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THE CONTRIBUTION OF MOLECULAR BIOLOGY IN THE ETIOLOGICAL DIAGNOSIS OF INFECTIOUS MENINGITIS

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ABSTRACT

Infectious meningitis is a vital emergency that needs rapid, efficient etiological diagnosis, and identification of the pathogens involved is crucial to reducing the health impact. The recent development of new syndromic multiplex PCR rapid diagnostic tests offers rapid, sensitive and specific diagnosis of infectious meningitis, even in cases of negative cultures or previous antibiotic therapy.

Our study evaluated the contribution of the FilmArray Meningitis/Encephalitis (M/E) panel to the diagnosis and management of infectious meningitis, comparing it with conventional culture, while highlighting the epidemiology of the pathogens implicated.

This retrospective study was carried out on 115 cerebrospinal fluid (CSF) from patients clinically suspected of having meningitis, analyzed by conventional methods and the FilmArray M/E panel test.

The majority of specimens came from patients hospitalized at the Avicenne Military Hospital in Marrakech (91.5%), mainly from the emergency department (34%), with a male predominance (sex ratio M/F = 1.87). The FilmArray Meningitis/Encephalitis panel showed an overall positivity rate of 22.6%, revealing a viral etiology in 52% of cases (mainly enteroviruses, 26%), bacterial in 44% (notably *Streptococcus pneumoniae*, 15%), and cryptococcal in 4% in association with cytomegalovirus CMV. The test detected 23 cases of meningitis not identified by culture, and showed excellent concordance with the culture for pneumococcus (98.6%).

Median time to results was significantly reduced 5h compared with 48h for conventional methods.

The syndromic FilmArray Meningitis/Encephalitis multiplex PCR panel provides fast and accurate identification of infectious meningitis pathogens, supporting early and targeted therapeutic strategies. However, it should complement conventional microbiology and be interpreted within the clinical-epidemiological context.

Keywords: Molecular biology; Diagnosis; Infectious meningitis; Multiplex PCR; FilmArray.

1 INTRODUCTION

Meningitis is an acute inflammation of the brain envelope, leading to abnormalities in the cerebrospinal fluid (CSF). This process extends throughout the subarachnoid space from the brain to the spinal cord, and the inflammation raises the number of white blood cells in the CSF.

A large number of infectious agents have been reported to cause meningitis, the most frequent being viral and benign in most cases, as opposed to bacterial meningitis, which is rarer but an extreme life-threatening emergency requiring immediate diagnosis and treatment. Other causes (parasitic or fungal) are less frequent.

As a result, infectious meningitis is a real diagnostic and therapeutic emergency, and early identification of the agents responsible for meningitis is of vital importance to enable rapid, appropriate, and effective therapy to reduce the associated morbidity and mortality.

Progress in molecular biology has made it possible to bring together all these pathogens in a minimum of analysis, and this has given rise to a new concept: the syndromic approach, which involves the simultaneous search for the microorganisms most frequently responsible for an infection that causes a syndrome.

In our context, the FilmArray® panel dedicated to meningitis and encephalitis is a fully automated in vitro diagnostic device designed to detect multiple nucleic acid targets contained in cerebrospinal fluid.

The purpose of this work is to demonstrate the contribution of molecular biology, particularly the FilmArray® Meningitis/Encephalitis (M/E) panel, to the etiological diagnosis of infectious meningitis.

2 MATERIALS AND METHODS

This is a retrospective descriptive study of 115 cerebrospinal fluid (CSF) samples collected between January 2018 and December 2020, from patients clinically suspected of having infectious meningitis, managed at the microbiology, virology and molecular biology laboratory of the Avicenne Military Hospital in Marrakech. Patients whose records were incomplete or whose CSF sample was not usable were excluded.

To ensure a complete diagnosis, each CSF sample was subjected to cytological study, direct examination after Gram coloration, conventional bacterial culture, and molecular analysis by multiplex PCR using the Meningitis/Encephalitis FilmArray panel (BioFire®, bioMérieux).

All data were then entered and analyzed using Microsoft Excel 2016. The main objective of the study was to evaluate the contribution of the FilmArray Meningitis/Encephalitis panel to the diagnosis of infectious meningitis, while describing its epidemiological aspects during the study period and highlighting the limitations of this technique.

3 RESULTS

During the study period, 65% of the patients were male and 35% were female, corresponding to a male-to-female ratio of 1.87. The majority of samples were obtained from hospitalized patients (91.5%), while 8.5% were from outpatients. Among the 105 hospitalized patients with suspected meningitis, 34% were admitted to the emergency department, 29% to the intensive care unit, 17% to the internal medicine department, 12.5% to the neurology department, and 7.5% to the neurosurgery department (Figure 1).

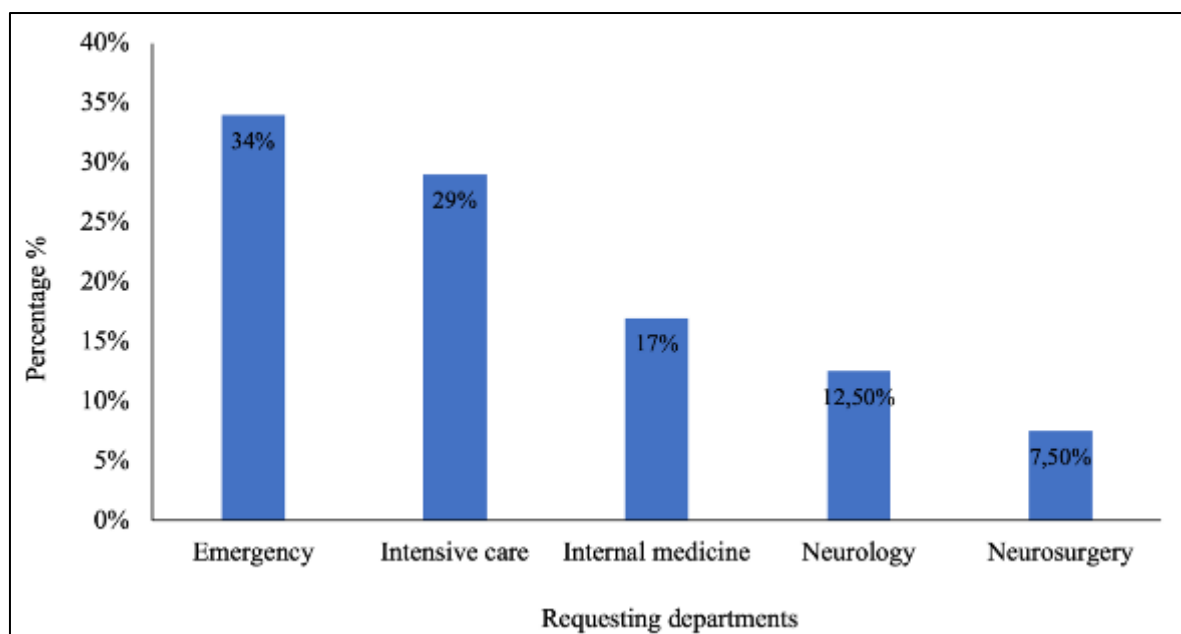


Figure 1: Distribution of samples by requesting department.

Among the 115 samples received by the microbiology laboratory during the study period, the FilmArray® Meningitis/Encephalitis (ME) panel detected at least one pathogen in 26 samples, corresponding to a positivity rate of 22.6%. In addition, one co-infection involving both CMV and *Cryptococcus neoformans/gattii* was identified among the 26 positive samples, corresponding to a co-infection rate of 3.8%. Regarding the distribution of the detected pathogens, enteroviruses were predominant and represented the most frequently identified group among the 27 pathogens detected overall during the study period (Figure 2).

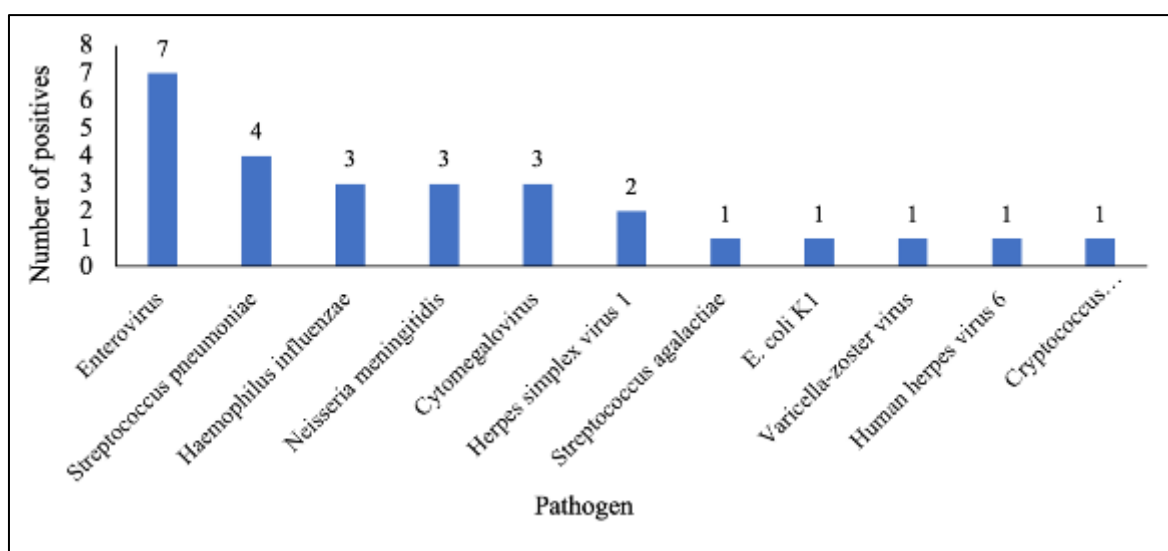


Figure 2: Pathogens detected by FilmArray.

The infectious agents identified in the meningitis cases included in our study were predominantly viral (52%), followed by bacterial pathogens (44%), while yeasts were markedly less frequent, accounting for only 4% of positive samples (Figure 3).

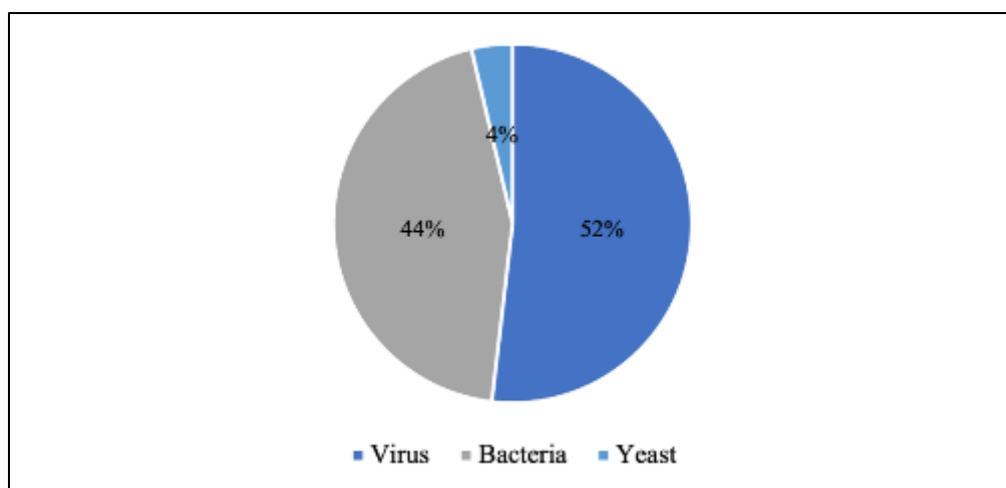


Figure 3: Distribution of infectious meningitis according to causal germ.

In our series, six pathogens were detected by conventional culture, corresponding to an overall positivity rate of 5.2%. *Streptococcus pneumoniae* was the most frequently isolated pathogen, accounting for 50% of the bacteria detected by culture, which was consistent with the FilmArray® ME panel results.

This was followed by *Acinetobacter baumannii*. In contrast to the FilmArray® multiplex PCR panel, conventional culture also identified cytomegalovirus, as well as *Staphylococcus aureus* and *Klebsiella pneumoniae*, which are bacterial pathogens not included in the FilmArray® Meningitis/Encephalitis panel (Table 1).

Regarding the agreement between conventional culture and FilmArray®, a concordance rate of 98.6% was observed for *Streptococcus pneumoniae*.

Table 1: Results of multiplex PCR testing on culture-positive samples.

Pathogen identified by culture	Number	FilmArray® result on the same sample
<i>Streptococcus pneumonia</i>	3	Streptococcus pneumonia
<i>Acinetobacter baumanii</i>	1	CytomégaloVirus
<i>Staphylococcus aureus</i>	1	Negative
<i>Klebsiella Pneumoniae</i>	1	Negative

The antimicrobial susceptibility of each identified bacterial strain was tested against selected antibiotics according to the guidelines of the French Society for Antimicrobial Susceptibility Testing (CASFM) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Among the three *Streptococcus pneumoniae* isolates identified, two were susceptible to all tested antibiotics, including all β -lactams, whereas one isolate showed resistance to penicillin G and oxacillin.

The *Acinetobacter baumannii* isolate was resistant to aminoglycosides and quinolones but remained susceptible to imipenem.

The single *Klebsiella pneumoniae* isolate was susceptible only to amikacin and cefoxitin.

The *Staphylococcus aureus* isolate was resistant to methicillin and cefoxitin but remained susceptible to vancomycin, linezolid, and teicoplanin.

In our series, the FilmArray® ME panel enabled the diagnosis of 23 cases of infectious meningitis despite negative conventional culture results (Figure 4).

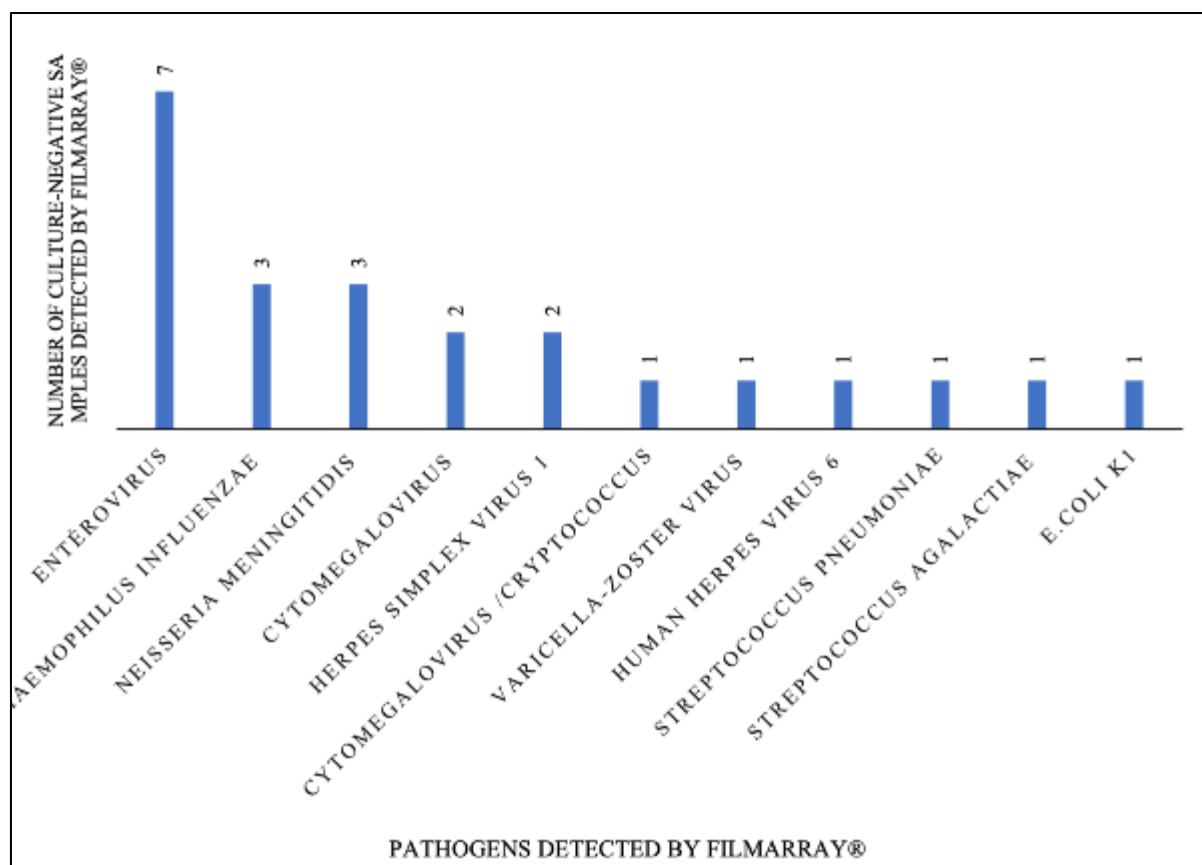


Figure 4: Culture-negative samples detected by FilmArray®.

Several steps were required before the results could be reported, including sample transportation from the requesting department (approximately 30 minutes), test registration (5 minutes), the pre-analytical phase involving sample and cartridge preparation (3 minutes), the analytical phase performed by the FilmArray® system (1 hour), and the post-analytical phase, including result communication and technical and biological validation (3 hours and 22 minutes). In our series, the median turnaround time for the FilmArray® Meningitis/Encephalitis panel was 5 hours.

In our series, enteroviruses were the most frequently detected viral pathogens, with a positivity rate of 26%, followed by cytomegalovirus (CMV) at 11%, herpes simplex virus type 1 (HSV-1) at 7.5%, and human herpesvirus 6 (HHV-6) and varicella-zoster virus (VZV) at 3.7% each (Figure 5).

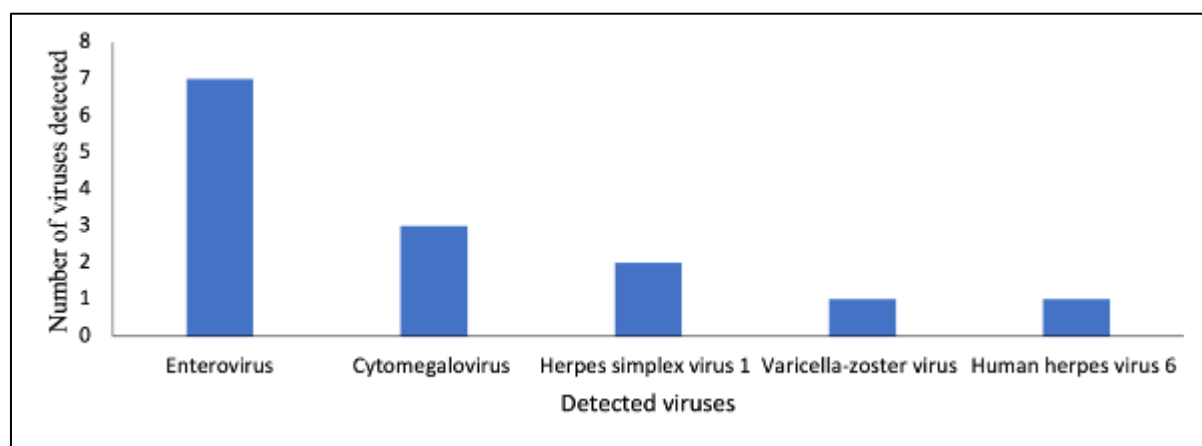


Figure 5: Distribution of viral pathogens detected by the FilmArray® Meningitis/Encephalitis panel.

4 DISCUSSION

Central nervous system infections, particularly infectious meningitis, represent a diagnostic and therapeutic emergency because of their potentially rapid progression and the severity of their complications. Etiological diagnosis traditionally relies on cerebrospinal fluid (CSF) analysis, including direct examination, culture, and, depending on the clinical context, antigen detection or molecular methods. However, the diagnostic yield of conventional methods may be limited, particularly following prior antibiotic administration and in viral infections. In this context, syndromic multiplex PCR techniques, such as the FilmArray® Meningitis/Encephalitis (ME) panel, have improved both the speed and the diagnostic yield of microbiological investigations. The FilmArray® ME panel simultaneously detects 14 pathogens, including bacteria, viruses, and yeasts, from a small volume of CSF, with an analytical processing time of approximately one hour [1,2].

In our study, a male predominance was observed, with 65% of patients being male and 35% female, corresponding to a male-to-female ratio of 1.87. This predominance should nevertheless be interpreted with caution, as sex is not a specific determinant of meningitis etiology. It may rather reflect the characteristics of the hospital population studied and the indications for requesting the FilmArray® test. Most samples were obtained from hospitalized patients (91.5%), which is consistent with the potentially severe nature of central nervous system infections and the need for rapid hospital-based management. The emergency department was the main requesting department (34%), followed by the intensive care unit (29%), internal medicine (17%), neurology (12.5%), and neurosurgery (7.5%). This distribution reflects the multidisciplinary nature of meningitis management and the predominance of patients requiring urgent or specialized care. A recent Moroccan study conducted in Tangier reported a similar distribution, with 37.1% of samples originating from the emergency department and 27.1% from intensive care [3]. This similarity suggests that molecular testing for central nervous system infections is mainly requested in hospital departments managing patients with acute or severe clinical presentations.

In our series, the FilmArray® ME panel detected at least one pathogen in 26 of the 115 samples tested, corresponding to a positivity rate of 22.6%. This diagnostic yield is within the range reported in several studies evaluating this technology. One clinical study reported a positivity rate of 23.6%, while other studies have shown variable rates depending on the population studied, inclusion criteria, and clinical setting [4,5]. A recent Moroccan study conducted in Tangier, however, reported a lower positivity rate of 14.9% among 402 CSF samples [3]. Such differences may be related to variations in the demographic and clinical characteristics of the populations, indications for testing, the proportion of patients who received antibiotics before lumbar puncture, and differences in local epidemiology. Therefore, positivity rates should not be directly compared without considering these factors. It is also important to emphasize that the 22.6% positivity rate observed in our study represents the proportion of positive samples and should not be interpreted as the prevalence of central nervous system infections in the general population.

The detection of 27 pathogens in 26 positive samples was explained by the presence of one co-detection involving cytomegalovirus (CMV) and *Cryptococcus neoformans/gattii*. The co-infection rate was therefore 3.8% among positive samples. Co-detections are a recognized phenomenon with syndromic molecular panels. In the recent Moroccan study conducted in Tangier, four bacterial and viral co-detections were identified among 60 positive samples, corresponding to 6.7% [3]. However, simultaneous detection of several pathogens should be interpreted cautiously because the presence of microbial nucleic acid in CSF does not necessarily mean that all detected microorganisms are responsible for the clinical syndrome. This issue is particularly relevant for certain viruses, including CMV and human herpesvirus 6 (HHV-6), whose detection requires careful correlation with the clinical context, immune status, and other laboratory findings [5,6].

In our series, viral pathogens predominated, accounting for 52% of detected microorganisms, compared with 44% for bacteria and only 4% for yeasts. This predominance of viral infections is consistent with several studies evaluating the FilmArray® ME panel. In the Moroccan study from Tangier, viruses accounted for 51.7% of detections, compared with 40% for bacteria and 1.7% for isolated fungal infections [3]. The predominance of viral infections in our study is also consistent with international studies showing that viruses constitute an important proportion of the etiological agents responsible for meningitis and encephalitis syndromes [4,5]. This finding highlights the particular value of molecular diagnostics, since many viruses are difficult or impossible to detect by conventional culture and their identification relies primarily on molecular methods.

Among the viruses detected in our study, enteroviruses were the most frequent, accounting for 26% of viral detections, followed by CMV at 11%, HSV-1 at 7.5%, and HHV-6 and VZV at 3.7% each. The predominance of enteroviruses is consistent with published data. Enteroviruses are among the leading causes of viral meningitis and are frequently detected by multiplex molecular panels. In the multicenter study by Leber et al., one of the first large-scale evaluations of the FilmArray® ME panel, enteroviruses were also among the most frequently detected pathogens [5]. The Moroccan study from Tangier, however, reported a higher frequency of HHV-6 than enteroviruses, illustrating the influence of age

and population characteristics on the etiological profile [3]. Rapid identification of enteroviruses is clinically valuable because it may help distinguish viral from bacterial meningitis and potentially contribute to reducing unnecessary antibiotic exposure when molecular findings are consistent with the clinical and laboratory presentation.

The relatively high frequency of CMV detection in our study should nevertheless be interpreted cautiously. Detection of CMV in CSF may be particularly relevant in immunocompromised patients, but its presence should not automatically be considered evidence of CMV neurological disease without correlation with clinical findings. A similar issue applies to HHV-6. A study evaluating the clinical use of the FilmArray® panel showed that a proportion of positive results could be considered clinically insignificant and emphasized the need to interpret molecular results in conjunction with the clinical context [6]. Therefore, the value of FilmArray® does not only lie in its ability to detect a pathogen, but also in its capacity to provide rapid information that can be integrated with clinical and biological findings.

Conventional culture identified only six pathogens in our series, corresponding to an overall positivity rate of 5.2%, compared with 26 positive samples detected by FilmArray®. This difference clearly demonstrates the added diagnostic value of multiplex PCR in central nervous system infections. In our series, FilmArray® identified 23 infectious meningitis cases despite negative conventional cultures. This may be explained by the higher analytical sensitivity of molecular methods, their ability to detect pathogens that are difficult or impossible to culture, and their reduced dependence on microbial viability. Culture yield may also be reduced following prior antibiotic administration. In the multicenter study by Leber et al., the FilmArray® ME panel demonstrated an important capacity to detect pathogens responsible for central nervous system infections, including cases in which conventional microbiological methods were negative [5]. Another study evaluating implementation of the panel in a hospital setting also demonstrated that FilmArray® results could be obtained within approximately one hour, whereas some reference investigations required several days [7].

Streptococcus pneumoniae was the principal bacterial pathogen recovered by culture in our study, accounting for 50% of cultured bacteria. This finding is consistent with the literature, as *S. pneumoniae* remains a major cause of community-acquired bacterial meningitis. The Moroccan study from Tangier also identified pneumococcus as the most frequently detected bacterial pathogen, with 10 cases among the positive samples [3]. The predominance of pneumococcus in our series emphasizes the importance of rapid identification, given the potentially severe course of pneumococcal meningitis and the need for appropriate antimicrobial therapy.

The concordance between culture and FilmArray® for pneumococcus should nevertheless be interpreted carefully. In the published data corresponding to our series, the reported concordance for *S. pneumoniae* was 75% [8]. If the value of 98.6% currently reported in your manuscript was calculated using another approach, the calculation method and denominator should be specified before retaining this value in the final version. This clarification is important because overall agreement, positive agreement, and negative agreement are different measures and should not be confused.

Culture also identified microorganisms in our series that are not targeted by the FilmArray® ME panel, including *Acinetobacter baumannii*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. This finding highlights a fundamental limitation of the panel: despite its syndromic approach, FilmArray® targets only a defined number of pathogens. The panel includes 14 bacterial, viral, and fungal targets commonly associated with central nervous system infections, but it does not cover all microorganisms that may cause meningitis or encephalitis [1,2,5]. This limitation has also been emphasized in the recent Moroccan study, which highlighted, among other limitations, the absence of *Mycobacterium tuberculosis* from the panel [3]. Therefore, a negative FilmArray® result cannot by itself exclude a central nervous system infection. Conventional culture remains essential, particularly for microorganisms not included in the panel and for antimicrobial susceptibility testing.

The antimicrobial susceptibility results in our study further support the importance of maintaining conventional microbiological methods. Two of the three pneumococcal isolates were susceptible to all tested antibiotics, whereas one isolate showed resistance to penicillin G and oxacillin. The *A. baumannii* isolate was resistant to aminoglycosides and quinolones but remained susceptible to imipenem. The *K. pneumoniae* isolate showed limited susceptibility, being susceptible only to amikacin and cefoxitin, whereas the *S. aureus* isolate was resistant to methicillin and cefoxitin but susceptible to vancomycin, linezolid, and teicoplanin. These findings clearly demonstrate that multiplex PCR and culture have complementary roles: FilmArray® provides rapid identification of selected pathogens, whereas culture enables confirmation of the microorganism, antimicrobial susceptibility testing, and detection of pathogens not included in the panel. FilmArray® should therefore not be considered a replacement for conventional microbiology but rather as a complementary diagnostic tool capable of accelerating etiological diagnosis.

Turnaround time represents another important aspect of our study. Although the analytical processing time of the FilmArray® system is approximately one hour, the median overall turnaround time in our series was five hours. This difference can be explained by the various pre- and post-analytical steps, including sample transportation, registration, sample preparation, result validation, and communication. Published data indicate that the analytical processing time

of the FilmArray® ME panel is approximately one hour [1,2,7]. In a study involving 705 hospitalized patients, the median time from lumbar puncture to availability of the FilmArray® result was 1.5 hours [6]. Therefore, the five-hour turnaround time observed in our study does not necessarily reflect a limitation of the analytical system itself but rather the organization of the pre-analytical and post-analytical workflow. Improving sample transportation and result validation could therefore further reduce the overall turnaround time and maximize the clinical benefit of this rapid diagnostic technology.

The clinical value of rapid diagnosis is particularly important in bacterial meningitis, in which delays in diagnosis and appropriate treatment may have serious consequences. FilmArray® provides rapid etiological information and may facilitate earlier optimization of antimicrobial therapy. Several studies have shown that rapid availability of FilmArray® results may influence antibiotic duration and patient management [6,7]. Nevertheless, rapid molecular results should not be interpreted in isolation. In a study evaluating clinical use of the panel, approximately one quarter of positive results were considered potentially clinically insignificant, highlighting the importance of correlation with clinical and laboratory findings [6]. This issue is particularly relevant for CMV and HHV-6 detections.

Overall, our findings demonstrate that the FilmArray® ME panel substantially improved the microbiological diagnosis of infectious meningitis in our series, with a positivity rate of 22.6% compared with 5.2% for conventional culture. The predominance of viral pathogens, particularly enteroviruses, is broadly consistent with both international and Moroccan studies [3–5]. The main advantages of this technology are its rapid turnaround time, its ability to simultaneously investigate multiple pathogens, and its capacity to identify infections that may remain undiagnosed by conventional culture. However, the detection in our series of bacteria not included in the panel, together with the possibility of molecular results of uncertain clinical significance, demonstrates that FilmArray® cannot replace conventional microbiological methods. The optimal diagnostic strategy therefore relies on a complementary approach integrating clinical findings, CSF cytology and biochemistry, direct examination, culture, antimicrobial susceptibility testing, and multiplex PCR. This complementary strategy is particularly important when clinical suspicion remains high despite a negative FilmArray® result or when infection with a pathogen not included in the panel is suspected.

5 CONCLUSION

The FilmArray® Meningitis/Encephalitis panel significantly improved the rapid etiological diagnosis of infectious meningitis compared with conventional culture, with a higher positivity rate and the detection of 23 infections despite negative cultures. Viral pathogens, particularly enteroviruses, predominated, while *Streptococcus pneumoniae* was the main bacterial pathogen. However, the detection of non-panel bacteria by culture highlights the continued importance of conventional microbiological methods and antimicrobial susceptibility testing. Overall, FilmArray® ME is a valuable complementary tool that can accelerate diagnosis and support timely, targeted management of patients with suspected central nervous system infections.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest

Statement of informed consent

Written informed consent for publication was not applicable, as this study did not include identifiable personal data or images of individual patients.

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