reference Laboratory, Children's University Hospital, Dublin, Ireland for performing real time PCR for *H. influenzae* in addition to al staff of the Microbiology Department, Children's University Hospital, Dublin, Ireland for their help with this work.

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