Meningitis Diagnostics Use Cases

Authors:
Laura Mazzola and Cassandra Kelly-Cirino
Foundation for Innovative New Diagnostics (FIND)
Chemin des Mines 9, Geneva, 1209, Switzerland, www.finddx.org

Abbreviations

CLIA	chemiluminescence immunoassay
CSF	cerebrospinal fluid
ECL	electrochemiluminescence immunoassay
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
LAT	latex agglutination test
LAMP	loop-mediated isothermal amplification
LFA	lateral flow assay
LP	lumbar puncture
NAT	nucleic acid test
Nm	*Neisseria meningitidis*
PCR	polymerase chain reaction
POC	point of care (test)
RDT	rapid diagnostic test
TPP	target product profile
WB	western blot

Introduction

This report describes the most critical diagnostics needed for meningitis outbreak control, as identified by the WHO Meeting Report: Developing a new generation RDTs for Meningitis in Geneva, March 2018.[1] Diagnostic "Use Cases" are presented as specific examples for testing within the patient care pathway for meningitis, identifying the needed diagnostic implementation and impact. Each Use Case defines a specific intended use, the clinical impact or goal, the target patient population and appropriate setting, and the skill level and training required for the person administering the test. Altogether, the Use Case parameters define the critical functionality and performance of a diagnostic test in the setting where it is most needed. With clearly defined Use Cases, it is then possible to assess whether existing diagnostics can meet the need or whether a push for development is required.

Meningitis Overview

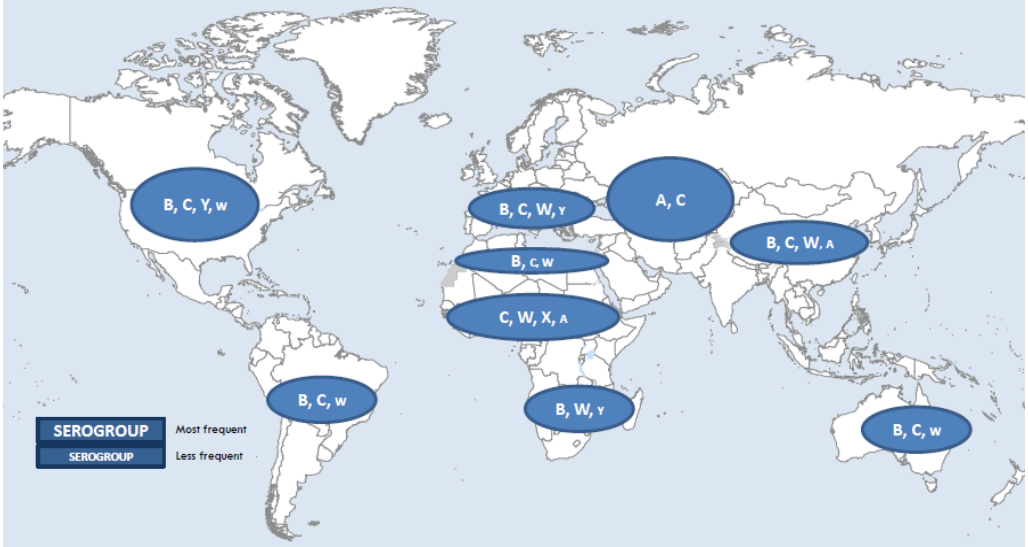
Meningitis is a serious infection of the meninges, the membrane surrounding the brain and spinal cord.[2,3] A variety of bacteria, fungi and viruses can cause meningitis. Meningococcal meningitis, caused by *Neisseria meningitidis* bacteria, is of particular concern due to its potential for large epidemics, causing severe brain damage and fatality in 50% of untreated cases. Meningococcal meningitis is observed worldwide, but the highest burden of the disease is in the "meningitis belt" of sub-Saharan Africa from Senegal to Ethiopia, with approximately 30,000 cases reported each year. In particular, meningitis is a major cause of death in children under 5 years old.

The most common symptoms of meningitis include a stiff neck, high fever, sensitivity to light, confusion, headaches and vomiting. [2,3] Even when diagnosed and treated early, 8%-15% of patients die within 48 hours of the symptom onset. Untreated meningococcal meningitis is fatal in 50% of cases; non-fatal meningitis may result in brain damage, hearing loss or a learning disability in 10%-20% of survivors. Nm bacteria are transmitted from person-to-person through droplets of respiratory fluids of carriers. The African dry season of December to June shows increased cases of meningococcal disease, likely due to crowded conditions combined with mucosal vulnerability from dust and common respiratory infections. Meningitis can occur at any age, but it has particularly virulence for babies and children.[2,4]

Neisseria meningitidis (Nm) causes the majority of meningitis epidemics in Africa, as well as the more severe meningococcal septicaemia. Other bacterial causes of meningitis include *Haemophilus influenza* type b, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Escherichia coli K1*, *Listeria monocytogenes*, and *Staphylococcus aureus*. Viral causes of meningitis include herpes simplex virus 1 and 2, varicella zoster virus, enterovirus, mumps virus, herpesvirus, parechovirus, cytomegalovirus, and measles virus.

Nm serotype distribution varies worldwide, with six Nm serogroups (A, B, C, W, X, Y) responsible for most epidemics in Africa (Figure 1). Notably, a new meningococcal meningitis clone of serogroup C is expanding in Sub-Saharan Africa, associated with a huge risk of a major epidemic in the next two years (2019-2020). This new strain is hyper invasive, population immunity is low, and it is easily spread to neighboring countries.[2,3] In 2017, 35% of confirmed cases were due to Nm serogroup C (NmC), 13% were NmX, 10% NmW, and 27% Streptococcus pneumoniae. The persisting high incidence of NmC meningitis is of major concern.[5]

Figure 1: Invasive Meningococcal Disease – Nm Serogroup distribution, 2018
Source: http://www.who.int/emergencies/diseases/meningitis/serogroup-distribution-2018.pdf



Treatment and Prevention

For bacterial meningitis, hospitalization and early treatment with antibiotics is the key to saving lives. Antibiotic prophylaxis for close contacts can also decrease the risk of transmission. Currently there is no universal vaccine against meningococcal (Nm) disease. Several serogroup-specific vaccines have been developed for prevention (preferably routine immunization) and as outbreak response for targeted vaccination in transmission hotspots.[2,3] Conjugate vaccines are used in routine immunization and prevention campaigns, which include monovalent vaccines for NmC, NmA, and a tetravalent vaccine for Nm serogroups A/C/Y/W. Used for patients above one years of age, these vaccines confer 5+ years of immunity. Polysaccharide vaccines are used in response to outbreaks, effective as bivalent (A/C), trivalent (A/C/W), or tetravalent (A/C/Y/W) Nm serogroups. Effective in patients above 2 years of age, these vaccines confer 3 years of protection but do not induce herd immunity. A recent protein-based vaccine against NmB has been introduced for both routine immunization and outbreak response. As of 2017, vaccines against meningitis-causing agents *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and mumps have been introduced into 135, 191, and 122 countries, respectively.

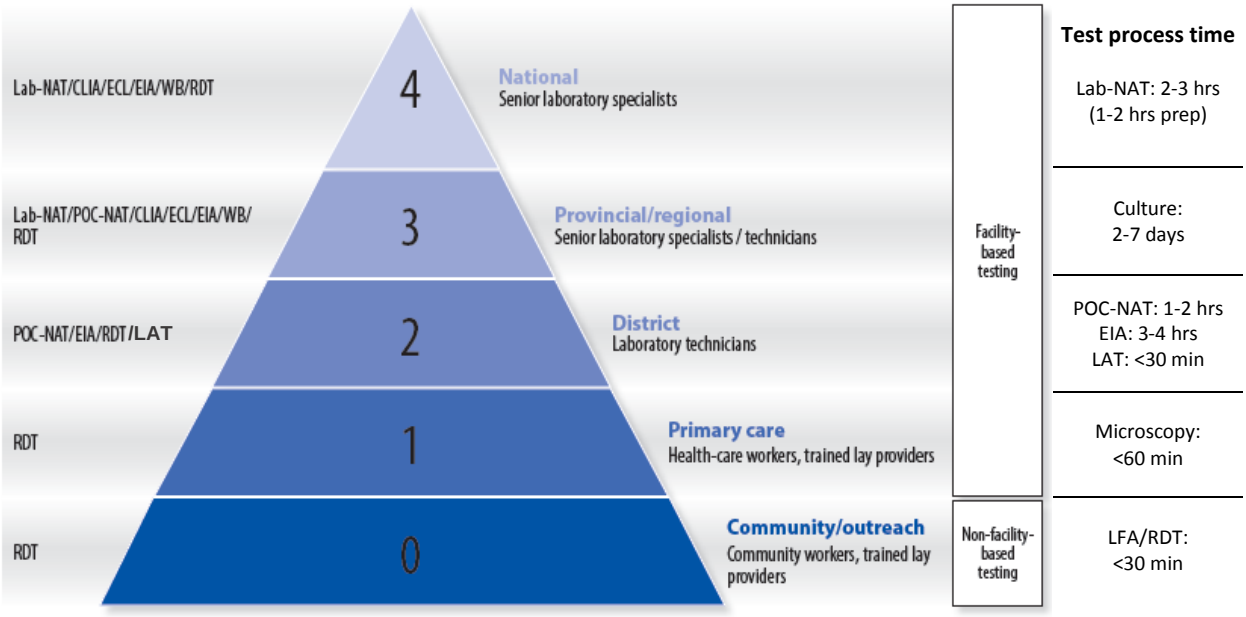
Diagnosis of Meningococcal meningitis

Rapid diagnosis and identification of the disease is essential to direct the appropriate interventions for treatment and epidemic control, particularly in settings where patients are first encountered in the early stage of an outbreak.[3,6,7] Tests generally have lower sensitivity following early antibiotic treatment, which drives the need for a rapid screening prior to initiation of treatment.[8,9] Diagnostic tests require different levels of laboratory infrastructure and training, depending on the test. Figure 2 presents an illustrative schematic for the kind of tests that can be supported within the specified laboratory settings, allowing for variation according to country infrastructure and support.

Meningitis can be diagnosed by clinical examination followed by a lumbar puncture for interrogation of the cerebrospinal fluid (CSF). For Meningococcal meningitis, the bacteria can sometimes be detected by microscopy

with the diagnosis confirmed by culture, agglutination tests, Nm protein antigen detection, or by nucleic acid tests such as PCR. Test process time (time from specimen collection to result) is representative for each process, and can include additional time (days to weeks) if specimen transport and batch processing are required. Commercial assays currently available are listed in Annex A.

Figure 2: Diagnostic Capacity and Laboratory Infrastructure
Source: Adapted from WHO 2017 Guidance for procurement of in vitro diagnostics and related laboratory items and equipment



Assay limitations

Culture. Culture-based testing requires the highest laboratory infrastructure for isolation and biosafety due to contamination issues. Culture typically takes up to 7 days after specimen preservation or transportation from remote facilities.

Nucleic acid tests. Nucleic acid tests (NAT) such as laboratory-based PCR are highly sensitive but require sophisticated laboratory infrastructure including biosafety cabinets to avoid contamination issues, as well as highly skilled laboratory technicians. Other assays such as LAMP are less susceptible to contamination but still require a modest laboratory environment and user training. Multiplex PCR panels have been developed for meningitis pathogens and syndromic diseases using PCR kits for (3 species per tube), and array-based platforms (14-20 species per array); these platforms require the highest level of skill and laboratory infrastructure.[10,11] At the other end of the spectrum, point-of-care (POC) nucleic acid tests are fully automated and can be run in a near-patient laboratory by clinic staff after moderate training, though POC meningitis assays are currently available only for tuberculosis meningitis.[12,13]

Immunoassays. Enzyme immunoassays (EIA/ELISA) are laboratory-bases assays that can be run in a more modest laboratory environment by a skilled laboratory technician. These tests are less prone to contamination than PCR but may be less sensitive to acute infection, depending on the protein (IgG, IgM, antigen) detected. They are not currently used for diagnosis of meningitis.

Latex agglutination tests. Latex agglutination tests (LATs) are available in most countries at district level laboratories (level 2), as they require laboratory equipment (refrigerator, centrifuge) and cold storage.[7] LATs require training and have multiple steps for processing, with separate reagents for each pathogen and serotype. Current LAT tests do not differentiate all known Nm serogroups; PASTOREX™ MENINGITIS (Bio-Rad, France) test can detect Nm serogroups A, B, C, and W/Y but does not differentiate between W and Y. Despite these limitations, the test is used for outbreak detection and identification of the responsible strain(s). Their role for individual diagnosis is less established.

Lateral flow assays (rapid diagnostic tests). Lateral flow assays (LFA/RDTs) generally do not require cold chain transport or storage, and can be performed after minimal training. For meningitis, these RDTs can be used with unprocessed CSF specimens. The two-dipstick CERMES/Pasteur RDT can differentiate four Nm serogroups (A, C, W, Y) under laboratory conditions and is being used in the peripheral health centers (Levels 1 and 2) of Niger;[14,15] in addition to a newer RDT for the Nm X serotype.[16] The three-device RDT called MeningoSpeed (Biospeedia, France) can differentiate five Nm serogroups (A, C, W, X, Y) and is currently under field evaluation.[5] Several assays for *Streptococcus pneumoniae* such as BinaxNOW™ (Alere, USA), an immunochromatographic LFA, are on the market and have demonstrated good performance with both urine and CSF.[17,18]

Use Cases: Meningitis Test Scenarios

For the top three test priorities identified by the WHO 2018 Meningitis Report,[1] diagnostic Use Cases are presented below for three key scenarios within the patient care pathway for meningitis. Each Use Case defines a specific intended use, the target patient population and appropriate setting, the skill level and training required for the person administering the assay, and the clinical impact or goal. For rural and hard-to-reach patients, assays are needed that can be performed in low-infrastructure peripheral clinics (Levels 0-1) as well as higher infrastructure hospital settings (Levels 2-4). As meningitis confirmation requires a lumbar puncture, CSF sampling may be carried out in health facilities with this capacity or may be limited to district and regional hospitals if capacity is limited in the health facilities (Use Case 1).

Use Case 1: Epidemic/outbreak setting (Africa) – Identification of Nm serogroup at peripheral level (health center or district hospital) for appropriate vaccine response

For response to a meningococcal meningitis outbreak, it is critical to quickly identify the Nm serogroup in order to guide the appropriate vaccine response. Where vaccination is possible, a RDT for screening might be sufficient without the need for confirmation of all tests. In the epidemic setting of the Meningitis belt, there is a need to identify the causative organism (meningococcal serogroup) rapidly at peripheral level (heath center/district hospital) to determine vaccine response.[1]

Use Case 1: Outbreak vaccine response (Africa)		
Clinical Impact	Appropriate vaccine response to an meningococcal epidemic/outbreak	
Intended Use	Detection and differentiation of *Neisseria meningitidis* serogropus A/B/C/W/X/Y	
Test Purpose	Screening assay at peripheral level – specimens sent to regional/reference laboratory for confirmation	
Type of Result	Qualitative detection of Nm and identification of serotype (or negative for Nm)	
Target Population	Patient meeting the clinical definition of suspect case of bacterial meningitis, presenting to health care facility	
Target Setting	**1A: Health facility, no LP capacity (L1)** Decentralized health care facility with minimal laboratory infrastructure. Facilities do not support lumbar puncture or centrifugation. Point-of-care RDTs may be performed.	**1B: Health facility, LP capacity (L1/L2)** Health care facility or near-patient hospital laboratory which supports lumbar puncture and centrifugation. A cerebrospinal fluid (CSF) sample from a suspect patient is tested within one hour from the time of collection.
Cold Chain Resources	None	4-8°C for storage, as required
Target User	Doctor, nurse, healthcare worker	Laboratory technician, as required
Specimen Type	Minimally invasive: capillary whole blood, oral fluid, urine, stool	LP/CSF, capillary whole blood, venous whole blood, serum, plasma, oral fluid, urine, stool
Sample Prep	Minimal complexity	Minimal-Moderate complexity (no laboratory-NAT)
Time to Result	Patient may need referral, <1 hour	Hospital in-patient, <6 hours
Test Throughput (maximum)	5-20 per day*	up to 50 per day*
Setting-Appropriate Test Format	LFA/RDT	LFA/RDT, LAT, EIA

*vaccine response will not need to track all patients

Use Case 2: Epidemic and endemic settings (worldwide) – Identification of bacterial meningitis/septicaemia at peripheral level (health clinic or hospital) to initiate antibiotic treatment (yes/no) for case management

For case management in both endemic and epidemic settings, it is critical to identify the type of pathogen (bacterial vs. viral) in order to initiate treatment at first contact with the patient, e.g. initiate antibiotics for bacterial infection. Serogroup identification for Nm is less important for clinical management, as it would not change the antibiotic regimen. This test would have the greatest impact when implemented at the peripheral healthcare level, where a capillary whole blood RDT would be ideal. Results would be integrated into clinical algorithms for treatment and referral.[1]

Use Case 2: Case management for treatment initiation (worldwide)		
Clinical Impact/Goal	Appropriate treatment response – initiate antibiotics yes/no	
Intended Use	Identify bacterial meningitis (vs. viral or non-meningitis disease)	
Test Purpose	Screening assay at peripheral level – specimens sent to regional/reference laboratory for confirmation	
Type of Result	Qualitative detection of bacterial meningitis	
Target Population	Patient meeting the clinical definition of suspect case of meningitis, presenting to health care facility	
Target Setting	**2A: Health clinic, no LP capacity (L0/L1)** Health care facility with minimal laboratory infrastructure, may include outreach. Facilities do not support lumbar puncture or centrifugation. Point-of-care RDTs may be performed.	**2B: Hospital, LP capacity (L1/L2)** Health care facility or near-patient hospital laboratory which supports lumbar puncture and centrifugation, may support POC-NAT. A cerebrospinal fluid (CSF) sample from a suspect patient is tested within one hour from the time of collection.
Cold Chain Resources	None	4-8°C for storage
Target User	Doctor, nurse, healthcare worker	Laboratory technician
Specimen Type	Minimally invasive: capillary whole blood, oral fluid, urine, stool	CSF, capillary whole blood, venous whole blood, serum, plasma, oral fluid, urine, stool
Sample Prep	Minimal complexity	Minimal-Moderate complexity (no lab-NAT)
Time to Result	Patient may need referral, <1 hour	Hospital in-patient, <1 hour
Test Throughput (maximum)	5-20 per day	up to 100 per day
Setting-Appropriate Test Format	LFA/RDT	LFA/RDT, LAT, EIA, POC-NAT (simple multiplex)

Use Case 3: Epidemic and endemic settings: Syndromic meningitis panel (minimum 10 pathogens) at hospital level (district/regional hospital) for case management: stopping or changing antibiotics

Since many of the symptoms of meningitis are similar to other endemic diseases, it is critical to differentiate the source of infection from other syndromic pathogens in order to determine the appropriate treatment regimen, including as switch treatment or terminate inappropriate treatment. Given the complexity of the assay, it would likely be implemented at hospitals with higher infrastructure. Ideally the test would differentiate pathogens such as *N.meningitidis, S.pneumoniae, H.influenzae* type b, Salmonella, Listeria, Group B streptococci, echovirus, coxsackievirus, varicella zoster virus, enterovirus, herpes simplex, Cryptococcus from CSF or venous whole blood. The assay needs to be highly specific and sensitive to influence case management (stopping /changing antibiotics).[1] The test happens at hospital level on samples from in-patients or on samples referred from a health facility that is geographically close.

Use Case 3: Case management to stop or switch treatment (worldwide)		
Clinical Impact/Goal	Appropriate treatment intervention – stop or switch treatment	
Intended Use	Detection and differentiation of meningitis infection (syndromic panel)	
Test Purpose	Diagnosis or aid for diagnosis (to confirm result of screening assay)	
Type of Result	Qualitative detection and differentiation of bacterial and viral pathogen(s) causing symptoms similar to meningitis	
Target Population	Patient meeting the clinical definition of suspect case of meningitis, presenting to health care facility	
Target Setting	**3A: Hospital (L1/L2)** Health care facility or hospital laboratory which supports lumbar puncture and centrifugation, may support POC-NAT. A cerebrospinal fluid (CSF) sample from a suspect patient is tested within three hours from the time of collection.	**3B: Regional Hospital (L3)** Sophisticated laboratory which supports lumbar puncture and centrifugation, POC/lab-NAT, EIA/ELISA. A cerebrospinal fluid (CSF) sample from a suspect patient is tested within three hours from the time of collection.
Cold chain Resources	4-8°C for storage	4-8°C, -20°C for storage
Target User	Laboratory technician	Laboratory technician / specialist
Specimen Type	CSF, capillary whole blood, venous whole blood, serum, plasma, oral fluid, urine, stool	CSF, capillary whole blood, venous whoel blood, serum, plasma, oral fluid, urine, stool
Sample Prep	Minimal-Moderate complexity (no lab-NAT)	Moderate-High complexity
Time to Result	Hospital in-patient, <6 hours	Hospital in-patient, <6 hours
Test Throughput (maximum)	5-20 per day	up to 100 per day
Setting-Appropriate Test Format	LFA/RDT, LAT, POC-NAT (simple multiplex), EIA if higher level lab	LFA/RDT, LAT, EIA, WB, POC-NAT (simple multiplex), lab-PCR

Meningitis diagnostics and use cases

The 2018 WHO Meningitis meeting report recommended priority goals for the development and implementation of point-of-care diagnostics for 1) rapid detection of *Neisseria meningitidis* serotype at the peripheral healthcare level to determine the appropriate vaccine response, 2) rapid identification of bacterial meningitis at the peripheral healthcare level for appropriate initiation of antibiotics, and 3) multiplex pathogen testing at the hospital level to influence case management treatment (stopping or changing antibiotics).

For these goals, diagnostic "Use Cases" have been presented for meningitis testing within the patient care pathway. Each Use Case defined a specific healthcare scenario for diagnostic implementation and impact; defining the necessary functionality and performance of assays in the setting where it is most needed. With clearly defined Use Cases, it is then possible to assess whether existing diagnostics can meet the need or whether a push for development is required. For clearly defined needs, a set of target product profiles (TTPs) can be developed as a framework for assay development to address the gaps in meningitis outbreak management. In particular, diagnostics for use at POC are needed at the peripheral level to rapidly identify bacterial meningitis and Nm serotype, in order to guide the appropriate treatment and vaccine response, respectively.

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Annex A

Pathogen:	Meningitis (including bacteria, viral, fungal infection)
UC 1A:	Use Case 1 - Differential detection of Nm serogroups; A (LFA/RDT)
UC 1B:	Use Case 1 - Differential detection of Nm serogroups; B (LFA/RDT, LAT, EIA)
UC 2A:	Use Case 2 -Identification of bacterial meningitis (vs. viral or non-meningitis disease); A (LFA/RDT)
UC 2B:	Use Case 2 - Identification of bacterial meningitis (vs. viral or non-meningitis disease); B (LFA/RDT, LAT, EIA, POC-NAT)
UC 3A:	Use Case 3 - Syndromic panel for detection and differentation of meningitis; A (LFA/RDT, LAT, POC-NAT)
UC 3B:	Use Case 3 - Syndromic panel for detection and differentation of meningitis; A (LFA/RDT, LAT, EIA, POC-NAT, lab-NAT)

Notes: *Presumptions: 1) bacterial meningitis tests must include Nm, 2) syndromic panels must include viruses and bateria*
"?" indicates kit appropriate for lab-NAT but could be packaged for POC-NAT
"combo" indicates multiple tests could be used in parallel to achieve intended use (e.g. Nm RDT + S.pneu RDT)

Assay Type	UC 1A	UC 1B	UC 2A	UC 2B	UC 3A	UC 3B	Developer	Assay/System	Regulatory status	Product Links	Sample Type	Assay Target
NAT kit							**ELITECH (FRA)**	**MGB Alert® Enterovirus, EBV Probe/Primers**	RUO	https://www.elitechgroup.com/north-america/product/ruos/	plasma, serum, CSF	detect **viruses**: nucleic acid sequences from Enterovirus, EBV
NAT kit							**genesig** (UK) (Primerdesign Ltd)	**Neisseria meningitidis PATH-N.meningitidis**	RUO	http://www.genesig.com/products/9364-neisseria-meningitidis	Purified PCR samples	Quantitative detection of **Neisseria meningitidis** superoxide dismutase (sodC) gene; separate kits for CMV, EBV, VZV, HIV, HSV, BKV, flu, lepto, lyme disease, mumps, enterovirus, parechovirus, streptococcus (SZ, SE, pneu)
NAT kit multiplex				?			**CerTest Biotec** (ES)	**MULTIPLEX H. influenzae + N. meningitidis + S. pneumoniae**	CE	https://www.certest.es/products/multiplex-h-influenzae-n-meningitidis-s-pneumoniae/	cerebrospinal fluid or blood samples	detection and differentiation of **bacteria:** Haemophilus influenzae, Neisseria meningitidis and/or Streptococcus pneumoniae
NAT kit multiplex							**CerTest Biotec** (ES)	**MULTIPLEX S. agalactiae, L. monocytogenes & E. coli**	CE	https://www.certest.es/products/multiplex-s-agalactiae-l-monocytogenes-e-coli/	cerebrospinal fluid, blood or culture samples	detection and differentiation of **bacteria:** Streptococcus agalactiae, Listeria monocytogenes and/or Escherichia coli
NAT kit multiplex				?			**Fast-track Diagnostics** (Malta, acquired by Siemens 2017)	**FTD Bacterial Meningitis**	CE	http://www.fast-trackdiagnostics.com/human-line/products/ftd-bacterial-meningitis/	Cerebrospinal fluid (CSF) and EDTA or citrated blood	Quantitative detection of **bacteria**: Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae

NAT kit multiplex							**Fast-track Diagnostics**	**FTD Neonatal Meningitis**	CE	http://www.fast-trackdiagnostics.com/human-line/products/ftd-neonatal-meningitis/	Cerebrospinal fluid (CSF) and EDTA or citrated blood sample	Quantitative detection of **bacteria**: Streptococcus Group B, Listeria monocytogenes, Escherichia coli
NAT kit multiplex							**Fast-track Diagnostics**	**FTD Viral Meningitis**	CE	http://www.fast-trackdiagnostics.com/human-line/products/ftd-viral-meningitis/	Cerebrospinal fluid (CSF) and blood (without heparin)	Quantitative detection of **viruses**: herpes simplex virus 1 and 2, varicella zoster virus, enterovirus, mumps virus, human parechovirus
NAT kit multiplex							**Fast-track Diagnostics**	**FTD Neuro 9**	CE	http://www.fast-trackdiagnostics.com/human-line/products/ftd-neuro-9/	Cerebrospinal fluid (CSF) and blood (without heparin)	4 tubes: Quantitative detection of **viruses**: human cytomegalovirus, Epstein-Barr virus, human adenovirus, herpes simplex virus 1 and 2, varicella zoster virus, enterovirus, human parechovirus, human herpesvirus 6 and 7, human parvovirus B19
NAT kit multiplex							**Fast-track Diagnostics**	**FTD EPA**	CE	http://www.fast-trackdiagnostics.com/human-line/products/ftd-epa/	CSF, blood (without heparin), throat swabs, sputum and stool	Quantitative detection of **viruses** enterovirus, human parechovirus, human adenovirus
NAT kit multiplex				?			**Sacace Biotechnologies** (Italy)	**NHS Meningitidis**	CE	https://sacace.com/neurological-infections.htm#s2	n/a	detection of **bacteria:** Neisseria meningitidis, Haemophilus influenzae and Streptococcus pneumoniae
NAT kit multiplex						X	**Seegene** (KOR)	**Allplex™ Meningitis Panel 1, 2, 3**	CE	http://www.seegene.com/neo/en/products/meningitis/allplex_meningitis_fp.php	cerebrospinal fluid (CSF)	Panel 1 (**Viruses**): Herpes simplex virus type 1, Herpes simplex virus type 2, Varicella-zoster virus, Epstein-barr virus, Cytomegalovirus, Human herpesvirus 6, Human herpesvirus 7; Panel 2 (**Viruses**): Parvovirus B19, Mumps virus, Parechovirus, Adenovirus, Enterovirus; Panel 3 (**Bacteria**): Haemophilus influenza, Streptococcus pneumoniae, Listeria monocytogenes, Neisseria meningitides, Group B Streptococcus, E.coli K1
NAT kit multiplex						X	**Seegene** (KOR)	**Seeplex® Meningitis ACE Detection Panels 1, 2, 3**	CE	http://www.seegene.com/neo/en/products/meningitis/seeplex_MENINGITIS.php	cerebrospinal fluid (CSF)	Panel 1 (**Viruses**): HSV 1, HSV 2, VZV (HHV3), EBV (HHV4), CMV (HHV5)(CE0086), HHV6; Panel 2 (**Viruses**): Enteroviruses; Panel 3 (**Bacteria**): Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenza, Listeria monocytogenes, Group B Streptococcus, (Streptococcus agalactiae)
NAT kit multiplex						X	**DiagCor** (KOR)	**GENOFLOW R14004**		http://www.medicalexpo.com/prod/diagcor-bioscience-incorporation-limited/product-83412-778647.html	CSF	detects 12 common **bacterial** pathogens for meningitis
NAT kit multiplex						X	**Pathofinder** (NL)	**MeningoFinder® 2SMART**	CE	http://www.pathofinder.com/products/twosmartfinder/meningofinder-2smart	cerebrospinal fluid (CSF)	**Viruses:** HSV 1/2, VZV, EBV, CMV, Human Herpesvirus 6/7/8, Human enterovirus, Parechovirus, Mumps, Measles; **Bacteria:** Listeria monocytogenes, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus agalactiae, Neisseria meningitides, Borrrelia burgoferi/miyamatoi, Echerichia coli K1
NAT kit multiplex platform						X	**BioFire Diagnostics** (USA) **/bioMerieux**	**Meningitis Encephalitis Panel (14 targets)**	CE	http://www.biofiredx.com/products/the-filmarray-panels/	CSF	**BACTERIA:** E.coli K1, H.influenza, L.monocytogenes, N.meningitides, Streptococcus agalactiae, Streptococcus pneumoniae; **VIRUSES:** Cytomegalovirus (CMV), Enterovirus, Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), Human herpesvirus 6 (HHV-6), Human parechovirus, Varicella zoster virus (VZV)
ELISA							**Dia.Pro** (IT)	**MENG IgG**	CE	https://www.diapro.it/index.php/products/elisa/serology/meningitis/meng-igg-detail	plasma, sera	determination of IgG antibodies to combined **N. meningitidis** groups ACWY Meningococcus, intended for the follow-up of patients administered with a meningococcal vaccine)

Latex agglutination		X		X			**Pastorex, BioRad**	**Pastorex Meningitis**	CE	http://www.bio-rad.com/en-uk/sku/61607-pastorex-meningitis-n-meningitidis-b-e-coli-k1-c-y-w135-h-influenzae-type-b-s-pneumoniae-group-b-streptococci-complete-kit-includes-controls-disposable-cards-sticks?ID=61607	CSF (Nm); CSF, serum, urine (non-Nm)	qualitative detection and differentiation of **N. meningitidis** A, B/**E.coli** K1, C, Y/W135, **H.Influenzae** Type b, **S. pneumoniae,** group B **streptococci**
Latex agglutination				X			**MKL diagnostics (Sweden)**	**Phadebact CSF Test**	CE	http://www.mkldiagnostics.com/products/phadebact-phadirect/meningitidis-infections.html	CSF	Four bottles: qualitative identification of **Streptococcus pneumoniae**, **Haemophilus influenzae** (type b), **Streptococcus** group B and **Neisseria meningitidis** (combined Nm groups A,B,C,Y and W135) antigens directly in spinal fluid
Latex agglutination		X		X			**BD/Fisher (USA)**	**Directigen™ Meningitis Latex Test System**	FDA CLIA	https://www.fishersci.com/shop/products/bd-directigen-meningitis-latex-test-system-meningitis-combo-test-cards-600-test-cards/l852480	CSF, serum, blood culture and urine	qualitative detection and differentiation of antigens to **H. influenzae** type b, **S. pneumoniae**, **N. meningitidis** groups A/Y, C/W135, and B/**E.coli** K1 in CSF, serum or urine. Can also be used for qualitative detection of antigens to group B **Streptococcus** in CSF and serum.
RDT/LFA			X combo	X combo			**Alere/Abbott**	**BinaxNOW Streptococcus pneumoniae Antigen Card**	CE	https://www.alere.com/en/home/product-details/binaxnow-streptococcus-pneumoniae.html	urine	qualitative detection of **S. pneumoniae** antigen in the urine of patients with pneumonia and in the cerebral spinal fluid (CSF) of patients with meningitis
RDT/LFA			X combo	X combo			**Biospeedia (FR)**	**PenumoSpeed**	CE	http://www.biospeedia.com/index.php/en/products-en/38-pneumospeed	CSF, urine	qualitative detection of **S. pneumoniae** capsule wall polysaccharides in urine and cerebrospinal fluid
RDT/LFA	X	X	X combo	X combo			**Biospeedia (FR)**	**MeningoSpeed**	CE	http://www.biospeedia.com/index.php/en/products-en/39-meningospeed	CSF	3 cassette tests: qualitative detection of **N. meningitidis** serogroups W/A, Y/C, X in cerebrospinal fluid
RDT/LFA	X	X	X combo	X combo			**CERMES/Pasteur Institute**	**CERMES RDT**	RUO	https://www.pasteur.fr/en/rapid-diagnosis-tests-meningococcal-meningitis	CSF	Two dipsticks: detection and differentiation of **N. meningitidis** polysaccharide (PS) antigens for meningococcus serotypes A, C, W135 and Y
RDT/LFA			X combo	X combo			**Vidia (Czch)**	**Rapid VIDITEST Streptococcus pneumoniae**	CE	https://www.vidia.cz/en/index.php/rapid-tests/diagnosis-of-respiratory-infection	urine	detection of **S. pneumoniae**
RDT/LFA							**Kypha**	no product listing		no product webpage		