TARGET PRODUCT PROFILE

for a gambiense human African trypanosomiasis individual test to assess infection in low prevalence settings

World Health Organization

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Process of document development

The development of this target product profile (TPP) was led by the WHO Department of Control of Neglected Tropical Diseases (NTD) following standard WHO guidance for TPP development. In order to identify and prioritize diagnostic needs, a WHO NTD Diagnostics Technical Advisory Group (DTAG) was formed, and different subgroups were created to advise on specific NTDs, including a subgroup working on the human African trypanosomiasis (HAT) diagnostic innovation needs. This group of independent experts included leading scientists, public health officials and endemic-country end-user representatives. Standard WHO Declaration of Interest procedures were followed. A landscape analysis of the available products and of the development pipeline was conducted, and the salient areas with unmet needs were identified. Through meetings and remote consultations, the subgroup developed use-cases for the hypothetical tools considered as the main gaps and gave them an order of priority. A template adapted to the HAT context was agreed and used for the development of HAT TPPs. The draft of this TPP (rated as priority N° 3) underwent several rounds of review by the subgroup members. The ensuing version was reviewed by the DTAG members. Draft version 0.1 was posted on the WHO website for public consultation for 28 days with a proforma comment form.

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1. Background

Human African trypanosomiasis (HAT) is a life-threatening parasitic infection transmitted by the tsetse fly, that is endemic in Sub-Saharan Africa. Having caused devastating epidemics during the 20th century, its incidence has fallen to historically low levels thanks to sustained and coordinated efforts over the past 20 years. Two trypanosome subspecies cause the disease, with distinct epidemiology: *Trypanosoma brucei rhodesiense* (*Tbr*), found in eastern and southern Africa, is harboured by wild and domestic animals which constitute its reservoir, being transmitted occasionally to humans; and *Trypanosoma brucei gambiense* (*Tbg*), in western and central Africa, with humans as the main reservoir, accounting for about 93% of the total caseload.

HAT diagnosis relies on laboratory techniques because clinical signs and symptoms are unspecific. Serodiagnostic tests exist only for *Tbg* and are based on the detection of specific antibodies, thus they are not confirmatory of infection. With the current low disease prevalence, the positive predictive value of serological tests is particularly low. Field-applicable tools include the card agglutination test for trypanosomiasis (CATT) used mainly in active screening by specialized mobile teams, and the rapid diagnostic tests that are more suitable for individual testing at point-of-care. Confirmation of *Tbg* infection requires microscopic examination of body fluids necessitating specific training. The best performing methods are laborious and reach 85–95% diagnostic sensitivity when performed by skilled personnel.

In gambiense HAT (g-HAT) it has long been observed that repeated rounds of screening followed by treatment of detected cases can bring down the prevalence substantially, and this has been the cornerstone strategy of g-HAT control and elimination. The expected advent of a safer and easy-to-use treatment, would allow for treating seropositive but microscopically unconfirmed individuals (widened treatment), leading to further depletion of the parasite reservoir. But there will be need of monitoring the presence of *Tbg* infection in the community to keep adapting the control strategy in each setting including its eventual stop. Moreover, in the framework of the HAT elimination targets, this tool would ensure the provision of key data to assess the elimination status in endemic countries.

2. Use case

An individual laboratory-based test to assess *Tbg* infection in low prevalence settings.

3. Technical scope

To support *Tbg* case detection in low prevalence settings. Used at individual level in suspects (e.g. serological, clinical, geographical proximity to confirmed cases) to determine if they are infected (ideally) or have been infected by *Tbg*.

It requires high specificity and good sensitivity. Sensitivity is not the first concern because this test is usually preceded by a screening test.

It is important to note that in some endemic settings, the capacities for HAT diagnosis by microscopy can be incomplete or absent due to lack of experience or expertise.

Ideally, implementable in-country, in national or sub-national reference laboratories. Acceptable at regional reference laboratories, knowing that shipping samples to other countries is often complex and subject to strict regulations. When shipping is required, infectivity of the shipped specimen should be reduced to zero or near zero.

Sampling: Ideally, blood from finger-prick, acceptable serum/plasma/blood stabilized in whatever carrier with a desired stability of the sample of 4 weeks at 40 °C, 12 months at 4 °C. It should require minimal sample processing, preferably without cold chain, to transfer samples to reference laboratories.

To help with the interpretation, it should be established for how long the test may remain positive in an individual after a *Tbg* infection has cleared: for example, antibody tests may remain positive for years. For molecular tests, the clearance of DNA and in particular RNA from blood has been observed within days. However, persistence of DNA in blood and cerebrospinal fluid (CSF) was observed in around 20% of patients long after treatment was considered successful, which remains to be explained.

4. Medical need

Currently, the diagnostic tools available in or near the field are not appropriate for determining *Tbg* infection due to the low sensitivity of simple microscopy tests and the low feasibility of more sophisticated tests with higher performance. In addition, the scarcity of cases leads progressively to a lack of experience in microscopy detection. This generates a situation where diagnosis is uncertain.

In settings with absence of performant microscopy, treatment could be decided based on the results of this test.

This test would also become very useful in the framework of a potential strategy of treating unconfirmed serological suspects on the spot, which is currently foreseen as possible with the advent of an oral, single-dose safe treatment. In such situations, this test could confirm or rule out *Tbg* infection a posteriori, allowing the epidemiological situation to be monitored.

Target product profile (TPP no. 3)

Diagnostic test attribute	Minimally acceptable	Desirable	Annotations
1. Intended use			
Target taxon/species/subspecies/type	*Trypanozoon*	*T. b. gambiense (Tbg)*	Currently, in g-HAT areas, any trypanosome seen microscopically in human body fluids warrants treatment, without discernment of the subspecies.
Target population	Individuals at increased suspicion for g-HAT after serological or clinical testing or because of close proximity to a g-HAT case.	Individuals at increased suspicion for g-HAT after serological or clinical testing or because of close proximity to a g-HAT case.	
Use of information obtained	Identification of present or past g-HAT infection. Raised suspicion level.	Identification of present g-HAT infection.	Ideally, a positive test should indicate g-HAT infection.
Type of specimen collected	Collected with discomfort to the patient proportionate to the health benefit	Minimally invasive or non-invasive specimen collection	Minimally invasive: e.g. finger-prick, venous blood; non-invasive: e.g. saliva, urine, tears.
Analyte to be detected	Antibodies, antigens of *Trypanozoon* or whole parasite or *Trypanozoon*-specific nucleic acids	*Tbg* specific antibodies, *Tbg* antigens, whole parasite or *Tbg* specific nucleic acids	The sampling should be done before treatment in case of molecular or antigen analytes. Antibodies may persist from a previous, already cured infection. This might permit to retrospectively establish if there was a *Tbg* infection or not, hence sampling can be done right after treatment.
Nature of the result	Qualitative	Qualitative	No need of quantitation
Infrastructure level and operating environment	Laboratory at national level, or even international reference laboratory	Laboratory at sub-national or national level	There may be a trade-off between international shipment of many samples and set-up of capacity to perform this test in endemic countries.
Intended user	Trained laboratory technician	Trained laboratory technician	

2. Assay performance characteristics (individual (patient) or population needs)			
Clinical sensitivity	> 90%	> 95%	It should be at least comparable to the most sensitive parasitological tests currently used. False negatives result in non-treatment with risk of death and yield lower incidence/prevalence estimates.
Clinical specificity	> 95%	> 99%	False positives lead to unnecessary treatment and overestimate of the disease incidence/prevalence. Specificity here is understood as in a HAT suspect population
Analytical specificity/ cross reactivity	*Trypanozoon*	*Trypanozoon*, with possibility to identify lower taxa (e.g. *Tbg* type 1)	Diagnosis and treatment are currently based on microscopy, at *Trypanozoon* subgenus level.
Analytical sensitivity	Corresponding to ≤ 50 parasites/mL	Corresponding to ≤ 10 parasites/mL	Tests detecting antigens or nucleic acid sequences, including secreted ones, may reach lower detection thresholds than those detecting whole parasites.
Repeatability Intra-reader agreement (different tests, same instruments/environ-ment, same sample, same reader)	Kappa > 0.92	Kappa > 0.96	
Reproducibility Inter-reader agree-ment (different tests, other instruments/ environ-ment, same sample, same reader or different readers)	Kappa > 0.9	Kappa > 0.94	Given the importance this test may take in verification of HAT elimination, repeatability and reproducibility should be as high as possible.
Quality control	Control of functionality included per batch	Control of functionality, positive and negative con-trols for batch testing and for kit testing	Depends on the test format. Positive and negative controls available, preferentially temperature stable. A proficiency panel would be useful.

3. Regulatory and normative needs			
Regulatory approvals and standards	Test components manufactured according to GMP (ISO 13485:2016)	CE marking or other comparable regulatory approval. QMS ISO 13485:2016	New CE marking rules, more demanding, may entail unrealistic production costs. Alternative registration (e.g. Australian Therapeutic Goods Administration) may be considered. Quality management system should be defined. Dependence on commercial availability.
Promotional and marketing material	Not applicable	Not applicable	
4. Health care system needs			
4.1. Environment description			
Operating environment	Can be operated at 10–30 °C at 40–70% relative humidity	Can be operated at 10–40 °C at 10–88% relative humidity	
Workflow requirements	Specimen preparation in the field in < 5 steps, minimal need for precision liquid handling, and minimal need for specialized material (generally available or provided in a specimen collection kit). Specimen can be tested in batches of < 8 without loss of reagent. Results available within 1 week after arrival to the test laboratory	Specimen preparation in the field in < 2 steps, no need for precision liquid handling, and no need for specialized material. Specimen testing in < 10 steps. Maximal automatization. Specimen can be tested individually without loss of reagent. Results available within 48 h after arrival to the test laboratory.	
4.2. Instrument and device characteristics			
Instrumentation needed	Requiring skills and devices usually present at laboratories at national or regional level	Requiring skills and devices usually present at laboratories at secondary level	Instrumentation and devices needed to perform testing may affect the number of laboratories that can perform the test.
4.3. Information and communication technology			
Test result	Test result scored visually or automatically	The test result is scored automatically	
Recording of results and data capture	Results recorded visually or automatically. Integrable into national data and reporting.	Results recorded automatically. Integrable into national data and reporting. Test results are stored for retrospective interpretation (e.g. electronic result, optical density or intensity, etc., electronic image or video).	

Transmission	Test results manually transmitted and entered into computer-databases	Data automatically integrated in server databases without need of additional equipment	Transmission should be flexible, depending on connectivity (Email, SMS, phone). Data format should be compatible with health care databases (JSON, DHIS2) supporting seamless transmission to them if required.
4.4 Reagent and control handling			
Reagents, storage and packaging	Tests run by series of ≤ 8 specimens. Tests accompanied by all necessary accessories and reagents for processing. Stable at 4–8 °C and 40–88% relative humidity for at least 12 months. Operating instructions and bench aids available. Reagents ready to use, or max 5 additional steps.	Individual tests accompanied by all necessary accessories and reagents for processing. Test stable at 4–45 °C and 40–88% relative humidity for ≥ 24 months. 1 week transport stress at 50 °C Transport not needing cold chain. Operating instructions and bench aids in each package. Reagents ready to use or max 2 additional steps needed.	The stability should consider the time frame for distribution from manufacturer, passage through customs and the limited number of tests that may need to be carried out in low prevalence settings.
4.5. Sample handling			
Sample volumes	Depending on the type of specimen. For blood (or serum or plasma) ≤ 5 mL.	Depending on the type of specimen. For blood ≤ 0.07 mL (finger-prick, capillary tube).	Extra specimen material can be collected at the same time for different remote tests if needed. For other tissues or body fluids, volumes can be specified later on.
Specimen collection and processing	Specific collecting devices provided as a kit. Some specimen processing (≤ 5 steps). Transfer of samples relatively urgent. Specimen shipment needs minimal security measures (minimal infection risk). Minimal stability of the sample of 3 days at 35 °C, 1–2 months at 4 °C.	Routinely used collecting devices, minimal or no specimen processing (≤ 2 steps). Transfer of samples not urgent (e.g. 4 weeks) and not requiring cold chain. Specimen shipment needs no special security measures (no infection risk). Desired stability of the sample of 4 weeks at 40 °C, 12 months at 4 °C.	Occasionally, left-over specimens could be preserved and transported under certain conditions
Waste management and biosafety	Amenable to standard biosafety measures for handling potentially infectious materials. Waste disposal in biosafety bin and sharps containers following standard guidelines.	Amenable to standard biosafety measures for handling potentially infectious materials. Waste disposal in biosafety bin and sharps containers following standard guidelines.	
4.6. Distribution, training and support			
Training (sampling)	Specific training needed (< 4 hours)	Basic training needed (< 1 hour)	
Training (laboratory testing)	Extended specific training needed (7 days)	Specific training needed (max 1–2 days)	

Instrument and test supply reliability	Supply guaranteed for ≥ 5 years after marketing. Manufacturer should replace non-functioning tests or instruments.	Supply guaranteed for ≥ 7 years after marketing. Manufacturer should replace non-functioning tests or instruments.	
Service and support response time	External support available. Support response within 1 week.	External support available. Support response within 1 day.	
5. Commercial and sustainability aspects			
Sustainability	Sustainable production	Sustainable production	As it is a non-profitable area, sustainable funding and a production/access innovative model is needed, with donors ensuring affordability. Advocacy needed.
Pricing of individual test	≤ 20 USD	≤ 5 USD	All logistics, operational laboratory costs, investments, hardware, shipment of material, sample collection and salaries are not included here. Specimen collection kits may contain materials for several test formats.

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