Category: Perspective

Title: Next Generation Rapid Diagnostic Tests for Meningitis Diagnosis

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ABSTRACT

Rapid diagnostic tests (RDTs) are increasingly recognized as valuable, transformative tools for the diagnosis of infectious diseases. Although there are a variety of meningitis RDTs currently available, certain product features restrict their use to specific levels of care and settings. For this reason, the development of meningitis RDTs for use at all levels of care, including those in low-resource settings, was included in the "Defeating Meningitis by 2030" roadmap. Here we address the limitations of available meningitis RDTs and present test options and specifications to consider when developing the next generation of meningitis RDTs.

INTRODUCTION

Meningitis is a disease caused by numerous pathogens: bacterial, viral, fungal, or parasitic. Symptoms typically include fever, stiff neck, confusion, and light sensitivity (CDC, 2019; Saez-Llorens and McCracken, 2003; van de Beek et al., 2006; Christie et al., 2017). Globally, meningitis affects 2.8 million people with nearly 319,000 deaths reported in 2016 (GBD Meningitis Collaborators, 2018). The largest burden of disease is in a region of sub-Saharan Africa known as the "meningitis belt" – extending from Senegal in the west to Ethiopia in the east (Lapeyssonnie 1963; Mueller et al., 2012; Koutangni et al., 2015) – where meningitis is endemic and seasonal outbreaks occur annually (Mueller et al., 2012; Koutangni et al., 2015).

Surveillance, outbreak investigations, and clinical management of meningitis are largely dependent on laboratory confirmation of meningitis associated pathogens from a sterile specimen, such as cerebrospinal fluid (CSF) and blood (WHO, 1999; WHO, 2019a). The gold standards for meningitis confirmation are culture, which requires a minimum of twenty-four hours, and polymerase chain reaction (PCR), capable of providing identification in a matter of hours (Griffiths et al., 2013; Wu et al., 2013). Laboratories in low-resource settings often lack the capacity to perform these confirmatory tests due to limited resources, infrastructure, or trained personnel (Waite et al., 2014; WHO, 2019a). However, rapid diagnostic tests (RDTs), developed to generate a diagnostic result in a single clinical visit, are adaptable to low-resource settings and provide a means to enhance meningitis diagnosis in these areas.

Increasing the accessibility of diagnostic tests at all levels of care, including those in low-resource settings, is a component of the recently published "Defeating Meningitis by 2030" roadmap. To achieve this goal the roadmap proposes the development of quality and affordable diagnostic tests (WHO, 2019b). Here we address the characteristics of current meningitis specific RDTs that limit their global implementation at various levels of care, options and specifications for next generation meningitis RDTs, and their value.

CHARACTERISTICS AND LIMITATIONS OF CURRENT MENINGITIS RDTs

A standard definition of RDTs has not been established, however tests that, at a minimum, provide a result in a short period of time (< 2 hours, including sample preparation) and are easy to perform or operate are generally considered RDTs (Emory University, 2020; WHO, 2020a). Meningitis tests that satisfied these minimum criteria were then assessed for use at appropriate health care levels based on their characteristics, cost, power requirements, and storage conditions. Their characteristics and limitations are discussed below.

Immunological-based platforms

Latex agglutination tests (LATs). Several LATs kits are commercially available and provide qualitative detection of antigens specific to a microbe (Table 1). The testing procedure, includes mixing specimens previously prepared (by boiling and centrifugation) with antibody coated latex beads/particles on a test card and observing for the appearance of agglutination, occurring in 20 minutes or less depending on the manufacturer (Table 1).

Most meningitis LATs can detect *Neisseria meningitidis* groups A (NmA), C (NmC), Y (NmY) or W (NmW), B (NmB)/*Escherichia coli* K1 (E. coli K1), *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* (Sp), and *Streptococcus* group B (Table 1). However, LATs do not distinguish between NmY and NmW or NmB and E. Coli K1; and do not detect Nmx (Table1) (Bio-Rad, 2008; Becton Dickinson, 2004; Remel, 2014). Given the continuing occurrence of cases and epidemics due to NmC and NmW, and the increasing prevalence of NmX, a RDT capable of detecting and differentiating all Nm serogroups is critical for case management, surveillance, and outbreak response, particularly in epidemic settings (Trotter et al., 2017; Sidikou et al., 2016; Lingani et al., 2015; Funk et al., 2014; Delrieu et al., 2011; Boisier et al., 2007). Also, the limited pathogen detection range reduces the tests efficacy in regions where other etiologies are more prevalent, such as the United Kingdom where viruses are the leading cause of meningitis among adults (Griffiths et al., 2018). As with any immunology-based test, the potential exists for cross-reactivity. Enteric bacteria cross-react

with NmA, NmB and NmC, and *Bacillus pumilus* with NmA (Robbins et al., 1972; Kasper et al., 1973; Vann et al., 1976), which may result in false positive reporting (Mani et al., 2007) with LATs.

For meningitis diagnosis by a rapid diagnostic test, the WHO reported sensitivity and specificity values of ≥ 85% as acceptable, depending on the assay and specimen type (WHO, 2016; WHO, 2020b). LAT performance generally fell short of this criterion. Overall, performance varied by kit/antigen, ranging from 7-100% sensitivity and 86-100% specificity when compared to culture and/or polymerase chain reaction [PCR] as the reference standard during laboratory verification; and 69-80% sensitivity and 81-94% specificity when evaluated in the field (Ingram et al., 1983; Hoban et al., 1985; Cuevas et al., 1989; Borel et al., 2006; Djibo et al., 2006; Rose et al., 2009; Waite et al., 2014, Uadiale et al., 2016). When compared to WHO reported values for an acceptable cost of a meningitis RDT per test, ≤ 20 United States Dollar (USD), (WHO, 2016; WHO, 2020b), LAT cost per test exceeded 20 USD in most instances (~15-66 USD). Other limitations include pre-test specimen preparation, use of powered scientific equipment (water bath and centrifuge required for pre-test specimen preparation), cold (2-8°C) storage, and the need for trained/experienced staff to perform the test. Countries in low-resource settings may experience intermittent power supply, therefore using RDTs dependent on electricity for operation or storage in these settings increases the likelihood of obtaining aberrant results.

Immunochromatographic tests. Capable of detecting antigens from a specific microbe utilizing capillary flow technology, immunochromatographic tests, also known as lateral flow tests, are small, standalone, point-of-care (POC) testing devices stored at room temperature (RT; 15-30°C) (Koczula and Gallotta, 2016; Mohd Hanafiah et al., 2017; Anfossi et al., 2019; Emory University, 2020). The testing protocol includes inserting the test into tubes containing 100 – 200 µl of specimen or adding a specimen directly to the test, then reading in 10 to 15 mins (Table 2). If the amount of specimen available for testing is low, the volume required to perform a lateral flow test (100 – 200 µl) is a limiting factor. Manufacturing of the paper-based lateral flow test is relatively easy and inexpensive (Koczula and Gallotta, 2016). However, the cost of the commercially available BinaxNow® (Antigen Card) and

BioSpeedia (MeningoSpeed and PneumoSpeed) lateral flow tests range from ~7-27 USD/test, which may still be relatively expensive for low-resource countries.

The BinaxNow® Antigen Card and BioSpeedia PneumoSpeed tests specifically detect Sp antigen (Table 2) with a high degree of sensitivity and specificity, >90% (Waite et al., 2014; BioSpeedia, 2020). The BioSpeedia MeningoSpeed test, capable of detecting Nm serogroups A, C, W, Y, and X has laboratory verification values ranging from 95.6-100% for sensitivity and 93.9-100% for specificity, when compared to either culture or PCR (BioSpeedia, 2020). Field sensitivity and specificity, when compared to PCR, were 92.7% and 93.8%, respectively at the species level; and 74.4-100% and 98.0%-100%, respectively at the serogroup level (Haddar et al., 2020).

A lateral flow test for the detection of Nm serogroups (A, C, Y, and W) was also developed by Centre de Recherche Médicale et Sanitaire (CERMES) and Institut Pasteur (Chanteau et al., 2006) prior to commercialization of the MeningoSpeed test developed by BioSpeedia, a spin-off from the Institut Pasteur. Although the CERMES duplex dipstick is not commercially available, its performance was assessed in field and laboratory settings (Rose et al., 2009; Rose et al., 2010, Terrade et al., 2013; Collard et al., 2014). In field settings, sensitivity and specificity of 91.5% and 84.6%, respectively, were reported (Collard et al., 2014). Laboratory verification sensitivity and specificity values were 100% using strains (Chanteau et al., 2006). For CSF specimens, there was 88-100% sensitivity and 97.1-100% specificity (Chanteau et al., 2006; Terrade et al., 2013). Similar high values have been obtained from the laboratory verification of the NmX dipstick (Agnememel et al., 2015), which is also not commercially available. The MeningoSpeed test includes the Nm serogroups detected by both the CERMES duplex dipstick and the NmX dipstick, however serogroup B is omitted. There are plans to incorporate the detection of NmB into future versions of the product. The antibodies will also be further developed to improve test performance (Haddar et al., 2020). Overall, meningitis lateral flow test performance generally meets the WHO's acceptable criteria for meningitis RDTs.

Like the LATs, each of the meningitis immunochromatographic tests described identifies only a small subset of pathogens known to cause meningitis. In the past, immunochromatographic tests have traditionally been low throughput, however the development of more high throughput testing options with the capability of detecting a broader panel of pathogens is in progress (Mohd Hanafiah et al., 2017; Anfossi et al., 2019).

Molecular-based platforms

Real-time polymerase chain reaction (rt-PCR) tests. The rt-PCR method has emerged as a common diagnostic test for the detection of pathogens due to its high sensitivity, fast run times, and ability to amplify nucleic acid from viable and non-viable pathogens (Espy et al., 2006; Kralik and Ricchi, 2017). Several meningitis rt-PCR platforms are available that provide results in < 2 hours, including single target (singleplex) detection and multi-target (multiplex) detection tests (Table 3).

Singleplex and multiplex tests using traditional rt-PCR often require an initial nucleic acid extraction procedure prior to the start of the rt-PCR assay (Wang et al., 2012). The Primer Design™ Ltd Neisseria meningitis kit, Allplex™ Meningitis assays, NHS Meningitidis Real-TM test, FTD/FTlyo meningitis tests, and the VIASURE PCR detection kit require deoxyribonucleic acid (DNA) extraction prior to rt-PCR, thus are more labor intensive and cost from ~6-19 USD/test. Clinical performance data for many of these tests is lacking (Primer Design™ Ltd, Allplex™, and FTD tests), however when available values were 100% for sensitivity and 60.64-100% for specificity (Mahdi et al., 2018; CerTest Biotec, 2019). Direct rt-PCR has been developed to eliminate DNA extraction and detect pathogens directly from CSF (Vuong et al., 2016), however a meningitis RDT utilizing the method is not yet available.

Advances in microfluidic channel technology have led to the production of test cartridges that combine the nucleic acid extraction and amplification steps. The FilmArray® platform utilizes the cartridge system to detect various viral, bacterial, and fungal pathogens (Meningitis/Encephalitis Panel), in less than one hour (Table 3). The Meningitis/Encephalitis Panel costs ~193 USD/test, operating on

BioFire® FilmArray® instruments only, and, based on several studies, has estimated sensitivity and specificity values of 90% and 97%, respectively (Tansarli and Chapin, 2020).

Although various rt-PCR tests exist, they do not detect all meningitis causative pathogens, are costly, some more than others, and are dependent on electrically powered PCR instruments (Table 3). The PCR instruments for most tests are also costly, surpassing the WHO reported acceptable cost of ≤ 5,000 USD (WHO, 2020b).

Loop-mediated isothermal amplification (LAMP) tests. Isothermal nucleic acid amplification is a rapid, specific, and efficient alternative to PCR (Notomi et al., 2000). The method is also low cost, and only requires a heat block or water bath for amplification (Notomi et al., 2000; Seki et al., 2018). The Eazyplex® CSF Direct platform is a commercially available meningitis LAMP testing system providing real-time fluorescent detection with 90.9% sensitivity and 100% specificity (D'Inzeo et al., 2020). The Eazyplex® CSF Direct test kit reagents are lyophilized and the kits, ranging in cost from 39.32-78.16 USD/test, are only compatible with the Genie® II instrument (~13,800 USD), which can be battery operated. While the Eazyplex® CSF Direct test kits are multiplex, the breadth of pathogen coverage is limited for each (Table 3).

NEXT GENERATION MENINGITIS RDTs

Tests that allow the generation of reliable results under varying environmental conditions is desired to better suit countries in Central America, South America, Southeast Asia, and sub-Saharan Africa that experience high temperatures and humid weather conditions. Countries in some of these regions also encounter frequent power disruptions. Therefore, tests that utilize alternative power sources, such as batteries, and reagents that do not require cold storage are more suitable for low-resource settings. In addition, the development of affordable tests and instrumentation would significantly enhance accessibility of these tests for low-resource countries. While the development and/or selection of lower cost tests, such as immunochromatographic, paper-based devices and microfluidic PCR-based plastic platforms, is a practical approach to lowering costs, large-scale

production of testing platforms can effectively lower cost as well. Exploring forward market mechanisms to fund early production of meningitis RDTs could permit large-scale production.

To create a diagnostic option for all levels of healthcare, the next generation of meningitis RDTs would also ideally incorporate the use of non-cerebral spinal fluid (CSF) specimens (e.g. urine and blood/serum). Acquiring CSF for meningitis diagnosis is a complex procedure performed by specifically trained medical staff. As a result, the procedure often precludes rapid clinical decision making at certain levels of care. Unfortunately, little is known regarding the detection, viability, and stability of meningitis associated pathogens and differential biomarkers in non-CSF specimens. Basic research exploring these areas would advance understanding and aid future RDT development.

Considering these factors, the intended use, most promising specifications, and value of next generation RDTs for meningitis are described.

Test for differentiation of bacterial and other non-bacterial infections

The care of patients with suspected meningitis largely depends on whether the cause of infection is bacterial or non-bacterial. Until a causative pathogen is identified, standard treatment for bacterial meningitis, ceftriaxone once daily for 5 days, is initiated (WHO, 2007). To guide clinical treatment at the POC level, an RDT capable of differentiating meningitis infection is needed.

Several studies have identified biomarkers capable of serving as indicators for bacterial infection in patients with suspected meningitis, and as such, can inform decisions on immediate case management. C-reactive protein (CRP), procalcitonin (PCT), heparin binding protein (HBP), glucose, and a two-transcript signature (interferon-induced protein 44-like [IFI44L] and family with sequence similarity 89, member A [FAM89A]) have emerged as leading biomarkers (detectable in CSF and/or blood, serum, and plasma) for differentiating acute bacterial meningitis infection from a viral infection with relatively high sensitivity (90%-100%) and specificity (91%-99.2%) (Linder et al., 2011; Tamune et al., 2014; Vikse et al., 2015; Herberg et al., 2016; Sanaei Dashti et al., 2017; Rousseau et al., 2019). Antibodies targeting protein biomarkers of meningitis infection can be captured by immunology based

RDT platforms. The lateral flow platform is an ideal candidate given its compatibility with all resource settings and healthcare levels due to features such as ambient storage, ease of use, standalone capability, low cost, and potential for high sensitivity (Koczula and Gallotta, 2016). Research and diagnostic companies are now utilizing advanced technology and analytical tools, to improve sensitivity and specificity of the lateral flow platform (Hsieh et al., 2017). Irrespective of the platform, the reliability of selected biomarker(s) should be assessed in studies involving patients from all regions where the test will be frequently used to ensure high performance.

The use of a biomarker RDT at the POC level should not delay initiation or prompt discontinuation of the standard antibiotic treatment for bacterial meningitis, however a non-bacterial RDT result could accelerate a clinician's exploration of other meningitis etiologies. Additionally, providing a diagnostic option at the POC level could promote routine CSF collection from patients with suspected meningitis, particularly in countries where the process is an integral component of meningitis disease surveillance.

Test for pathogen identification at healthcare facilities

Enhancing the ability of laboratories at healthcare facilities, such as hospitals at the peripheral and intermediate levels, to identify the causative pathogen of suspected meningitis cases can greatly improve patient diagnosis and care. To be effective, the test should be able to detect most meningitis pathogens (bacterial, viral, fungal, and parasitic), at a minimum the "Category A" high priority pathogens listed in the multi-pathogen meningitis in vitro diagnostic test target product profile (TPP; WHO, 2020b), with a high degree of sensitivity and specificity. Multiplex molecular-based platforms satisfy these criteria; they are high performance and allow a single clinical specimen to be tested for multiple pathogens in a single reaction or a single run (Notomi et al., 2000; Markoulatos et al., 2002). The "Category A" pathogen list includes region-specific pathogens often excluded from currently available molecular-based platform. Therefore, the development of an affordable multiplex molecular-

based platform that detects the “Category A” pathogens would benefit all resource settings by providing a diagnosis that can rapidly inform the clinical treatment of patients.

Availability and use of a multiplex molecular-based next generation RDT could also reduce the emergence of antibiotic resistance given the current practice to administer antibiotics to patients with suspected meningitis in the absence of laboratory confirmation. Antibiotic resistance is not yet an issue for Nm; however, there is concern for Hi and Sp (WHO, 2007; Kim et al, 2016; Kohler et al., 2019)).

Test for pathogen characterization to enhance surveillance and outbreak response

In epidemic settings, healthcare facilities require rapid identification of the causative pathogen to inform outbreak management efforts. In the meningitis belt, where most meningitis outbreaks are caused by Nm (Agier et al., 2017; Trotter et al., 2017; Fernandez et al., 2019), serogroup identification is also needed to direct an appropriate mass vaccination response. Providing peripheral level facilities with an affordable RDT that differentiates Nm serogroups can lead to early identification of outbreaks and eliminate delays in the activation of mass vaccination campaigns. The lateral flow RDT platform, as described previously, is a setting appropriate option that can provide this capability. Additionally, monitoring data collected from this test may also reveal regional epidemiologic trends in the incidence or prevalence of meningitis disease that could inform decisions on public health prevention measures.

SUMMARY

As meningitis continues to devastate populations around the world, the need for appropriate meningitis RDTs cannot be understated. Their availability and use can significantly improve patient care, surveillance, and outbreak response; and lead to a reduction in meningitis morbidity and mortality worldwide. The characteristics of several immunological and molecular-based meningitis RDT platforms have been discussed along with their limitations to highlight the need for next generation meningitis RDTs and the value of their development. While the next generation sequencing technology is also increasingly utilized as a diagnostic platform in clinical settings due to its ability to detect various pathogens from culture and clinical specimens, the time to result and cost are limitations that exclude the

technology as a viable next generation meningitis RDT platform in the foreseeable future (Chiu and Miller, 2019). The WHO has prioritized the development of a molecular-based multiplex meningitis RDT capable of detecting a broad panel of pathogens. As a first step, the WHO engaged partners in the drafting of a TPP for the RDT, which will serve as a research and development guide for potential developers/manufacturers. Next steps, including market analysis and the development of TPPs for other identified testing needs, will depend on collaborative partnerships and the identification of funding mechanisms.

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TABLE LEGEND

Table 1. Summary of commercially available latex agglutination tests, their features, and limitations.

Kit	Antigens to:	Specimen Type	Time to Result	No. of Tests per Kit	Cost per Kit (USD[“])	Limitations
Wellcogen™ Bacterial Antigen Kit	*Streptococcus* group B, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Neisseria meningitidis* groups A, C, Y or W, *Neisseria meningitidis* group B/ *Escherichia coli* K1	Blood culture, plate culture[±], CSF[#], serum, urine	3 minutes	30	1967.00[+]	• Costly • Not all meningitis etiological agents are detected • Cold storage required • Operation by trained/experienced staff • Cross-reactivity with other bacterial species
Pastorex™ Meningitis	*Neisseria meningitidis* groups A, C, Y or W, *Escherichia coli* K1, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Streptococcus* group B	Blood culture, CSF[#], serum, urine	5 to 10 minutes	25	384.91[≠]	
BD Directigen™ Meningitis Latex Test System	*Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Neisseria meningitidis* groups A, B, C, Y or W, *Escherichia coli* K1, *Streptococcus* group B	Blood culture, CSF[#*], serum[*], urine	15 to 20 minutes	90	2464.89[§]	

[*]Only specimen types for *Streptococcus* group B
[±]Additional specimen type for *Neisseria meningitidis* group B and *Escherichia coli* K1
[#]Cerebrospinal fluid
[“]United States Dollar
[+]Fisher Scientific
[≠]Bio-Rad (United Kingdom: £315.00), price not available on United States website
[§]VWR

Table 2. Summary of immunochromatographic tests, their features, and limitations.

Test	Antigens to:	Specimen Type	Time to Result	No. of Tests per Kit	Cost per Kit (USD[“])	Limitations
Abbott™ BinaxNow™ Antigen Card	*S. pneumoniae*	CSF[#], urine	15 minutes	22	374.00[§]	• Not all Nm serogroups are detected • Sp serotypes are not detected • Not all meningitis etiological agents are detected • Large specimen volume required for test
BioSpeedia MeningoSpeed	*N. meningitidis* groups A, C, Y, W, and X	CSF[#]	3 to 10 minutes	20	545.40	
BioSpeedia PneumoSpeed	*S. pneumoniae*	CSF[#], urine	3 to 15 minutes	20	136.40	
CERMES Duplex Dipstick	*N. meningitidis* groups A, C, Y and W	CSF[#]	10 to 15 minutes	NA	NA	
NmX Dipstick	*N. meningitidis* group X	CSF[#], bacterial suspensions in PBS	10 to 15 minutes	NA	NA	

Abbreviations: *S. pneumoniae, Streptococcus pneumoniae*; *N. meningitidis, Neisseria meningitidis*

[#]Cerebrospinal fluid

[“]United States Dollar

[§]Abbott Rapid Diagnostics (formerly Alere)

NA – not applicable; test not commercially available

599 **Table 3.** Summary of commercially available molecular rapid diagnostic tests and their features.

Test	Targets	Specimen Type	Time to Result	No. of Tests per Kit	Cost per Kit (USD[«])	Test-specific Instrument Cost (USD)	Limitations
FilmArray® Meningitis/Encephalitis Panel	14 bacterial, viral, and yeast targets (including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*)	CSF[#]	1 hour	30	5,790.00[¥]	85,000[¥*]	• Costly • Not all meningitis etiological agents are detected • Labor intensive • Testing procedure requires use of electrically powered equipment
VIASURE *H. influenzae + N. meningitidis + S. pneumoniae* Real Time PCR Detection Kit	3 bacterial targets	CSF, blood	~ 2 hours[£]	96	1,273.00-1,364.00[^]	NA	
FTD Viral meningitis	6 viral targets (Herpes simplex 1 and 2, Varicella zoster virus, Mumps virus, Enterovirus, Human parechovirus)	CSF, blood	~ 90 minutes [£]	32	436.96	NA	
FTlyo Viral meningitis	6 viral targets (Herpes simplex 1 and 2, Varicella zoster virus, Mumps virus, Enterovirus, Human parechovirus)	CSF, blood	~ 90 minutes [£]	32	483.65	NA	
FTD Bacterial meningitis	3 bacterial targets (including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis)*	CSF, blood	~ 90 minutes [£]	32	370.20	NA	
FTlyo Bacterial meningitis	3 bacterial targets (including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis)*	CSF, blood	~ 90 minutes [£]	32	410.22	NA	
FTD Neuro 9	10 viral targets (including Epstein-Barr virus, Human adenovirus,	CSF, blood	~ 90 minutes [£]	32	682.20	NA	

	Herpes simplex 1 and 2, Varicella zoster virus, Enterovirus, Human parechovirus, Human herpesviruses 6 and 7, Human parvovirus B19)						
NHS Meningitidis Real-TM	3 bacterial targets (including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis)*	CSF	~ 45 minutes to 1 hour[£]	50	840.00	NA	
Allplex™ Meningitis-B Assay	5 bacterial targets (including *Escherichia coli* K1, Group B *Streptococcus*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Neisseria meningitidis*)	CSF	~ 2 hours[£]	100	1,860.00	31,311[≠]	
Allplex™ Meningitis-V1 Assay	7 viral targets (Cytomegalovirus, Epstein Barr virus, Herpes simplex virus type 1 and 2, Human herpes viruses 6 and 7, Varicella zoster virus	CSF	~ 2 hours[£]	100	1,860.00	31,311[≠]	
Allplex™ Meningitis-V2 Assay	5 viral targets (Adenovirus, Enterovirus, Human parechovirus, Mumps virus, Parvovirus B19)	CSF	~ 2 hours[£]	100	1,860.00	31,311[≠]	
Primer Design™ Ltd Neisseria meningitidis Superoxide dismutase (sodC) gene genesig® Standard and Advanced Kits	*Neisseria meningitidis*	All types	~1 hour[£]	150	924.80-1,147.50	NA	
Eazyplex® CSF	3 viral and 4 bacterial targets (Herpes simples virus types 1 and 2, Varicella zoster virus,	CSF	~30 minutes	12	937.94	13,872.51[α]	

	Haemophilus influenzae, Neisseria meningitidis, Streptococcus agalactiae, Listeria monocytogenes)						
Eazyplex® CSF Direct V	3 viral targets (Herpes simples virus types 1 and 2, Varicella zoster virus)	CSF	~30 minutes	12	471.78	13,872.51[α]	
Eazyplex® CSF Direct M	6 bacterial targets (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus agalactiae, Listeria monocytogenes, Escherichia coli* K1)	CSF	~30 minutes	12	606.57	13,872.51[α]	

^Cost for 12 8-well strips and 96 well plate

NA – compatible with a variety of instruments

[#]Cerebrospinal fluid

“United States Dollar

[¥]BioFire®

[*]BioFire® FilmArray® Torch base plus two module boxes

[£]Does not include sample preparation

[α]Genie® II instrument

[≠]CFX96™ Bio-Rad