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Evaluation of the FilmArray™ Meningitis/Encephalitis panel with focus on bacteria and *Cryptococcus* spp

Nestor D.[a,*], Thulin Hedberg S.[a,b], Lignell M.[c], Skovbjerg S.[c,d], Mölling P.[a,b], Sundqvist M.[a,b]

[a] Department of Laboratory Medicine, Clinical Microbiology, University Hospital, Örebro SE-701 85, Sweden
[b] Department of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro SE-701 82, Sweden
[c] Department of Bacteriology, Clinical Microbiological Laboratory, Sahlgrenska University Hospital, PO Box 435, SE-405 30 Gothenburg, Sweden
[d] Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg, PO Box 480, SE-405 30 Gothenburg, Sweden

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ABSTRACT

Purpose: Molecular methods provide fast and accurate detection of both bacteria and viruses in the cerebrospinal fluid (CSF) causing infection in the central nervous system (CNS). In the present study we evaluated the bacterial detection performance of the fully automated FilmArray™ Meningitis/Encephalitis (ME) panel (bioMérieux) by comparing it with culture and multiplexed in-house PCR.

Methods: Three sample types were analysed; Contrived samples with known bacterial/fungal concentration (n = 29), clinical samples from patients with verified cause of CNS infection (n = 17) and external quality assessment (EQA) samples (n = 11). Another six samples were purposely prepared with multiple targets to evaluate multiplex capacity.

Results: The FilmArray™ had a slightly higher limit of detection for *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes* and *Streptococcus agalactiae* compared to in-house PCR methods but performed equal or better when compared to culture. The FilmArray™ ME panel detected the expected pathogen in 17 of 17 clinical samples and yielded detection of three additional viruses of which one was confirmed with comparator techniques. All but one of the EQA samples were correctly detected.

Conclusions: The results of this study are promising and the FilmArray™ ME panel could add to the diagnostic algorithm in CNS-infections. However, the limit of detection for the important pathogens *N. meningitidis* and *S. pneumoniae* could be improved.

1. Background

Infections in the central nervous system (CNS) are associated with high morbidity and for some pathogens also mortality. The pathogen panorama is diverse and clinical assessment solely is not sufficient to discriminate between bacterial and/or viral origin (Brouwer et al., 2012). Molecular methods are now widely used for the detection of CNS infection, especially for viral aetiology, and has been proven more sensitive than traditional microbiological methods (i.e. Gram stain and culture), especially in cases where antibiotic treatment has been commenced before sampling (Welinder-Olsson et al., 2007; Meyer et al., 2014; Brink et al., 2015; Rath et al., 2014). In addition, the rapid detection of less harmful pathogens requiring no therapeutic intervention (i.e. Enterovirus infections) may entail reduced antibiotic prescribing and cost savings (Lu et al., 2002; Giulieri et al., 2015). However, in-house molecular techniques are usually in need of specialised laboratory personnel and thus limit their use to regular working hours.

The fully automated FilmArray™ Meningitis/Encephalitis (ME) panel (BioFire/bioMérieux, Salt Lake City, USA) detects a broad range of CNS pathogens including viruses, bacteria and *Cryptococcus* spp. (Table 1). The ME panel was FDA-cleared in 2015 and evaluation studies have confirmed clinically relevant sensitivity for the viral targets included, yet the data on bacterial and fungal detection performance was limited in the original papers (Wootton et al., 2016; Leber et al., 2016). Recently, Liesman et al. demonstrated a good ability for bacterial detection in clinical samples, yet the limit of detection in terms of bacterial load was not studied (Liesman et al., 2018). The aim of the present study was to evaluate the analytical performance of the FilmArray™ ME panel, with focus on bacterial and fungal targets compared to culture and in-house PCR methods; both technically by

* Corresponding author at: Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, SE-701 85 Örebro, Sweden
E-mail addresses: david.nestor@regionorebrolan.se (D. Nestor), sara.thulin-hedberg@regionorebrolan.se (S. Thulin Hedberg), marie.lignell@vgregion.se (M. Lignell), susann.skovbjerg@vgregion.se (S. Skovbjerg), paula.molling@regionorebrolan.se (P. Mölling), martin.sundqvist@regionorebrolan.se (M. Sundqvist).

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Table 1
The pathogens included in the FilmArray Meningitis/Encephalitis panel.

Bacteria	Viruses	Fungi
Streptococcus pneumoniae	Enterovirus	***Cryptococcus neoformans***[a]
Neisseria meningitidis	Herpes Simplex Virus 1	*Cryptococcus gattii*
Haemophilus influenzae[a]	Herpes Simplex Virus 2	
Listeria monocytogenes	Varicella Zoster Virus	
Streptococcus agalactiae	Cytomegalo Virus	
Escherichia coli[a]	Human Herpes Virus 6	
	Human Parechovirus	
	Epstein Barr Virus	

In bold the pathogens primarily evaluated in this study.
[a] Compared to culture only.

determining detection limits of the most common CNS pathogens in our setting and by using stored CSF samples with verified pathogens.

2. Materials and methods

The study was conducted at two geographically distinct sites in Sweden, Örebro University Hospital, Örebro (ÖUH) and Clinical Microbiological Laboratory, Sahlgrenska University Hospital, Gothenburg (SU). The analyses were performed using the FilmArray™ ME RoU (Örebro) and IVD (SU) panel in accordance with the manufacturer's instructions (BioFire).

2.1. Contrived samples and EQA panels

In total 29 contrived bacterial and fungal samples were analysed. At ÖUH, two colonies from overnight cultures of *Streptococcus pneumoniae* (ATCC 49619), *Neisseria meningitidis* (MC58) (Tettelin et al., 2000), *Listeria monocytogenes* (CCUG 51681) and *Streptococcus agalactiae* (ATCC 15305) were separately mixed with negative CSF and diluted in negative CSF from 1:1 to $1:10^6$. The diluted contrived samples were analysed with the FilmArray™ ME panel and with in-house PCR to compare the detection level in the two molecular assays. The detection limits of the in-house has previously been tested to be 10^2 cfu/mL for *S. pneumoniae* and *N. meningitidis* and 10^3 cfu/mL for the remaining two bacterial targets (Hedberg et al., 2009). An external quality assessment (EQA) panel with six samples from a three-laboratory comparison panel for the detection of bacteria causing CNS infections (2014, *Haemophilus influenzae* n = 2, *S. pneumoniae* n = 2, *N. meningitidis* n = 2) was analysed using the FilmArray™ ME panel. This panel had previously been analysed using the in-house PCR method at ÖUH (Hedberg et al., 2009).

At SU, suspensions of *S. pneumoniae* (CCUG 33638), *N. meningitidis* (CCUG 8661), *L, monocytognes* (CCUG 15527), *S. agalactiae* (CCUG 4208^T), *H. influenzae* (CCUG 29539), *Escherichia coli* (CCUG 24^T) and *Cryptococcus neoformans* (CCUG 19558 T) were diluted in PBS and cultured on blood agar plates (prepared at Substrate Department, Clinical Microbiological Laboratory, Sahlgrenska University Hospital) for the determination of the number of colony forming units (cfu). The dilutions corresponding to 1–10 cfu/mL were analysed with the FilmArray™ ME panel and cultured on blood agar plates. In addition, suspensions of *Streptococcus mitis* (CCUG 63687) and *Streptococcus pseudopneumoniae* (CCUG 47366) (McFarland 0.2) were included for the analysis of the specificity of the FilmArray™ ME panel. Also, one EQA panel with five samples distributed by Equalis AB (National provider of External quality assessment, Uppsala, Sweden) (*H. influenzae* n = 1, *S. pneumoniae* n = 1, *N. meningitidis* n = 1, *S. pneumoniae* + *N. meningitidis* n = 1, *H. influenzae* + *N. meningitidis* n = 1) was included for analysis. The EQA panel had previously been analysed with an in-house PCR based on previously published protocols (Salo et al., 1995; Abdeldaim et al., 2010).

2.2. Clinical samples

Seventeen frozen CSF samples from patients with CNS infections were retrieved for this evaluation. The samples had previously been analysed with an in-house PCR method (Hedberg et al., 2009) at ÖUH (*n* = 13) or cultured at SU (*n* = 4), for details see Table 3.

2.3. Samples with multiple targets

Six additional samples were run in the FilmArray™ ME panel. These were prepared with multiple targets to evaluate the multiplex capacity and to test the risk for nucleotide competition. Four of the clinical bacterial samples (two each of *S. pneumoniae* and *N. meningitidis*) previously positive in the in-house PCR, were mixed in a 1:1 ratio with contrived samples of Herpes simplex virus 2 (HSV-2) and Varicella zoster virus (VZV) with theoretical concentrations of 100 and 1000 copies/mL. These were prepared from standards of HSV-2 (HSV2QC01, 32.000 copies/mL) and VZV (VZVQC01, 10.000 copies/mL) both from Qnostics Ltd. Glasgow, Scotland, UK. Additionally, two samples of negative CSF were spiked with four targets (*N. meningitidis*, *S. pneumoniae*, HSV-2 and VZV). High bacterial concentration (approx. 250 cfu/mL (estimated from (Hedberg et al., 2009)) and low viral concentration (approx. 25 copies/mL) in one sample and vice versa in the other (approx. 25 cfu/mL and 250 copies/mL).

3. Results

3.1. Sensitivity of bacterial/fungal targets

The FilmArray™ ME panel showed a lower sensitivity for all tested bacterial targets compared to in-house PCR (ÖUH) (Hedberg et al., 2009). The detection limit was estimated to be five times lower for *S. pneumoniae*, *N. meningitidis* and *S. agalactiae* and ten times lower for L. *monocytogenes* (Supplementary Material Table 1). When compared to culture, all bacterial and fungal suspensions tested (*S. pneumoniae, N. meningitidis, L. monocytogenes, S. agalactiae, H. influenzae, E. coli* and *C. neoformans*) were detected using the FilmArray™ ME panel at a theoretical concentration of 1–10 cfu/mL, while only the L. *monocytogenes* suspension was culture positive in that dilution (Table 2).

3.2. Clinical and EQA samples

The FilmArray™ ME panel detected the expected pathogen in 17 out of 17 frozen clinical samples (Table 3) and detected all but one target in the EQA panels tested. The *N. meningitidis* target in the mixed sample with *N. meningitidis* + *H. influenzae* sample was missed, yet the sample was only analysed once.

3.3. Multiplex capacity and specificity

In the mixed clinical/contrived samples one of the eight possible targets (*S. pneumoniae*) remained undetected. In the clinical samples the FilmArray™ ME panel detected three additional pathogens: two *S. pneumoniae* positive samples were also positive for Human herpesvirus 6 (HHV-6) and one *N. meningitidis* was also positive for *S. pneumoniae*. The *S. pneumoniae* was successfully verified using inhouse PCR (ÖUH) while the HHV-6 positivity could not be reproduced using in-house PCR methods (SU) (Kullberg-Lindh et al., 2011). The FilmArray™ ME panel detected all four pathogens in the two contrived samples containing *N. menigitidis, S. pneumoniae*, HSV-2 and VZV in different concentrations. The spiked negative control samples with *S. pseudopneumoniae* and *S. mitis* were reported negative.

4. Discussion

This study evaluated the analytical performance of FilmArray™ ME

Table 2
Comparison of sensitivity between culture and FilmArray™ ME panel.

Target	Theoretical concentration (CFU/ml)	Culture, visually assessed growth (CFU)	FilmArray ™ ME panel
		Result	Result
Streptococcus pneumoniae (CCUG 33638)	> 1000	> 100	na[1]
	101–1000	21	na
	11–100	2	na
	1–10	0	Detected
Neisseria meningitidis (CCUG 8661)	> 1000	70	na
	101–1000	5	na
	11–100	0	na
	1–10	0	Detected
Listeria monocytogenes (CCUG 15527)	> 1000	> 1000	na
	101–1000	> 100	na
	11–100	50	na
	1–10	8	Detected
Streptococcus agalactiae (CCUG 4208^T)	> 1000	> 100	na
	101–1000	18	na
	11–100	3	na
	1–10	0	Detected
Haemophilus influenzae (CCUG 29539)	> 1000	> 100	na
	101–1000	16	na
	11–100	2	na
	1–10	0	Detected
Escherichia coli (CCUG 24^T)	> 1000	> 100	na
	101–1000	17	na
	11–100	2	na
	1–10	0	Detected
Cryptococcus neoformans (CCUG 33638^T)	> 1000	> 1000	na
	101–1000	100	na
	11–100	9	na
	1–10	0	Detected

Only the lowest concentration was analysed with Film Array™
[1] na = Not Applicable.

Table 3
Clinical samples analysed with the FilmArray ME panel previously analysed with culture (n = 4, 1 each of the four species) and an in-house PCR method (n = 13, *S. pneumoniae* n = 11, *N. meningitidis* n = 2) (Tettelin et al., 2000).

Pathogen	Positive samples FilmArray/in-house method (PCR/culture)
Streptococcus pneumoniae	12[a]/12 (11/1)
Neisseria meningitidis	3[b]/3 (2/1)
Haemophilus influenzae	1/1 (0/1)
Cryptococcus neoformans	1/1[c] (0/1)

[a] Two of the *S. pneumoniae* positive samples were also tested positive for Human Herpes Virus 6 (HHV-6) using the FilmArray™ ME panel. These results could not be verified using in-house PCR.
[b] One sample also positive for *S. pneumoniae*, this was verified with in-house PCR.
[c] Negative with culture but positive using Cryptococcal antigen test.

panel with focus on bacterial targets and *Cryptococcus* spp. We used in-house PCRs as comparator method and not only Gram stain and culture (Wootton et al., 2016; Leber et al., 2016). When compared to in-house PCR the FilmArray™ ME panel showed a 5–10 fold lower sensitivity for *S. pneumoniae, N. meningitidis, L. monocytogenes* and *S. agalactiae*. However, when compared to culture, the FilmArray™ ME panel showed a 10–100-fold higher sensitivity for all targets but for *L. monocytogenes*. One *N. meningitidis* target in the EQA samples was missed which is hard to address. The exact concentration of the target was not stated and the sample had been stored frozen before analysis which might have affected the result. Based on the results from the clinical samples the sensitivity seemed clinically relevant as all pathogens were identified. These results are supported by Liesman et al. regarding bacterial targets (Liesman et al., 2018). However, in the same study the FilmArray™ failed to detect 24 of 50*C. neoformans/C. gattii* originally identified using the antigen Cryptococcal Antigen Lateral Flow Assay test (CrAg LFA). We had only one clinical sample with *Cryptococccus neoformans* in this study (originally confirmed with antigen testing) and the detection of *Cryptococcus* spp. needs further research (O'Halloran et al., 2018). The clinical performance of the FilmArray™ ME was thus considered substantially equal to the in-house method even though a higher analytical sensitivity would have been preferred. The specificity of the FilmArray™ ME panel was considered very good as only 2 out of 272 possible targets (0.7%) in the clinical samples could not be verified (both HHV-6). A low rate of HHV-6 positivity with the FilmArray™ ME panel that could not be confirmed and/or associated with disease has been observed in previous studies (Leber et al., 2016; O'Halloran et al., 2018; Green et al., 2018) also leading to inappropriate treatment (O'Halloran et al., 2018).

One of the clinical advantages of the FilmArray™ ME panel is the ability to detect both bacterial and viral targets in the same analysis. In this study the system was able to detect all targets but one in the multiple positive samples indicating a good ability for multiple detections. The clinical importance of dual infections in CNS is, however, not yet fully elucidated. Lately, Labská et al. reported detection of HSV-1, HSV-2, VZV and HHV-6 in patients with Tick-Borne Encephalitis (TBE) and Enteroviral meningitis (Labská et al., 2015) and a recent case-report described intrathecal HSV-1 reactivation during acute pneumococcal meningitis (Ericsdotter et al., 2015). Both studies concluded that the risk of reactivation of HSV-1 should be kept in mind if patients with CNS infections do not improve as expected. The historical lack of data on co-infections in CNS could partly be because clinical laboratories, so far, have not systematically tested for multiple targets. The increased use of syndromic panels for CNS infections will probably bring more light on this issue.

The FilmArray™ ME panel has a broad capacity with 14 targets. Yet, other studies have highlighted that some important CNS pathogens, such as West Nile virus, *Histoplasma capsulatum* and *Mycobacterium tuberculosis*, are not included (Wootton et al., 2016; Gomez et al., 2017). In our setting, Tick-Borne Encephalitis virus (Lundkvist et al., 2011) and *Borrelia burgdorferi* are additional common causes of CNS infections and it is important to note that a negative FilmArray™ ME panel does not exclude infection in the CNS. This is further emphasized by this study where we noted a slightly lower sensitivity compared to inhouse-PCR for several bacterial targets. Additionally, the panel does not give any information on antibiotic susceptibility. In our view the FilmArray™ ME panel thus ideally should be used in parallel with other routine diagnostic methods. In advantage, the FilmArray™ ME panel might be effective even after initiation of antibacterial treatment (not evaluated in this study) and the decreased turn-around time might have a positive impact on antimicrobial stewardship (Soucek et al., 2017; Eichinger et al., 2018). Recently, Naccache et al. assessed the clinical utility of the FilmArray™ ME panel in a prospective study and appreciated the negative predictive properties of the kit (Naccache et al., 2018). No preparation of CSF specimen is required and the hands-on time is < 3 min.

5. Limitations of this study

This study has some important limitations. The comparison of the FilmArray™ ME panel to in-house PCR should be regarded as relative rather than quantitative, as the exact detection limits in cfu/mL and viral copies/mL, respectively, were not verified in this study. Also, different dilution series were used in the two study sites. In addition, most of the samples were only analysed once in the FilmArray™ ME panel due to the relatively high cost of the test. Clinical data and patient characteristics were not collected for the positive clinical CSF samples. Also, the study contained a limited sample size.

6. Conclusion

The FilmArray™ ME panel displayed a higher sensitivity compared to CSF culture but a slightly lower sensitivity for all tested bacteria compared to in-house PCR. The clinical importance of this remains to be elucidated and should be interpreted with caution due to the limited number of samples analysed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mimet.2019.01.003.

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