Target product profile for a rapid, low-cost test to aid bacterial meningitis surveillance

Characteristic	Minimal	Preferred
Intended use	**Intended use for meningococcal vaccine response -** A public health test to rapidly detect meningococcal infection in suspected meningitis cases to inform outbreak investigation and vaccine response in the African meningitis belt	**Intended use for bacterial meningitis surveillance –** In addition to the minimal requirements, the test should identify other causative pathogens of bacterial meningitis to support routine surveillance in low-and-middle income countries, in non-outbreak settings[1]
Target use setting	Primary health care settings including health posts (Level 1 and above[2])[3] that have the necessary equipment and trained staff to perform lumbar punctures for CSF collection	Primary health care settings including health posts (Level 1 and above[2])[3]
Test format[4]	An instrument-free, single-use, disposable test kit that requires no additional laboratory equipment to perform the test procedure including sample preparation. The test kit includes all materials required for the test procedure, including devices, reagents or other consumables to test one individual, included in a packaged, self-contained kit. No additional consumables are required except for specimen collection. (A reader as an optional tool for result interpretation is acceptable)	Same as minimal except option from the manufacturer to purchase test kits with or without lumbar puncture sample collection kits for CSF collection (if a CSF sample is required)
Result display and interpretation	Visual interpretation of qualitative (yes/no) test results with the naked eye with minimal instructions for interpretation by the user required. In addition, results could be obtained with a reader system[5] that supports result interpretation	

[1] The test is not intended to support decision making about patient management

[2] Ghani AC, Burgess DH, Reynolds A, Rousseau C (2015). Expanding the role of diagnostic and prognostic tools for infectious diseases in resource-poor settings. *Nature* 528: S50-52

[3] Use of rapid testing at various health facilities levels are described in Annex 10 of Standard operating procedures for surveillance of meningitis preparedness and response to epidemics in Africa

[4] Other test formats (e.g. molecular tests) to support the intended use of bacterial meningitis surveillance appropriate for use above level 1 facilities are of importance to support surveillance, but are outside of the scope of this TPP

[5] Reader system requirements are defined by a WHO TPP for readers of rapid diagnostic tests (https://www.who.int/publications/i/item/9789240067172)

Characteristic	Minimal	Preferred
Target population	All patients, excluding neonates, meeting the suspect case of meningitis clinical definition presenting to a health care facility[6]	Same plus the inclusion of neonates
Target pathogens	**Intended use for meningococcal vaccine response –** Detection and differentiation of *Neisseria meningitidis* (Nm) serogroups A, C, X, Y, W	**Intended use for meningococcal vaccine response –** differentiation of Nm serogroup B in addition to minimal targets for this intended use
	Intended use for bacterial meningitis surveillance – Detection and differentiation of Nm serogroups A, B, C, X, Y, W; *Haemophilus influenzae* type B (Hib); and identification of *Streptococcus pneumoniae* (Spn)	**Intended use for bacterial meningitis surveillance –** minimal plus differentiation of Spn serotype 1
USER REQUIREMENTS		
Target users	The target users to perform the test include community health workers with minimal training and any health worker with a similar or superior training level	
User training	User is able to conduct the test correctly after half a day of training with the provided job aid	User is able to conduct the test correctly after a brief review of instructions with the provided job aid
PERFORMANCE CHARACTERISTICS		
Specimen	Cerebral spinal fluid (CSF)	CSF, urine or venous whole blood, or ideally capillary whole blood
Clinical Sensitivity[7]	≥ 90% for each pathogen	≥ 95% for each pathogen
Clinical Specificity[8]	≥ 90% for each pathogen	≥ 95% for each pathogen
Test Failure (invalid) Rate	No more than 5%	No more than 1%

[6] Case definitions of bacterial meningitis are described in Standard operating procedures for surveillance of meningitis preparedness and response to epidemics in Africa

[7] Clinical reference standard for performance to be measured by PCR or culture and include performance assessment with at least 95% confidence interval with any sample types included in the product claims and appropriate to the intended target population. Clinical testing should be conducted in intended use settings with intended users.

[8] Preference for higher specificity tests over highly sensitive tests when developing tests for these intended use cases

Characteristic	Minimal	Preferred
Analytical specificity and assay interference	Ability to differentiate Nm serogroups A, C, X, Y and W and no cross-reactivity with Nm serogroup B, Spn, and Hib Minimal cross-reactivity with pathogens and/or common endogenous and exogenous interferents (listed in Table 1) acceptable.[9]	Ability to differentiate between all target pathogens Minimal cross-reactivity with pathogens and/or common endogenous and exogenous interferents (listed in Table 1) acceptable.[9]
TEST PROCEDURE CHARACTERISTICS		
Sample Collection and Storage	CSF sample is obtained by lumbar puncture by appropriately trained staff and tested within 3 hours of collection without refrigeration[10]	CSF sample is obtained by lumbar puncture by appropriately trained staff and tested within 24 hours of collection without refrigeration Blood and/or urine sample collection according to recognized standards[11]
Sample Volume	500 µL of CSF	One drop of CSF (around 30-40uL), blood volumes typically collected from fingerstick preferred (<50uL) and standard urine collection procedures
Specimen preparation	Easy to perform sample processing that requires no additional laboratory equipment	Integrated; no sample preparation required by the user

[9] These pathogens/substances should be tested at clinically relevant concentrations, included in a risk evaluation, and listed in the IFU.

[10] CSF collection, storage and transport for diagnostic testing are described in Standard operating procedures for surveillance of meningitis preparedness and response to epidemics in Africa and https://apps.who.int/iris/handle/10665/70765

[11] CLSI GP16-A3, GP42, GP39, GP44

Characteristic	Minimal	Preferred
Ease of Use	Easy to perform test procedure and result interpretation by the intended user with a minimal steps; no precision pipetting and no timed steps (except for the read window of the test result). Reagent reconstitution is acceptable if very simple to do and all liquids, including water, are already provided in the test kit. Over 95% of users must be able to complete the test procedure, read the result, interpret it correctly and understand the results.	The minimal requirement, but with a maximum of three operator steps and no reagent reconstitution required. Over 99% of users must be able to complete the test procedure, read the result, interpret it correctly and understand the results.
Time to result[12]	≤60 minutes	≤10 minutes
Stability of valid result (read window)	At least 15 minutes (after which results may be *false* or *invalid*). Clear language in the instructions for use regarding test reading.	Same, but ≥1 hour (after which results give *invalid* rather than *false* results)
Internal controls	Procedural (reagent-addition) control internalized in each test as an indicator of instability or expiration	Procedural (specimen-addition/sample adequacy) control internalized in each test as an indicator of instability or expiration
External controls	Positive and negative controls available for purchase separately	Positive and negative controls provided in each box of test kits
OPERATIONAL CHARACTERISTICS		
Test kit stability and operational conditions[13]	18 months, stable between 2-30°C, 70% humidity; tolerates up to 48-hours > 40°C; any associated equipment must meet or exceed these requirements[14]	24 months, stable between 2-40°C, 90% humidity; tolerates up to 48-hours > 45°C; any associated equipment must meet or exceed these requirements.

[12] Including time from sample preparation to test result

[13] https://extranet.who.int/pqweb/sites/default/files/documents/WHO-BS-TGS-2_20172304.pdf

[14] Based on specifications in the WHO TPP for point of care test for prior infection with SARS-CoV-2 (https://www.who.int/tools/target-product-profile-database/item/tpp--for-a-point-of-care-test-for-prior-infection-with-sars-cov-2)

Characteristic	Minimal	Preferred
Shipping/Transport conditions[13]	Temperature stress (48 hours with fluctuations up to 50 °C and down to 0 °C) and no cold chain required for storage or transport with indicator of temperature of humidty excursions that would render invalid or low performance results	
Open test kit stability	>1/2 hour for single-use test after opening the pouch	>1 hour for single-use test after opening the pouch
Bio-safety	None apart from waste management and the use of non-sterile gloves	
Waste disposal	Standard biohazardous waste disposal or incineration of consumables, no high-temperature incineration required	Test cassettes and consumables designed to minimize environmental footprint during standard biohazardous waste disposal processes
PRICING AND ACCESSIBILITY		
Target list price[15] **per test**	<$8 USD	<$5 USD
Regulatory requirements	ISO 13485 QMS and WHO pre-qualification ERPD recommendation	Minimal plus certified QMS (ISO 13485 or MDSAP) and authorized for use by a reference regulatory authority including a stringent pre-market assessment

[15] List Price– the price the manufacturer has arrived at for the product, taking into account the cost of goods and other factors (e.g., margin); the list price does not include any volume or other discounts or potential markup for distribution or other costs, including freight, taxes, etc. This cost is assumed a volume production and the prices listed in the TPP are considered for public health preferential pricing in low- and middle-income countries only. This price excludes any cost of a reader.

Table 1: List of potential interference substances and cross-reactive pathogens

Potential Interfering Substances (as applicable)	Potential Cross-Reactive Pathogens
Iodine	Echoviruses
Haemoglobin	Coxsackieviruses
Bilirubin (conjugated and unconjugated	Varicella zoster virus
Serum proteins (e.g., Human serum albumin)	Herpes simplex virus type 1 and 2
Triglycerides	Malaria
Cholesterol	HIV
Antibodies against the expression systems used to generate recombinant antigens (e.g., E. coli, yeast, insect cells	*Streptococcus agalactiae*
Human anti-mouse (HAMA) or other heterophile antibodies	*Escherichia coli K1*
Biotin	*Listeria monocytogenes*
Rheumatoid factor	*Mycobacterium tuberculosis*
ANA anti-nuclear antibodies	*Klebsiella sp.*