

Challenges in Diagnosing Human African Trypanosomiasis

Evaluation of the MSF OCG project in Dingila, DRC

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My thanks go out to everyone in Europe or DRC, who are too numerous to mention here, who helped me in launching my search for an answer to an enigma that has been puzzling me for years and years: How to explain the high numbers of sleeping sickness cases reported in Bas-Uélé?

Thank you to everyone for your hospitality and your kindness.

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Summary

Between late 2010 and the end of 2014 and under extremely difficult conditions, Médecins sans Frontières (MSF) carried out a project to combat Human African trypanosomiasis (HAT), also known as sleeping sickness, in the Dingila, Ango and Zobia regions of Orientale Province in the Democratic Republic of Congo (DRC) - Map 1.

HAT in DRC is caused by *Trypanosoma brucei gambiense* and is transmitted by the tsetse fly (*Glossina* genus) of the Palpalis group.

Without effective treatment, virtually all first-stage HAT patients and one hundred per cent of second-stage patients will die.

It is a fact that when the project began, HAT was a public health problem in Bas-Uélé. As a result, large numbers of patients were treated and many lives were undoubtedly saved.

The quality of the treatment and management of the side effects provided by MSF were exemplary. The mortality rate during treatment was very low. Operational support and logistics supplied through MSF's coordination activities in Bunia were also remarkable.

Unfortunately, an unquantifiable number of persons were, at the start of the project, falsely reported as having HAT, based on inaccurate capillary tube centrifugation (CTC) test results.

These falsely determined HAT patients were generally treated with pentamidine, currently the least toxic HAT medication, the side effects of which are nevertheless considerable.

The negative consequences of this erroneous diagnosis had to be serious at the individual family level and for the community as a whole.

By and large, the overall impression of the project was considered positive by the National Sleeping Sickness Programme (NSSP).

However, improved staff training (of both nationals and expats), more appropriate internal supervision, strict quality control (both internal and external) and more effective supervision on the part of the laboratory technicians (nationals and expats), international experts and the NSSP should, in future, improve the project's performance.

Abbreviations

AS	active screening
CATT	card agglutination trypanosomiasis test
CNS	central nervous system
CSF	cerebrospinal fluid
CTC	capillary tube centrifugation test
DNDi	Drugs for Neglected Diseases initiative
DRC	Democratic Republic of Congo
GRH	general referral hospital
HA	health area
HAT	Human African trypanosomiasis
INRB	Institut National de Recherches Biomédicales, Kinshasa, DRC
ITM	Institute of Tropical Medicine (Anvers)
LNP	lymph node puncture
mAECT	mini Anion Exchange Centrifugation Test
MSF	Médecins sans Frontières
MSF OA	MSF operational centre Amsterdam
MSF OCG	MSF operational centre Genève
MSF-CH	MSF Suisse
NC	new HAT cases
NECT	nifurtimox eflornithine combination therapy
NGO	non-governmental organisation
NSSP	National Sleeping Sickness Programme
PS	passive screening
Stage I	first stage of HAT (where the central nervous system is not affected)
Stage II	second stage of HAT (where the central nervous system is affected)
TD	coloured thick drop
WCC	white (blood) cell count

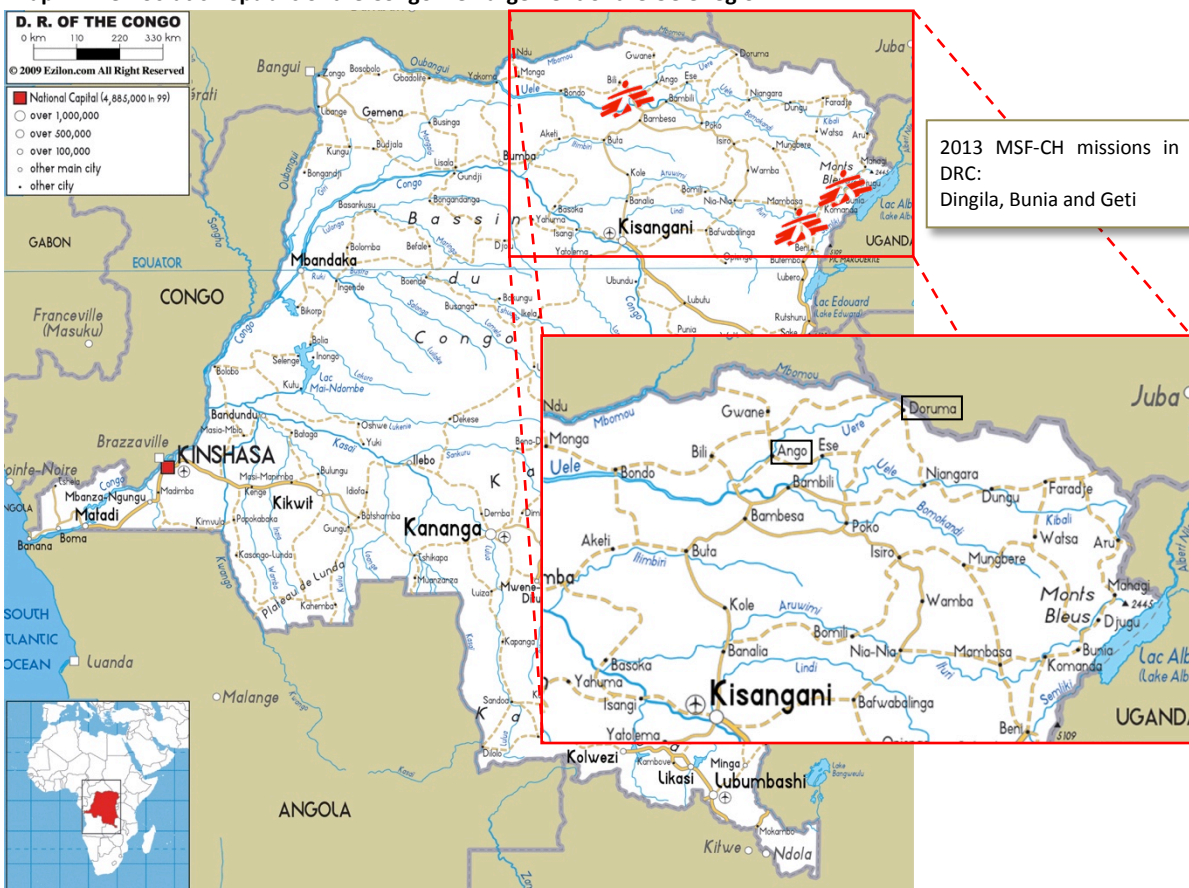
1. Introduction

1.1 Background

1.1.1 Brief history of the Dingila HAT project

Médecins Sans Frontières Suisse (MSF-CH) undertook a project to combat Human African trypanosomiasis (HAT), or sleeping sickness, in May in the Uele districts (Doruma, Banda, and Bili), in Orientale Province of DRC. At the time, the prevalence reported in the Doruma and Ango health districts (4.1%) made that part of Orientale Province one of the most active HAT centres in the world (see Map 1, below).

Map 1 – Democratic Republic of the Congo – enlargement of the Uele region



HAT as seen in DRC is caused exclusively by *Trypanosoma brucei gambiense* and is transmitted by the tsetse fly (*Glossina* genus) of the Palpalis group.

An exploratory MSF-CH mission to Dingila and Amadi, Bas-Uélé in December of 2009 was conducted on a small sample of 630 persons, on a semi-random basis. The total blood Card Agglutination Trypanosomiasis Test (CATT) was positive in 104 persons (16.5%) (See Appendix 5.9 - Table 4). There were no CATT dilutions done. From the positive blood CATTs, 28 new HAT cases (4.44%) were reported (presence of trypanosomes). Just 2 lymph-node punctures were positive (9.52% of 21 punctures performed; 7.14% of confirmed new cases).

The CTC was positive in 26 individuals (25% of CTCs performed; 92.86% of confirmed new cases). The proportion of Stage 1 HAT patients was extremely high, at 24 (85.71%).

The evaluator felt that these results needed to be interpreted. A positive blood CATT rate this high and new confirmed HAT cases were surprising. Further, a 25% confirmation rate from CTC tests is extraordinary. Finally, a rate of 86% of patients at HAT Stage 1 was highly unimaginable.

Following this mission, MSF-CH decided to refocus its project in Dingila on a central HAT axis, with an HAT team based in Dingila. Screening for HAT began in September 2010.

The MSF-CH HAT project in Doruma carried on, with interruptions caused by the lack of security in the region, until March 2012, and was later resumed by MSF OCA (Operating Centre Amsterdam).

An exploratory mission carried out in Ango in January 2011 (i.e. slightly more than one year after screening began in Dingila) reported a very high prevalence of 7%. This rate was based on the number of persons whose CATT 1:16 dilution was positive, but there was no parasitological confirmation done.

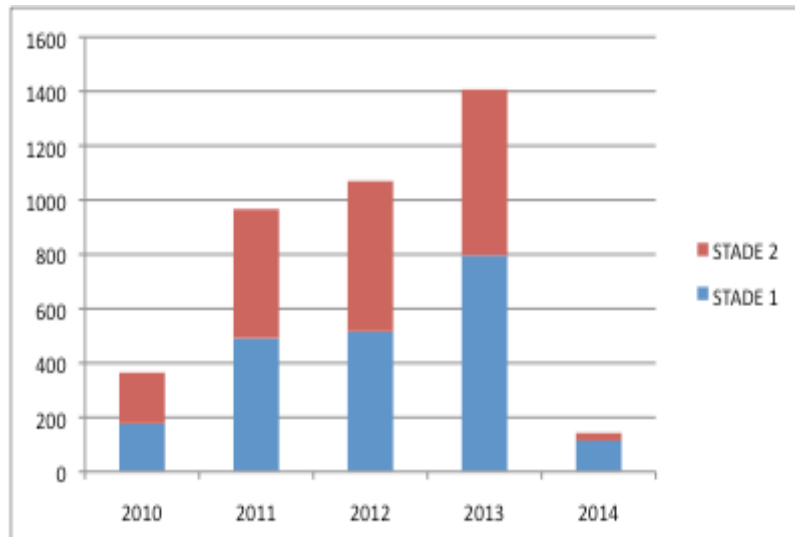
In January 2012, MSF established a second HAT team, based in Ango, to beef up the active screening capacity in endemic parts of Bas-Uélé, with mobile teams based in Dingila, Ango and Zobia.

The number of new cases reported was very high, with a maximum of 1,407 in 2013 (1.5%), out of 75,002 persons screened.

Table 1: - Confirmed new HAT, serologic and relapse cases reported by the Dingila HAT project

TOTAL DIAGNOSTIQUÉ										
		PASSIF				ACTIF				TOTAL
		Tryp +	Sérol	Rechute	Total	Tryp +	Sérol	Rechute	Total	
2010	STADE 1	108	33	2	143	27	7	0	34	177
	STADE 2	135	18	0	153	32	3	0	35	188
	TOTAL	243	51	2	296	59	10	0	69	365
2011	STADE 1	159	21	0	180	276	35	0	311	491
	STADE 2	193	8	2	203	251	14	8	273	476
	TOTAL	352	29	2	383	527	49	8	584	967
2012	STADE 1	13	0	0	13	497	6	0	503	516
	STADE 2	21	0	4	25	516	3	10	529	554
	TOTAL	34	0	4	38	1013	9	10	1032	1070
2013	STADE 1	30	0	1	31	763	2	0	765	796
	STADE 2	15	0	5	20	583	0	8	591	611
	TOTAL	45	0	6	51	1346	2	8	1356	1407
2014	STADE 1	7	9	0	16	43	55	0	98	114
	STADE 2	0	0	0	0	25	1	3	29	29
	TOTAL	7	9	0	16	68	56	3	127	143
TOTAL		681	89	14	784	3013	126	29	3168	3952

Table 2: - Number of new HAT cases reported between end of 2010 and end of 2014



1.1.2 HAT screening and diagnostic methods

Diagnosing HAT is based on the detection of trypanosomes in the lymph, blood and/or cerebro-spinal fluid.

Early diagnosis is rare because specific signs are absent in the first stage of HAT (Stage I), when the trypanosomes have not yet entered the central nervous system (CNS). In the second stage (Stage II), once trypanosomes have entered the CNS, the symptoms become more suggestive of HAT but are not yet specific. Serological screening tests¹ make it possible to identify large numbers of suspected cases to be identified.

The total blood CATT is currently the only screening test that is being used systematically in DRC. It is easy to administer but it is not a diagnostic test because of the high rate of false-positive tests that can result. As a result, any diagnostic suspicions must be confirmed through parasitological testing, which often have to be repeated over several days because they are not sufficiently sensitive either.

On the other hand, approximately 10% of HAT patients exhibit false-negative total blood CATT test results. To reduce this error rate, cervical lymph nodes need to be systematically palpated in the entire population presenting for screening. After that, a lymph-node puncture and an examination of the lymph extracted from “typical lymph nodes” need to be performed (preferably independently of the CATT results.)

However, if the CATT is repeated on a diluted sample of plasma (dilution CATT), a considerable portion of those persons who showed false positives on the blood CATT will have a negative result. Generally speaking, a dilution of approximately 2 to 4 times higher than that used for the blood CATT is used for active screening. Using a higher CATT dilution (1:8 or 1:16) makes it possible to target parasitological confirmation tests on a limited number of persons, who are then examined using more sensitive diagnostic methods – the CTC (capillary tube centrifugation) and the mAECT (mini Anion Exchange Centrifugation Technique).

For more technical information on HAT, please see Appendix 5.3 – Technical concepts relating to Human African trypanosomiasis caused by *trypanosoma brucei gambiense*.

¹ Such as the Card Agglutination Trypanosomiasis Test (CATT)



Reactive CATT (for 50 tests) and control sera

1.1.3 Current methods of treating HAT in DRC

Untreated, virtually all Stage Is and one hundred per cent of Stage IIs are fatal. Further, one effective treatment plays a crucial role in reducing the transmission of HAT.

Stage I is treated with pentamidine (1 intramuscular injection per day for 7 days). It can be administered in the health centres or by mobile HAT teams. However, even though pentamidine is less toxic than NECT (nifurtimox eflornithine combination therapy), its side effects are not inconsiderable.

Stage II is currently being treated almost exclusively with NECT, a combination of nifurtimox (oral, for 10 days) and eflornithine (1 slow IV perfusion every 12 hours, for 7 days). This is a complicated regimen and its use is limited to certain specialised health centres and hospitals, but even though NECT is much less toxic than melarsoprol (which for over half a century had been the only drug capable of curing Stage II), its toxicity is not insignificant.

1.1.4 Suspicions of possible overdiagnosis

Starting in 2013, Headquarters, the HAT referent in Geneva, and MSF-CH Coordination began to ask a number of questions about the program:

- Why were so few clinical signs of suspected HAT being seen?
- Why were white cell counts in the cerebrospinal fluid low, on average?
- Why, on visits of officials from MSF-CH Headquarters or from the DNDi (Drugs for Neglected Diseases Initiative) were trypanosomes only being seen very rarely?
- Why did prevalence decline very little from one active screening to another?

Following a strengthening of internal control over the HAT mobile teams in Dingila there was an almost immediate substantial drop in the number of new cases detected during active screening. In addition to internal corrective measures (retraining of teams and strengthened supervision) instituted in February 2014, a new diagnostic tree was introduced (Appendix 5.5).

In mid-February 2014, Nicolas Bebronne from the Institute of Tropical Medicine in Anvers (an expert in HAT diagnostic techniques) toured the HAT projects in Doruma and Dingila to evaluate all the serological and parasitological techniques used by the screening teams. He spent four days with the teams in Dingila and not a single trypanosome was seen from a screening of over 500 persons. But he did have an opportunity to evaluate how the teams operated and concluded that there was no lack of technical capacity among the Dingila teams.

During the second quarter of 2014 the overall prevalence had declined to below 0.5%, where it had previously never gone below 1% (even after three active screening programs). MSF-CH decided to arrange for an external evaluation, with the intention of paying special attention to the diagnosis, the medical aspects and the mechanisms that may have contributed to the situation of overdiagnosis (see terms of reference in Appendix 5.1).

1.2 Methodology

The methodology used in carrying out this evaluation consisted of an analysis of the available literature, various interviews with the personnel involved, and a field visit to DRC from 20 April to 6 May 2015.²

A series of interviews (via Skype) with officials from MSF-CH Headquarters were conducted prior to the field trip.

During the field visits, a series of interviews were held, involving various officials from the HAT project:

As part of the field visit to Bunia, the following groups were interviewed:

- the MSF-CH coordination team
- three former players from the Congo HAT project lab (who worked in logistics and administration)
- in Ariwara, the HAT referent for the MSF Dingila project

Field visit, Dingila project and interviews with:

- civilian and medical authorities
- the laboratory team from the DNDi (Drugs for Neglected Diseases initiative) fexinidazole study
- the laboratory supervisor from Bunia, who had been seen previously
- officials from the Dingila general reference hospital (GH)
- a number of former HAT patients from the GRH and the Mission district
- about twenty individuals who worked for the Dingila HAT project

In addition, I was able to make a number of observations and checks of the diagnostic and screening techniques used in the DNDi laboratory at the Dingila GH, as well as a repeat of the tests on a person who had been declared HAT-positive 3 years previously and who had refused a lumbar puncture and was never treated.

² See list of references in the appendices.

Field visit, Kinshasa portion:

- MSF officials
- NSSP management
- officials in charge of the DNDi fexinidazole study
- the head of the Disease Control Directorate of the Ministry of Health

At the Dingila GH, I located the passive screening records, the post-therapeutic follow-up records and a number of other documents.

1.3 Limitations

Evaluating a project that ended in late 2014 is certainly not easy. In addition, statistical analysis of data of doubtful reliability makes no sense.

The active screening records and numerous project-related documents were not organized in such a way as to allow the evaluator to perform a rapid, systematic assessment.

2 Results

Combatting a chronic endemic illness such as HAT can only succeed if the technical specifics and peculiarities of the disease are taken into account. To help understand this report, a number of technical concepts relating to HAT are described in Appendix 5.3.

MSF-CH carried out this project under extremely difficult conditions. In 2009, during the HAT exploratory mission, Bas-Uélé had no emergency or development funds available. The Ministry of Health, through its NSSP, had requested support for this extremely difficult-to-access region (insecurity and disastrous condition of the roads, poor communications, etc.), where qualified human resources were rare and the health system was virtually devoid of equipment.

2.1 Screening and diagnosis under the Dingila HAT project

The term *passive screening* is used when a health service screens for HAT in persons who present to a health service for examination of their own initiative.

The term *active screening* is used when a health service (normally mobile teams) organises a village search for new active cases of HAT.

In its annual report, MSF deemed the 2010 screening in Dingila to be passive screening. In actual fact, this was active screening within the boundaries of the GH, following education and mobilisation of the population. Blood CATT was done out of the GRH for all persons who participated in the screening. Those who were CATT blood positive were referred to the MSF laboratory for additional testing.

The most sensitive test used in detecting trypanosomes is the mAECT (mini anion exchange centrifugation technique) but it is not always available. It is done at the INRB (Institut de Recherches Biomédicales) [Biomedical research institute] in Kinshasa, with support from the ITM (Institute of Tropical Medicine) in Anvers. At times production is interrupted due to technical problems and sometimes it is difficult to keep up with the demand. When the mAECT was used, a 1:16 CATT dilution was not done systematically.

This explains why, between 2010 and March 2014, the diagnostic tree used with the MSF project changed, depending on the availability of the mAECT (Appendix 5.4). This diagnostic tree is the same as those used in other regions where HAT is endemic but in DRC, the mobile teams from the NSSP palpate and examine lymph nodes systematically, and on persons for whom the blood CATT was negative.

Until March 2014, palpation of the lymph nodes was not done systematically—only for persons whose total blood CATT was positive.

Therefore, until March 2014, the blood CATT was the only entry point into the screening chain.

The 1:4 dilution (CATT 1:4) occupied a central location on each diagnostic tree; it was supposed to be used for all persons with a positive blood CATT. If the CATT 1:4 was negative the individual was considered as not having HAT, but approximately 10% of HAT patients have a negative blood CATT.

Where the CATT 1:4 was positive, a capillary tube centrifugation (CTC) test was done to look for trypanosomes in the blood.

Following a negative CTC test result, a CATT dilution of 1:16 was performed when the mAECT was not possible. Where it was possible, the mAECT was used to look for trypanosomes in the blood, and the CATT 1:16 was not done.

A lumbar puncture (LP) was done in the case of anyone who showed a positive trypanosome lymph-node test, a positive trypanosome CTC, a positive trypanosome mAECT or a positive CATT 1:16 (also when trypanosomes were not detected).

The cerebrospinal fluid (CSF) was examined to determine whether the patient was at HAT Stage I or Stage II: white blood cell count per microlitre (WCC/ μ L) and search for trypanosomes.

Those with a positive CATT 1:16, but showing no evidence of trypanosomes were considered new serological cases and were treated.

It is evident that no new serological cases can be detected during periods where the CATT 1:16 is not done.

2.1.1 Statistical results from the project

The screened population rose by 12,281 in 2010 to 75,002 in 2013. In 2014, 33,931 persons were screened. The project shut down at the end of 2014 and the total number of those who participated in the screening was 192,555. It should be noted that the total number of new HAT cases reported was 3,909, broken down as follows:

- 3,694 (1.91% of persons screened) were confirmed new cases (in which trypanosomes were reported);
- 215 were new serological cases (CATT \geq 1:16 positive, trypanosome-negative). Cases where the CATT dilution was <1:16 were not considered new serological cases and were not treated, except if they were confirmed new cases. Out of a total of 3,909 cases, 3,783 were treated (2,018 for Stage I, 1,765 for Stage II). The total number of relapses reported was 43, 37 of which were then treated.

2.2 Observations supporting a hypothesis of overdiagnosis

As part of this evaluation, we noted, among other things, a series of events throughout the length of the project that helped support the hypothesis of overdiagnosis of HAT. These events are listed below:

- Effective with the end of 2012, numerous individuals who had previously been diagnosed with HAT by the mobile team were retested and all the retests proved negative.
- The prevalence dropped less rapidly than expected and remained above 1%, even after 3 or 4 active screening tours in the same areas.
- In mid-2013, there were virtually no patients presenting symptoms that were highly suggestive of HAT.
- There were virtually no lymph-node tests that were positive, but in areas where there was a high prevalence of HAT, the lymph nodes of large numbers of patients were positive for trypanosome.
- The confirmation rate for positive CATT 1:4 (in patients where trypanosomes were detected) was very high.
- The rate for patients detected at Stage I remained very high (approximately 50%), even after several active screening rounds in the same areas.
- The number of white blood cells in the CSF was generally very low (rarely >50 WCC/ μ L) compared with other HAT foci.

2.2.1 Erroneous conception of the significance of the CATT and overly positive readings

The fact that the CATT is a screening test, and not a diagnostic test, was not sufficiently well understood by the teams in Dingila. They seemed to think that in most persons with a positive CATT 1:4 that trypanosomes could be found. This conception undoubtedly contributed to the uncritical way they saw the CTCs and their conviction that everything that moved under the microscope was a trypanosome. This erroneous notion was not corrected until February 2014.

Therefore, the overly positive reading may explain the very high rate of positive blood CATTs reported in the region.

During this evaluation mission, the evaluator noted that the three experienced technicians on the DNDi laboratory team appeared to be familiar with the various techniques: CATT, dilution CATTs, CTCs, buffy-coat mAECTs and the CSF test (counting of white blood cells, modified simple centrifugation). However, on one visit, the evaluator noted a discrepancy in the blood CATT readings done by two technicians on one person who had presented for consultation.

Virtually all the technicians at the national laboratories, as well as those from the Doruma HAT project and the Dingila HAT project, had been trained by the same national laboratory supervisor. Whenever these technicians claimed to have seen a trypanosome in the CTC, the specialists carrying out an evaluation mission³ were never able to confirm the results (not even with an mAECT). The slides and cover glasses were dirty and quite often artefacts were undoubtedly mistaken for trypanosomes.

This error has been corrected since the use, beginning in March 2014, of special reading chambers that are cleaned on a regular basis and pure water is being used. As a result, the number of positive CTCs has declined dramatically.

2.3 Extent of overdiagnosis

It is obvious that from the beginning of the Dingila HAT Project (end of 2010) a considerable number of persons has been reported as having HAT, based on false-positive CTC results, and this went on until the second quarter of 2014.

It is impossible to go back and quantify the number of individuals who were falsely diagnosed with HAT. The most that can be done is to attempt to arrive at a highly approximate estimate of the number of actual HAT cases detected. In effect, one may assume that those persons whose lymph-node, mAECT or CSF tests were positive were genuine HAT patients, along with a large proportion of persons whose CATT 1:16s were positive. If these data in the EpiTryps database can be mined, they need to be compiled.

Overly positive blood CATT readings from the start of the project up until the second quarter of 2014 undoubtedly led to a work overload. For each questionable blood CATT a venous puncture and a CATT 1:4 was done, but the questionable blood CATTs should have been considered negative.

In addition, it is likely that the suspicious CATT 1:4s (with barely perceptible agglutinations) were considered positive. This resulted in a considerable number of completely unnecessary mAECTs and/or CATT 1:16 tests.

The same is true for the questionable CATT 1:16s (with barely perceptible agglutination) that were considered positive. This resulted in a considerable number of unnecessary lumbar punctures and treatments.

³ End 2013, Olivier Denis, Laboratory Referent, MSF Belgique, and end February 2014, Nicolas Bebronne from ITM

The negative consequences for persons erroneously declared ill with HAT had to have been considerable: unnecessary treatment with toxic drugs, risk of side effects (immediate and long-term), physical and psychological suffering, no doubt sometimes intense, and often stigmatisation.

Beginning in February 2014, corrective measures were taken in Dingila, including (a) reinforced supervision by an official from the DNDi laboratory, (b) introduction of a new diagnostic tree (Appendix 5.6), (c) use of clean equipment (thereby preventing microorganisms or other particles from moving beyond the capillary tubes and having them falsely mistaken for trypanosomes), and (d) introduction of the use of systematic lymph-node palpation for each person as part of the screening process.

2.4 Impact of corrective measures

There was a considerable difference in the results from the first quarter and those from the second quarter of 2014 (see Table 3).

Table 3 – 2014 Screening for HAT in Ganga Zone – Dingila nord

Lab test – New cases	First Quarter 2014			Second Quarter 2014			Total for 2014		
	# of tests done	# of tests positive and/or WCC >5/mm ³ or tryp pos.	% of tests positive	# of tests done	# of tests positive and/or WCC >5/mm ³ or tryp pos.	% of tests positive	# of tests done	# of tests positive and/or WCC >5/mm ³ or tryp pos.	% of tests positive
Total blood CATT	5,834	162	2.78%	7,838	143	1.82%	<i>Already an impact</i> 13,672	305	2.23%
CATT 1:4	158	103	65.19%	142	95	66.90%	300	198	66.00%
LNP	14	0	0.00%	3	0	0.00%	17	0	0.00%
CTC	103	29	28.16%	95	0	0.00%	198	29	14.65%
mAECT	74	5	6.76%	95	2	2.11%	169	7	4.14%
CATT 1:16	4	2	50.00%	93	23	24.73%	97	25	25.77%
LP	27	12	44.44%	21	0	0.00%	48	12	25.00%
Stage unknown (LP Refused)		9	25.00%		3	12.00%		12	19.67%
Suspected		53	0.91%		73	0.93%	0	126	0.92%

For example, the team in Dingila nord, before corrective measures had been taken, reported that out of 103 CTCs in the first quarter of 2014, 29 (28.16%) were positive, whereas from March 2014 in the second quarter and after corrective measures had been instituted, 95 CTCs were done and none of them were positive. Also, just two mAECTs were positive in the second quarter (the only HAT cases confirmed) out of a total of 95 mAECTs done.

Following introduction of the new diagnostic tree, CATT dilutions of 1:16 were systematically done on persons who were CATT 1:4 positive and in whom trypanosomes had not been detected. As a result, the number of positive CATT 1:16s in the second quarter was 23 (24.73% of the 93 CATT 1:16s done; 0.29% of 7,838 persons screened).

2.5 Treatment during the Dingila HAT project

It is useful to remember that without effective treatment virtually all HAT Stage I and one hundred per cent of Stage II cases are fatal and that effective treatment plays a critical role in reducing transmission (by eliminating trypanosomes from the blood of patients).

MSF-CH focused a great deal on the quality of treatment. Treatments were given under the best possible conditions.

Mortality rates for Stage I cases (treated with pentamidine) were 0.1% and 0.23% for Stage II cases (treated with NECT). In both cases, these mortality rates were very low, compared with what was seen in many other HAT treatment centres.

Post-therapeutic treatment was virtually non-existent. Treated patients rarely returned for follow-up, primarily because they were afraid of the lumbar puncture and the fact that they no longer felt that they were patients. As a result, few treated HAT patients came to the GRH laboratory in Dingila for post-treatment follow-up. Out of 257 monitored between September 2010 and August 2014, there were 12 relapses.

2.6 Internal and external supervision of screening, treatment and quality control

It is true that interpreting the changes in HAT prevalence was not easy in this region because of the uncontrolled movement of large numbers of displaced persons. The population was unstable and the fact that prevalence declined less than expected in areas that had already been actively screened was apparently attributed to a reintroduction of new HAT patients coming from elsewhere.

Internal supervision of screening by national lab supervisors

There were 3 national lab supervisors (one per team) and they worked independently. However, the first supervisor had trained the other two “on the job” and had also trained virtually all the other individuals involved in the MSF Dingila screening project on the job. Previously, he had also trained virtually all the lab staff working on the Doruma HAT project.

The same supervisor as well as all the others had never, during all those years, received any additional training or adequate supervision. Only one training course on the fexinidazole study into good clinical practices was given, but since this supervisor had had a very long experience with MSF in combatting HAT, everyone (including the MSF lab supervisors and international experts) had full confidence in him.

Internal supervision of screening by expat MSF lab supervisors

There was a succession of 5 expat laboratory technicians, one of whom did not speak French. Their service periods were too short for a project such as HAT, and their skill levels varied. No one suspected a problem of overdiagnosis.

Supervision of screening by the National Sleeping Sickness Control Programme (NSSP)

The supervision on the part of the NSSP was inadequate. It carried out a number of missions in the region and relations with NSSP management were good, but the NSSP exploration teams never really worked together in the same location. As a result, they were in no position to judge the quality of the screening or the diagnosis work done by the others.

Internal quality control and external quality control

These controls were not systematically applied.

2.7 Perceptions of the Dingila HAT project

Perceptions of former employees of the Dingila HAT project

According to three former employees interviewed in the MSF-CH coordination centre in Bunia the project worked well, logistics were good, the shutdown was premature and on short notice, and the population did not want MSF to end the project.

Perceptions of NSSP management

The NSSP realises that MSF worked under some extremely difficult security and logistical conditions. According to NSSP management this was a good project, and one that would not have been possible without the budget and the logistics provided by MSF.

However, cooperation was not always the best; among other things there were issues regarding the diagnostic tree that was being used and the collection and reporting of data (which should be harmonised between MSF and the NSSP in order to avoid interpretation-related problems).

The NSSP wished that there had been better cooperation with respect to staff training. The NSSP also expressed a wish to be involved from the very start in the supervision of future HAT projects, ideally through the use of joint (MSF/NSSP) teams.

2.8 HAT situation in Dingila following MSF's departure

Since MSF left, there has been no screening whatsoever at the GRH lab.

The two persons who perform the routine work examine coloured thick drops for malaria and fresh blood for microfilaria, but have no experience in looking for trypanosomes. Neither do they perform lymph-node punctures.

The head of the laboratory has the theoretical skills and is familiar with the screening and diagnostic techniques because she is involved with the fexinidazole study, but up until now she has seen trypanosomes just once (in an mAECT). She went into the field with the screening team, but she had difficulty identifying trypanosomes in CTCs. She saw some “things that were moving” but wasn't sure if they were trypanosomes.

At the current time, there is no more equipment or reagents for carrying out a CATT. There is no longer any inventory of drugs for treating HAT.⁴

Screening and diagnosis can be done only at the DNDi laboratory but the population is not aware of this possibility. Also, the team at the DNDi laboratory will only be staying in Dingila for a few months more.

⁴ However, there were a number of donations from MSF-CH before the project ended.

3 Conclusions

MSF-CH conducted this project under extremely demanding conditions. In 2009, at the time of the HAT exploratory mission, it was very difficult to access Bas-Uélé. There was a general state of insecurity, the roads were in abominable condition and communications were difficult. Qualified human resources were rare and the health structures virtually unequipped.

HAT was a real problem in Bas-Uélé and is still endemic there.

Without doubt, when the project started, HAT represented a public health problem in Bas-Uélé.

Unfortunately, because of a not insignificant problem of overdiagnosis we will never know what proportion of persons treated were genuine HAT patients. Although in the second quarter of 2014, the reported prevalence everywhere was <0.5%, new serologic cases included, and just two new confirmed HAT cases were detected (through the mAECT), HAT remains endemic in Bas-Uélé.

Overdiagnosis was systematic from the start of the project and was not the result of a deliberate act.

There is an accumulation of evidence to show that, since the project began, there was a major problem of overdiagnosis and a number of cases were erroneously declared to be HAT patients, based on false-positive CTC results.

In December 2009, during the exploratory mission, the numbers were already what can be described as astonishing and should have triggered a rigorous verification of the reading of the results.

Beginning in mid-2011 there were numerous incidents where persons had been declared HAT-positive, were re-examined, and the retests proved negative.

In mid-2013, MSF-CH HQ, the HAT referent in Geneva, and the MSF-CH coordination unit began to question how the teams were operating. HAT prevalence was declining less quickly than expected and remained >1%, even after 3 or 4 rounds of active screening. None of the detected patients showed symptoms that were highly suggestive of advanced Stage II HAT. The teams were doing very few lymph node punctures and the tests of lymph nodes were rarely trypanosome positive. The rate of confirmed CATT 1:4s remained very high. The proportion of patients at Stage I had been stagnating since the start of the project at around 50%. The number of white blood cells in the CSF of newly reported cases was very low, rarely >50 WCC/ μ L.

It is unfortunate that only the CATT 1:4 was performed systematically and that the CATT 1:8 was never done. Because the CATT 1:4 yields results that are similar to those of the blood CATT, this dilution has too low a specificity to support the veracity of all positive CTCs.

In March 2014, a new diagnostic tree was introduced. From then on, the lymph nodes were supposed to be systematically palpated on all persons screened and each suspicious blood CATT needed to be considered negative.

The difference between the results from the first and second halves of 2014 was enormous. For example, before corrective measures had been taken, the Dingila nord team reported that out of 103 CTCs in the first quarter of 2014, only 29 (28.16%) were positive, whereas effective March 2014, in the second quarter, and after corrective measures had been implemented, 95 CTCs, were done, with none showing positive results.

Overdiagnosis consequences

Looking back, it is impossible to quantify the number of persons who were erroneously diagnosed with HAT. It can be assumed that virtually all the false-positive cases had a normal CSF and that they therefore received a less toxic form of treatment (using pentamidine). Further, MSF paid a great deal of attention to the quality of the treatment given to patients and to the treatment of side effects. MSF

assumed the costs associated with human resources, drugs and equipment invested in arranging the screening resulting from the overdiagnosis.

It should be remembered that without effective treatment of all Stage I cases and one hundred percent of Stage II cases of HAT are fatal and that effective treatment plays a critical role in reducing transmission (by eliminating trypanosomes from the blood of patients).

Mortality rates for Stage I cases (treated with pentamidine) were 0.1% and the rate for Stage II cases was 0.23% (treated with NECT). In both cases, the mortality rates were very low, compared with what was seen in many other HAT treatment centres.

Key factors contributing to the dysfunction of the Dingila HAT project

Virtually all the laboratory personnel on the MSF teams (in both Doruma and Dingila) were trained by a single laboratory supervisor who, himself, had not had any upgrading and additional training, and supervision was not always adequate in the latter years. The consequence of this is that all staff on the MSF teams shared the same conceptions and convictions (sometimes erroneous) and probably committed the same mistakes.

The way the blood CATT, the CATT 1:4 and the CATT 1:16 were read in too favourable a manner led to a high number of unnecessary tests and incorrect treatments of serologically false cases. The incorrect reading of the CTCs using inappropriate and unclean equipment led to erroneous diagnoses in a not inconsiderable number of false HAT patients. The lack of supervision and inadequate monitoring were also contributing factors. A complex disease, coupled with a highly sophisticated diagnostic tree, led to the need to simplify the indicators and the diagnostic system, such that non-experts would be able to supervise the program.

Supervision was inadequate, both on the part of the supervisors and the national HAT referent physician and on the part of the MSF ex-pat laboratory technicians. In addition, proper supervision by the NSSP was not adequate.

4 Recommendations

Preliminary: In the recommendations I have not taken into consideration any of the individual rapid screening tests still in the process of validation. If a highly sensitive and specific rapid test becomes available, these recommendations will need to be revisited, but such tests would obviously be attractive for use in passive screening, while the CATT would continue to have an important role in active screening.

Thematic	Recommendations	When
Exploratory missions	<ul style="list-style-type: none"> The team's technical capabilities, whether or not testing was performed as directed by the producer, and the proper reading of their results need to be verified. For exploratory missions, use the diagnosis tree suggested in Appendix 5.7, where a 1:4 dilution is replaced by a 1:8 dilution. 	<ul style="list-style-type: none"> Before each exploratory mission For each exploratory mission
Passive screening	<ul style="list-style-type: none"> In endemic regions, arrangements need to be made for passive screening in the GRHs and in the referral health centres. Where the CATT and the mAECT are unavailable, continue performing simple diagnostic testing (fresh blood, coloured thick drops, and lymph-node examinations). The ability to perform these simple tests needs to be taught, mastered and maintained. Follow the diagnostic tree proposed in Appendix 5.8 for passive screenings. 	<ul style="list-style-type: none"> In all cases In all cases For each passive screening
Active screening	<ul style="list-style-type: none"> Active screening should target first the villages where patients detected by passive screening come from, along with all neighbouring villages. Repeat the active screening at regular intervals (6 months to a year) until no new cases are detected. Stop active screening when no new cases are detected as a result of two screening rounds (provided the participation rate is >80%). Follow the diagnostic tree proposed in Appendix 5.9 for active screenings. 	<ul style="list-style-type: none"> In active screening If new cases are detected If no new cases detected through active screening For each active screening
Examination of CSF	<ul style="list-style-type: none"> Single-use counting chambers must be used. Otherwise the Fuchs-Rosenthal is the most appropriate for counting white blood cells in the CSF. The method used to count white blood cells and the appropriate formula to be applied, based on the type of counter used, must be verified. 	<ul style="list-style-type: none"> Whenever possible At all times

	<ul style="list-style-type: none"> • Look for trypanosomes when counting WCCs. • Perform a simple modified centrifugation, where centrifuge and special collector tubes are available. 	<ul style="list-style-type: none"> • When counting WCCs • Where these tools are available
Treatment and post-therapeutic follow-up	<ul style="list-style-type: none"> • Treat new serologic cases (positive CATT 1:16, trypanosome negative) if the NSSP strategy recommends it. • Examine the CSF of each new patient to determine the stage of the disease and prescribe the appropriate treatment. • Stop examining the CSF systematically for 2 years following treatment. Except for sick persons who want it and those whose health condition is deteriorating. 	<ul style="list-style-type: none"> • When recommended by NSSP • For each new patient • During post-therapeutic follow-up
Data collection and analysis	<ul style="list-style-type: none"> • Update EpiTryps software or replace it with a new, more user-friendly program. • Include data required by NSSP for its annual report. • Make a systematic distinction between confirmed new cases (trypanosome-positive) and new serologic cases (CATT 1:16 positive, trypanosome negative). • Make a systematic distinction between Stage Is and Stage IIs. • Analyse mortality and side effects based on treatment regimen. • Results must be analysed based for each round of active screening. 	<ul style="list-style-type: none"> • As soon as possible • As data is collected • For each analysis • For each analysis • For each analysis • For each round of screening
Training of national staff	<ul style="list-style-type: none"> • Ensure that national staff are not all trained by just one person; include practical training. • Ensure that at least one laboratory technician on each team has received training outside the MSF HAT project. • Collaborate with the NSSP on the implementation of training courses. • Initiate a continuing education program. • Arrange for the HAT referent physician to complete a practicum in a hospital where large numbers of cases are treated. 	<ul style="list-style-type: none"> • At all times • For any new team • Prior to and during each training course • Regularly • Prior to the start of each project
Training of expat staff	<ul style="list-style-type: none"> • Ensure that ex-pat laboratory technicians have a critical knowledge of the country's language. • Hold training courses for several weeks in areas where trypanosomes are frequently detected, 	<ul style="list-style-type: none"> • Before each mission leaves • Before each mission leaves

	<p>preferably in cooperation with the NSSP.</p> <ul style="list-style-type: none"> Ex-pat laboratory technicians must be familiar with the clinical signs of HAT. 	<ul style="list-style-type: none"> Before each mission leaves
Internal supervision	<ul style="list-style-type: none"> Ensure continuous verification of results as per the producer's instructions. Ensure that regular verification of CATT readings is carried out by laboratory supervisor. Ensure that each positive parasitological test is confirmed by a second, experienced person. Counting of white blood cells from the CSF, preferably using single-use counting chambers, needs to be done by at least two experienced persons. If there is a discrepancy between the results, counting must be repeated on a new sample. Any discrepancies between the lab results and clinical signs observed need to be rigorously verified. 	<ul style="list-style-type: none"> At all times At all times At all times Whenever WCCs in the CSF are counted Whenever there is a discrepancy between lab and clinical signs
External supervision	<ul style="list-style-type: none"> Organise missions with outside experts when active screening is in progress. Systematically verify test results reliability and not just analyse recorded results. Arrange for supervision by the NSSP at the start of the project and then once each year. Plan for supervision by outside experts (e.g. Anvers Institute of Tropical Medicine) at the start of the project and then once each year. 	<ul style="list-style-type: none"> During active screening Regularly At start of each project, then once per year At start of each project, then once per year
Internal quality control	<ul style="list-style-type: none"> Systematically perform a CATT 1:8 and a CATT 1:16 on all new cases. Then determine if there is a discrepancy between the parasitological and serologic results. At regular intervals, perform a CATT 1:4 and all parasitological tests on a sampling of persons whose blood CATT results were negative. At regular intervals, perform all screening and diagnostic tests in parallel and serial CATT dilutions of up to 1:32 to confirm that there is no discrepancy in the results. Systematically draw and keep a coloured thick drop from each person declared a patient. Then have them examined in a blinded test by a different MSF team. If there is only one MSF team, send the thick drops to an outside laboratory. 	<ul style="list-style-type: none"> Each new case Every 3 months, for one week Every 3 months, for one week For each person declared positive When there is only one team

External quality control	<ul style="list-style-type: none"> • Have a thick-drop sample examined at regular intervals by an outside laboratory (NSSP or National Institute of Biomedical Research in Kinshasa). • Send serum or plasma samples or filter-paper samples from patients declared positive to a lab that can do trypanolysis. 	<ul style="list-style-type: none"> • Every 3 months • At regular intervals
Continuity/ Exit strategy	<ul style="list-style-type: none"> • Train a sufficient number of local laboratory staff to ensure continuity of passive screening (lymph-node examination, coloured thick drops, CSF examinations) and high-quality treatment. • Make sufficient quantities of equipment, reagents and medications available to local health services. 	<ul style="list-style-type: none"> • Throughout the length of the project • During exit phase

5 Appendices

5.1 Terms of reference

Terms of reference for a critical review of the MSF-CH program in Dingila, DRC

Ordered by:	Operations Directorate – Cell 3
Length of evaluation:	1 month to 6 weeks
Field visit:	<1 week (one evaluator)
Period under evaluation:	2010 - 2014
ToR developed by:	Michel Quéré, Souheil Reiche, JCC, Mica Serafini
With support from:	Vienna Evaluation Unit

The primary stakeholders (Committee) to be consulted on the Terms of Reference and the process and on return of the results are:

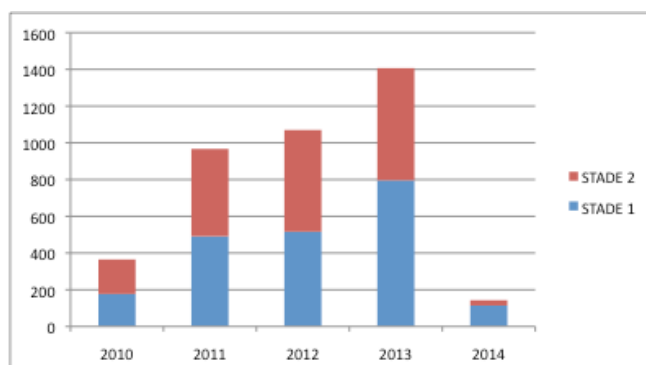
- JCC (Director of Operations, OCG) and Mica (Medical Director, OCG)
- Cell 3: Michel Quéré and Souheil Reiche
- Francois Chappuis
- Esther Sterk
- Roberto de la Tour
- Field team: Head of Mission, Medical Coordinator, Field Coordinator, ...

1. BACKGROUND

MSF-CH initiated a Human African Trypanosomiasis (HAT) project in **May 2007** in Haut-Uélé (Doruma, Banda, and Bili). At the time, the high rates of prevalence observed in the Doruma and Ango health areas (4.1%) made that part of Orientale Province in DRC one of the most active centres in the world. An HAT exploratory mission in the area in **December 2009** showed a high prevalence of the disease: in Dingila, 17 cases out of 440 persons screened (3.86%) and in Amadi 11 cases out of 190 persons screened (5.89%). Following this exploratory mission, MSF decided to refocus the project on a central HAT axis.

A HAT evaluation done on Ango in January 2011 showed a high rate of incidence (7%) in the Area. In **January 2012**, MSF created a **second team based in the Ango Health Area** to augment our active screening capacity around Dingila.

The programme was developed and the following table shows the number of cases diagnosed between 2010 and 2014.



However, beginning in 2013, Headquarters, the HAT referent, and the Co-ordinations Unit began to raise questions regarding the programme, based on a diverse series of arguments, such as:

- Why are we finding so few clinical signs?
- Why are CSF WCC counts on average low, and dropping rapidly?
- Why, on visits from Headquarters or from DNDI, were we seeing very few trypanosomes?
- Why was the prevalence declining only slightly from one round to another?

Bas on all this, the decision was made to request an external evaluation.

Early **2014** saw a significant decline in the number of positive cases from active screening, with a high probability that this reduction was the result of a previous systemic problem of overdiagnosis. Overall, we observed a prevalence of less than 0.5%, and therefore decided to skip the previously planned final rounds in each health area and shut the project down at the end of the year.

Overdiagnosis

The most significant event that affected the project was therefore the issue of overdiagnosis, and the essential question is understanding how we arrived at that point and what the consequences of it are.

There were a number of dubious incidents where individuals were originally diagnosed as patients by the mobile clinics and who, when re-screened, proved to be HAT-negative. The most significant of these incidents occurred in January 2014. Four patients tested positive for HAT and were selected to participate in the fexinidazole project. These same patients were tested a second time and all proved to be HAT-negative.

In response, MSF bolstered its control measures in order to avoid the same thing happening again. They primarily strengthened the control system with 2 laboratory technicians and scheduled a number of follow-up visits by supervisors.

Once these measures were put into place there was an immediate and very significant drop in the number of HAT-positive cases. After three years in the area where the health areas consistently showed an incidence greater than 1%, and this even after 3 or 4 rounds of screening, suddenly the incidence rate for all health areas dropped to virtually zero cases. At the end of January, the highest reported prevalence was 0.4% and the average for all health areas screened after January was 0.1%.

In March 2014, Nicolas Bebronne from the Belgian Institute of Tropical Medicine visited the project to assess the serologic and parasitological techniques used by the HAT mobile screening team in Doruma (MSF/Operational Centre Amsterdam) and Dingila (MSF/Operational Centre Geneva). Mr Bebronne spent four days with the mobile teams and found only one positive case, and this from having observed the screening of more than 500 persons. He had an opportunity to evaluate the capacity of our teams and concluded that they were well trained and that there was no lack of technical capacity within the group. One of the hypotheses was therefore that the overdiagnosis was not a problem stemming from their ability to identify the parasite, but rather from deliberate actions on the part of certain members that were designed to prolong their employment with MSF (by extending the lifespan of the project).

2. GENERAL OBJECTIVE

The general objective was to critically examine the Dingila project with an emphasis on the medical aspects, the diagnosis and the programme that led to the overdiagnosis.

3. SPECIFIC OBJECTIVES

- Document, prepare a synthesis and an analysis, with an emphasis on the overdiagnosis, through interviews with those involved and a review of existing documentation (annual report, funding plans for 2010-2014, critical incident report by Dr Joshua; external evaluation by Anvers);
- Describe the overdiagnosis events;
- Evaluate the scope and extent;
- Analyse the consequences for the population and for the patients;
- Analyse the impact as it relates to the project and to MSF;
- Evaluate what did not work and what led up to that. What is the internal issue relating to the quality of service provided that led up to that;
- Evaluate implementation of the measures taken to rectify the problem;
- Understand, in order to avoid having the same type of problem repeated in other similar projects;
- Analyse communications with the authorities.

4. KEY EVALUATION QUESTIONS

- What are the reasons for the unexplained change in the HAT incidence curve and the inconsistencies observed? Were they the result of the overdiagnosis or something else (such as bad data management)?
- What is the scope of this problem?
- What are its consequences with regard to the population:
 - Did the patients who were in good health receive treatment for HAT?
 - How much? For how long?
- What are the ramifications for MSF?
 - What are the material damages (costs)?
 - What are the immaterial damages (for example regarding the credibility of MSF with the Ministry of Health, the WHO or other stakeholders)?
 - For advocacy?
- What is the problem within the internal quality management system that may have led to this situation?
 - Management structure
 - Supervision system
 - Data management
 - ???
- What measures were implemented to remedy this?

5. EXPECTED RESULTS and use of the results of the evaluation

Evaluation report in French, including:

- One version for internal use and another version for the Ministry of Health, the WHO and other stakeholders.
- Translation of the report into English for internal use.
- Presentation to Cell(s), Ops, MoSu.

6. IMPLEMENTING THE EVALUATION / METHODOLOGY

- Data collection: review of existing literature (annual report, budget 2010-2014, critical incident report by Dr Joshua; external evaluation by Anvers, etc.);

- Interviews of persons involved in various OCs (in person or remotely) and this 1 week prior to travelling to the field:

List of interviewees	
Souheil Reaiche	Programme Manager, Cell 3
Michel Quéré	Medical Officer, Cell 3
Jean-Clément Chabrol	Director of Operations, OCG
Micaela Serafini	Medical Director, OCG
Roberto Delatour	Laboratory Consultant
Francois Chappuis	Tropical Disease Counsellor
Esther Sterk	Team Leader, Tropical Diseases
Olaf	DNDI (neglected diseases), OCG

- Field interviews with:
 - The MSF coordination team: head of mission, medical coordinator, field coordinator, etc.
 - Hospital authorities, their national counterparts, regional DNDI, authorities in Kinshasa, ...
- Analysis of data:

Establish a chronology of the most important events over the past 5 years.

Use critical incident analysis tools (e.g. change analysis, cause and effect, contributory factors, etc.) to establish a link between the underlying causes and the consequences.

7. AVAILABLE DOCUMENTATION

- Annual Report;
- Draft 2010-2014 budget report;
- Critical incident report done by Dr JOSHUA; ANVERS external evaluation report;
- SITREP;
- ANVERS external evaluation report;
- HQ Coordination visit reports.

8. PROFILE(S) OF EVALUATOR(S)

Evaluator No. 1:

- Medical profile
- Must have management experience
- Must have practical experience with MSF
- Must speak French

If necessary, a short-term (up to 10 working days), possibility of one technical support person (Evaluator No. 2):

- Must have technical familiarity with HAT programmes.

5.2 List of interviewees

[First name, Last name, Title]	[Function]
Adelaide Ouabo	Medco, MSF-CH DRC, Bunia
Benoît Kebela	Medical Director, Disease Control Directorate, Ministry of Health, DRC, Kinshasa
Céline Motta	Dmedco, MSF-CH DRC, Bunia
Dominique Amisi	Physician, Area Head, Dingila
Félix Dingikuta	Medical Liaison Officer, MSF Intersection, Kinshasa
François Chappuis	Physician, HAT Referent, MSF OCG
Gigi Biye Batiga	MSF-CH Assistant Lab. Technician, Dingila
Gisèle Kumita	Laboratory Supervisor, Dingila GH
Gomète Mokili	MSF-CH Laboratory Team Supervisor, Dingila
Jacque Makabuza	Physician, NSSP, Kinshasa
Jean Albert Kabulu	DNDi Laboratory Supervisor, Dingila
Jean Louis Lumazila	Medical Director, Dingila GH
Jean Pierre Tshibangu	MSF-CH Laboratory Team Supervisor, Dingila
Jeroen Beijnsberger	Medco, MSF Belgium, Kinshasa
Joses Dinanga	National Lab. Supervisor, DNDi, Kinshasa
Josué Amici Heradi	HAT Referent Physician, MSF-CH, Dingila
Kevin Coppock	MSF-CH Head of DRC Mission, Bunia
Laurent Cibue	DNDi Laboratory Technician, Dingila
Lumbala Crispin	Medical Director, NSSP, Kinshasa
Micaela Serafini	Medical Director, MSF OCG
Michel Quere	Physician, Head, Cell 3, MSF OCG
Michel Sambili	MSF Physician, Dingila
Nicolas Bebronne	Technician, HAT referral laboratory, Anvers Institute of Tropical Medicine
Philémon Mansinsa	Head, Vector Control, NSSP
Roberto de La Tour	Lab. Referent, MSF OCG
Wifried Mutombo	Medical Researcher, DNDi fexinidazole study

5.3 Technical Concepts Relating to HAT

Technical concepts relating to Human African trypanosomiasis caused by *trypanosoma brucei gambiense*

Simon Van Nieuwenhove, May 2015

Fighting an endemic disease such as Human African trypanosomiasis (HAT), or sleeping sickness, can only be successful if sufficient consideration is given to the technical specificities and peculiarities of the disease.

1. Transmission of HAT

In order to be able to transmit HAT, the tsetse fly (*glossina*) must first become infected from the blood of a patient with the disease. If it takes its first taste of blood from an animal or a healthy person (whose blood does not contain any trypanosomes), it will normally not be able to become infected after that, and will therefore not be able to transmit the disease during its lifetime.

The crucial factor in determining the scope of transmission is the number of untreated HAT patients living in endemic areas. In fact, trypanosomes in the blood of these persons constitute a “human trypanosome reservoir” from which new generations of glossina will be able to infect themselves (and thereby become HAT vectors).

Defining the prevalence and the incidence of HAT is complex, and these clues change as control measures change. For example, upon each active screening (AS), the prevalence is reduced (because with effective treatment trypanosomes are eliminated from the blood of patients). Personally, I prefer the term “rate of infection” (RI): (number of new cases detected per year divided by the population screened) x 100.

The *gambiense* form of HAT seen in the Democratic Republic of Congo (DRC) generally evolves chronically (over a period of from several months to more than 10 years).

As a result, HAT may remain prevalent for a very long time at a low level (residual endemia) based on a small number of patients, but as the “human reservoir” passes a critical threshold, transmission will accelerate because greater numbers of glossina will become infected from patients, and HAT will slowly but surely return to hyper-endemic, or even epidemic, levels.

2. Clinical aspects and evolution of HAT

HAT is a serious chronic disorder in terms of morbidity and mortality that has a harmful effect on the socio-economic development of the infested areas and leaves severe permanent sequelae in large numbers of patients who were too late in receiving treatment.

First stage of HAT

In the first stage (Stage I) there are not what could be called typical symptoms: irregular fever, headaches, itching, muscle pain, joint pain, puffiness in the face, general malaise, etc. These symptoms are often attributed to other infections (including malaria or viral or bacterial infections).

As a result, a HAT diagnosis is frequently missed when the disease is in Stage 1. When diagnosed, virtually all the patients who were detected through passive screening have already been patients for several months (often for several years) and have generally been in several times for consultations with health services without a diagnosis of HAT being made.

The acute manifestations of HAT have a tendency to diminish, even without specific treatment. Many patients are able to establish a fragile balance with trypanosome and manage to lead apparently normal lives, often for many years.

Second stage of HAT

Trypanosomes invade all organs but often do not enter the brain for several years (Stage II). Once they have entered the central nervous system, behavioural disorders (often involving aggressiveness) begin to appear and become progressively worse. Sleep rhythm disturbances lead to a very advanced stage of HAT and produce “sleeper” (hence the name of the disease) and bedridden patients.

The clinical picture is therefore very heterogeneous. Advanced HAT and other types of insanity, other neurological syndromes or black-magic manifestations are often confused, and this frequently results in a (very) late diagnosis.

The final phase of HAT appears similar to terminal cancer or the final stages of AIDS: extreme weight loss and malaise, inability to move and to feed oneself, severe neurological disorders, total apathy, and bed-ridden state. This creates a problem of making a differential diagnosis in those areas where there is a high prevalence of AIDS. In addition, confusion in the minds of the general population between the terminal stages of HAT and of AIDS results in HAT patients often being brought in too late (or not at all) to a place where they can get medical attention. In fact, family members are generally convinced that whatever the case there is no cure possible.

It should be mentioned that without effective treatment Stage II HAT is 100% fatal. The patient dies in a coma or succumbs to the consequences of an opportunistic infection.

3. Active screening for HAT

Active screening occurs when the health service (usually mobile teams from the NSSP or certain NGOs) organise a search for new HAT cases in the villages.

Up until the early 1990s, active screening was almost exclusively based on the palpation of “typical cervical lymph nodes” followed by a lymph-node puncture (LNP) and a parasitological examination of the juice from the lymph node. Coloured thick drops were also examined, but rarely as a general practice.

However, despite the relatively low sensitivity of the tests used at the time, the prevalence of HAT was, in the past, sometimes reduced to a residual level as a result of rounds of active screening conducted at intervals of approximately 6 months (maximum 1 year), repeated over numerous years. Also, before independence in many cases attendance at active screening sessions was compulsory (absence resulted in prosecution). As a result, there was a 100% participation rate.

Now, although more sensitive tests are available, the ability to properly perform and accurately read the LNP and the coloured thick drop blood tests must be maintained at all cost. In effect, the day that donors withdraw their support for the purchase and distribution of more sensitive tests, the LNP and the thick drop tests will still remain within the reach of health services.

At the present time, the total blood CATT (Card Agglutination Trypanosomiasis Test) is the one screening test that is used almost universally in DRC. This test identifies persons whose blood contains trypanosome antibodies. It should be remembered that the CATT is a screening test and not a diagnostic test, so an individual could have a positive blood CATT without having HAT (false-positive blood CATT).

The blood CATT is an excellent method of rapidly screening a population and makes it easy to identify individuals who require additional testing, but with this test there is a not inconsiderable number of false-positive results.

If the CATT is repeated on a sample of dilute plasma or serum (CATT dilution), a significant portion of those persons who were false-positive on a blood CATT will show a negative result. Normally, a dilution

approximately two to four times higher than for the blood CATT is used in active screening. The specificity of the CATT dilution increases with the dilution (a CATT 1:32 is more specific than a CATT 1:16, a CATT 1:8 and a CATT 1:4).

The use of a high enough dilution (1:8 or 1:16) makes it possible to target parasitology confirmation tests on a limited number of persons, where the probability of actually being infected with HAT is high. They can then be tested with the most sensitive tests currently available.

Some national programmes recommend treating with a positive CATT $\geq 1:16$, even if trypanosomes are not detected. These persons are then considered “new serological cases.”

At present, the blood CATT is too often the only criterion for entering the screening chain, but approximately 10% of genuine HAT cases show a negative blood CATT result. They are therefore not detected if just the positive blood CATT results undergo additional testing. The cervical lymph nodes of the entire population present for screening should be systematically palpated, followed by an examination of the juice of “typical lymph nodes” (see above), preferably independently of the CATT results. This procedure would make it possible to locate new cases from false-negative blood CATT tests and it could especially serve as a permanent quality control for serological screening. If trypanosomes are found in the lymph node juice and the CATT is continually negative, the CATT reagent would have to be checked to see if it is still good.

4. Passive screening for HAT

Passive screening occurs when a fixed health unit screens for HAT in persons who present for consultation on their own initiative.

DRC has two types of fixed units that perform passive screening: the Treatment and Control Screening Centres, specialized NSSP centres, and certain hospitals and health centres.

5. Diagnosing HAT

Simple parasitological tests

The parasitological examination of the lymph node juice drawn by means of a lymph-node puncture (LNP) of the cervical lymph nodes, the fresh blood test and the coloured thick drop test are methods that are easy to perform and inexpensive, but relatively lacking in sensitivity.

During screening rounds, it is not necessary to examine all puncturable lymph nodes because that would take much too long and there are numerous different reasons to explain why lymph nodes can become enlarged. Only the so-called “typical” lymph nodes need to be examined—those that are enlarged, soft and painless.

In persons who are CATT-positive or who show clinical signs that are suggestive of HAT, any “non-typical” lymph nodes should also be checked for trypanosomes.

Concentration techniques (referred to in DRC as “sensitive methods”)

Some tests, described as “concentration tests,” such as the Capillary Tube Centrifugation Test (CTC or WOO), the mini Anion Exchange Centrifugation Test (mAECT) and the Buffy Coat mAECT, are in theory much more sensitive than regular microscopic examinations. In reality they are only more sensitive when the directions are followed to the letter, the equipment is in good condition, the reagents have been properly stored, and the reading is done accurately. They take longer to do, require centrifugation of the samples and are (much) more expensive.

We need to remember that even with the buffy coat mAECT, tests repeated over several days do not always end up yielding evidence of trypanosomes.

Therefore, a negative parasitological test does not exclude the presence of HAT, whereas the detection of trypanosomes is sufficient to confirm the diagnosis.

Examination of the cerebrospinal fluid (CSF)

CSF is obtained via lumbar puncture (LP). Most patients fear this procedure and it needs to be performed under conditions where there is sufficient sterility by an experienced member of staff.

Examination of the CSF is required to determine the stage of HAT and in order to be able to prescribe appropriate treatment.

Patients who do not have any trypanosomes in their CSF and who have ≤ 5 white blood cell count (WCC) per μL CSF are considered to be at Stage I and can be cured with pentamidine. This medication does not penetrate sufficiently far enough into the central nervous system to cure Stage II HAT.

Those with >5 WCC/ μL and/or trypanosomes in their CSF are considered to be at Stage II and can only be cured with medication that penetrates far enough into the CSF (see below).

Although examination of the CSF is, strictly speaking, not a diagnostic technique (and, for ethical reasons, cannot be one) it often (even during the counting of white blood cells) helps detect trypanosomes in some Stage II patients.

At present, the modified simple CSF centrifugation technique (done with special collection tubes) has significantly increased the likelihood of finding trypanosomes in the CSF.

Examination of the CSF is also done during the post-therapeutic follow-up in order to determine whether or not there has been a relapse of HAT.

If the CSF contains a high number of red blood cells, the count result is not reliable and the CSF will need to be re-examined after approximately one week.

Supervision of testing

In order to avoid false-negative results, the parasitological tests must be done as soon as possible after the samples have been drawn, because the trypanosomes quickly become less mobile and die).

To prevent false-positive test results, each positive examination must be confirmed by a second, experienced and competent person.

The counting of white blood cells in the CSF must be done by at least 2 persons with experience (in different counting chambers) and the average will represent the final result. In the event of a major discrepancy in the results, the count must be redone, using a new sample.

A rigorous quality control system must be instituted and maintained, otherwise healthy persons could be made to undergo unnecessary lumbar punctures and treatments with toxic medications or the diagnosis of HAT in patients could be missed.

6. Treating HAT

All anti-HAT medications are toxic.

Since 2001, they have been supplied at no charge by the World Health Organisation (WHO) but these medications are expensive and as a result the quantities that the WHO is able to supply are not unlimited. Strict control over their use is imperative. The costs of shipping these medications are also very high.

Only melarsoprol (Arsobal), eflornithine (DFMO, Ornidyl) and nifurtimox (Lampit) penetrate far enough into the central nervous system to be able to cure Stage II patients. They are much more toxic (especially melarsoprol) than pentamidine and their treatment regimes are much more complicated to administer.

Treating the first stage of HAT

The only medication currently being used in DRC to treat Stage I is pentamidine. It does not penetrate far enough into the central nervous system to cure Stage II. It is given by intramuscular injection (once per day for 7 days) and can be handled in certain outlying health centres. The proper injection technique must be used in order to prevent the product from damaging the sciatic nerve.

Although pentamidine is less toxic than the drugs used for Stage II, the side effects are not inconsiderable; they include hypotension (vertigo and, in some cases, a state of shock), nausea, vomiting, pain and sterile abscesses (necrosis rarely) at the injection site, hypoglycemia, and hyperglycemia (very rarely permanent diabetes).

Treating the second stage of HAT

With melarsoprol

Melarsoprol was, up until the beginning of this century, the only drug available in most treatment centres that could cure HAT Stage II.

It is administered by slow intravenous injection. Its toxicity is highly feared (especially in acute reactive encephalopathy) and there is significant mortality associated with treatment (1 to 10%). Further, the last several decades have seen a significant number of failed treatments (up to 25% in some endemic areas).

Melarsoprol is still being administered as a first-line treatment for Stage II where new treatment regimes cannot be used (because the other medications are not available or conditions do not allow them to be administered properly).

At present, it can also be used (alone or in combination) for treating relapses following the administration of eflornithine or NECT (see below).

With eflornithine

Eflornithine is a cytostatic, and although it is considerably toxic it is much less toxic than melarsoprol.

Used in monotherapy, eflornithine is administered using a slow intravenous perfusion (every six hours) for 14 days. As a result, its use should be limited to those health units that are well equipped and have sufficient numbers of dedicated and experienced nursing staff.

The primary side effects include encephalopathy (rarely), convulsions, diarrhea, vomiting, anorexia, neutropenia, and septicemia (resulting from non-sterile intravenous perfusions).

Currently, eflornithine monotherapy has been replaced by NECT as the first-line treatment for HAT Stage II.

With NECT (nifurtimox-eflornithine combination treatment)

NECT is a treatment that involves a combination of nifurtimox (oral) and eflornithine (using a slow IV perfusion). The advantages of this regimen are: its shorter duration (eflornithine for 7 days instead of 14), reduced amounts of eflornithine (50% of the total monotherapy dose), greater ease of administration (eflornithine every 12 hours instead of every 6 hours) and the probable reduction in the risk of developing resistance to the treatment. However, administering it is still very complicated so it should be limited to those health centres that are well equipped and have sufficient numbers of dedicated and experienced nursing staff.

The major side effects of NECT include nausea, vomiting, convulsions, encephalopathy (rarely), anorexia, and psychiatric disorders (especially agitation).

Impact of treatment on the transmission of HAT

It must be pointed out how singularly important treatment is in reducing transmission. In effect, one effective treatment destroys the trypanosomes in a patient and thereby reduces the “human reservoir” from which newly hatched tsetse flies can become infected.

Accordingly, an accurate diagnosis followed by an effective treatment will be curative for the individual patient but will also have a preventive effect with respect to the general population (because of a reduction in transmission).

Treatment costs

In principle, there is no cost for the diagnosis and treatment of HAT patients in DRC but under the system of cost recovery, those patients who are treated in the health units must bear other expenses (expenses for travel, hospitalisation, laboratory tests, adjuvant medications, injection equipment, etc.). This can result in major lag times between diagnosis and treatment or even result in refusal of treatment.

Because treatment (as soon as possible after diagnosis) is the most important factor in reducing transmission, it seems critical that it be given at no cost.

7. Post-therapeutic follow-up

Since relapses (failure of treatment) can manifest themselves belatedly, in the past each patient treated was supposed to be monitored for 24 months (parasitological tests and examination of the CSF every 6 months).

In actual fact, goodly numbers of patients never reported for follow-up testing and most rarely presented after 6 months.

Within the context of the fight against HAT, the current tendency is to no longer insist that patients return every 6 months following treatment. They are informed that they should come back in for post-therapeutic examination as soon as they observe a deterioration in their state of health. In this, the education and cooperation of the patient's family are critically important.

Limiting the number of lumbar punctures to just one (for prescribing treatment) will undoubtedly help substantially increase the screening participation rate.

However, as part of the clinical studies with new substances, a regular post-therapeutic follow-up for a sufficiently long period is still required.

8. Impact of HAT on society

Without effective treatment, Stage II HAT is 100% fatal. Because of its chronic nature (lasts from several months to over 10 years), and its progressive attack on the patient's physical, mental and intellectual capacities, HAT causes not only intense individual suffering but also results in considerable loss of economic productivity.

HAT negatively impacts fertility (abortions or amenorrhea in women and impotence in men).

Mental effects (irreversible reduction in intellectual potential, behavioural disorders, insanity, etc.) and physical effects (neurological disorders, etc.) persist in patients who were too late in receiving treatment.

Therefore, large numbers of persons remain dependent on society for life, even after effective treatment of the infection (elimination of the trypanosomes).

CONCLUSION

Up until now, no health-care organisation (not even the DRC's NSSP) has so far been able to detect a resurgence of HAT before the problem has taken on huge proportions. This is due not only to the frequent shortages of equipment and reagents or the lack of trained health care personnel, but also to the insidious nature of HAT (non-specific symptoms) and its highly chronic evolution.

Attendance at health care services in DRC is often very low and the will or the resources (human and material) for diagnosing HAT is often lacking, so it can develop in silence, even where health care services are close at hand.

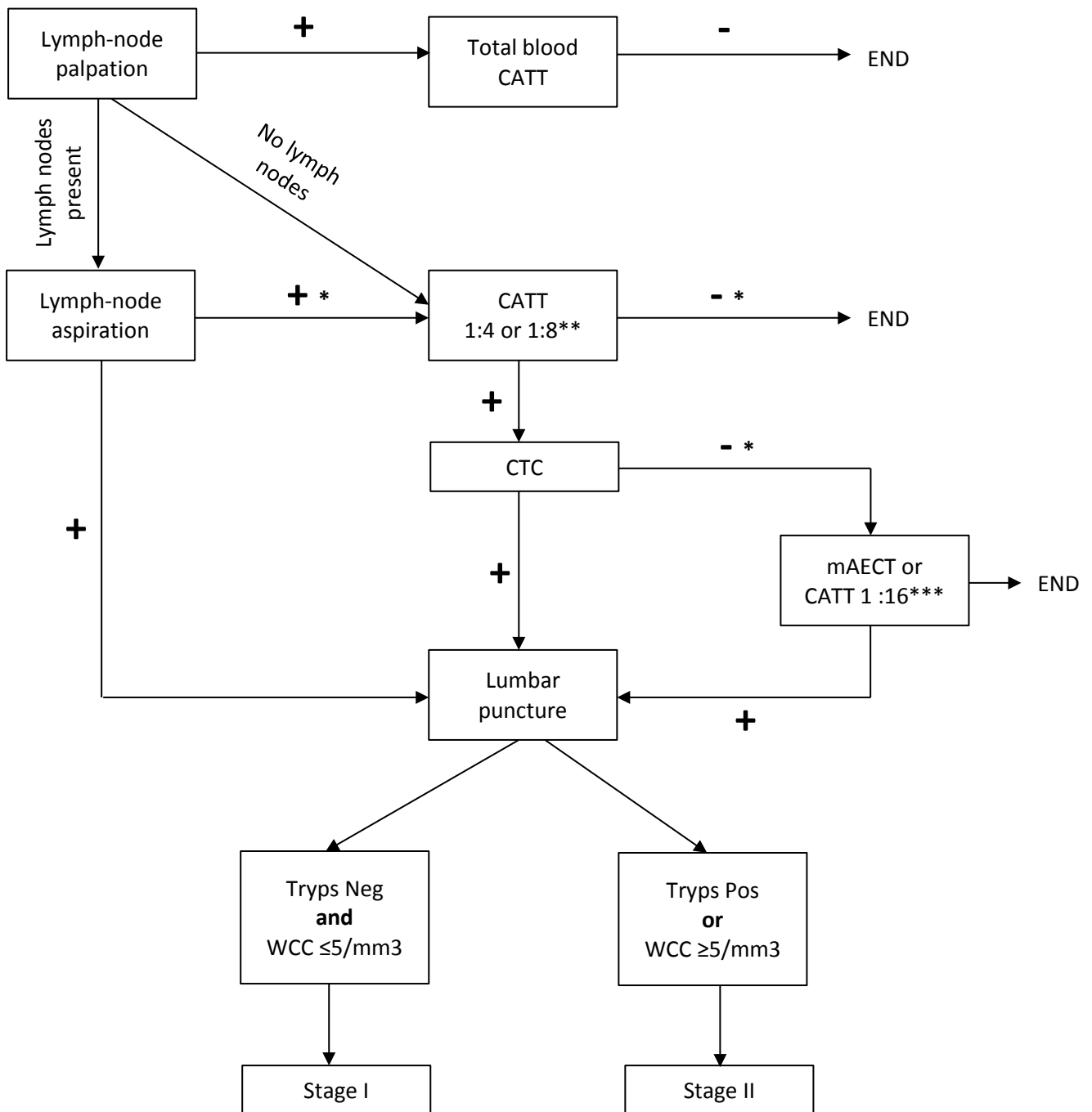
As a result, active screening (which is necessary in order to achieve a relatively rapid reduction in prevalence) has, in the past, almost never been begun at a point where prevalence was still low.

However, reoccurrences of the *gambiense* form only appear explosive. They are normally the result of a long process of slow, but gradually increasing, transmission.

It must also be realised that even with the most effective diagnostic techniques currently available, even if 100% of the at-risk population presented for active screening (which is only wishful thinking) and even if all the required resources were available (which is very far from being the case), it would be impossible to identify the last remaining sleeping sickness patient in the population or even to eradicate the last tsetse fly.

Therefore, even in areas where the prevalence has actually declined to below 0.1%, there will inevitably be recurrences if epidemiological surveillance, active and passive screening, treatment and post-therapeutic follow-up are not maintained at an adequate level.

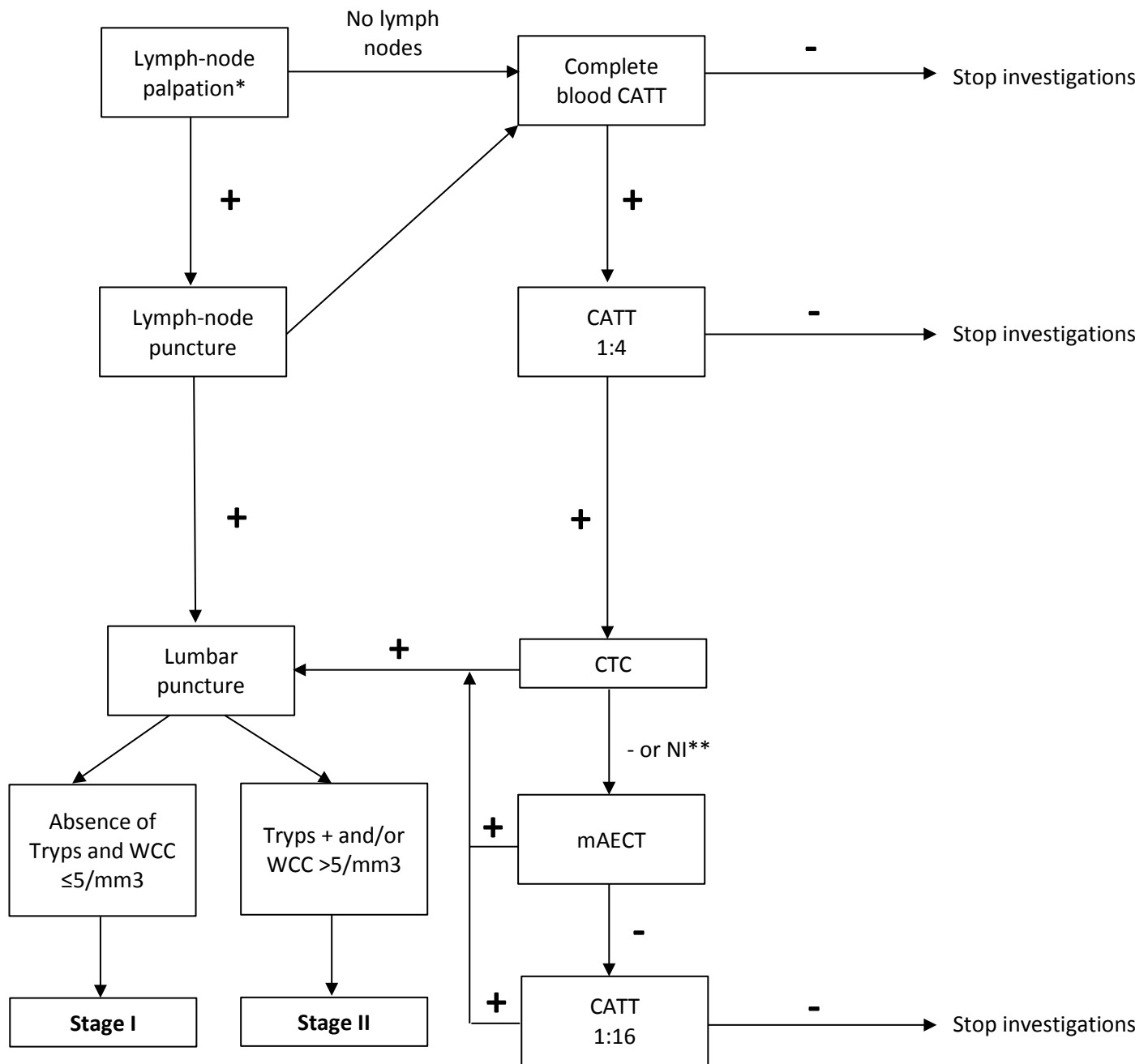
5.4 Diagnostic tree for HAT with and without mAECT



Note:

- * If clinically suspected, go to next step of diagnostic tree
- ** If prevalence <1%, go to CATT 1:8 dilution
- *** CATT 1:16 if mAECT not available and prevalence >1%

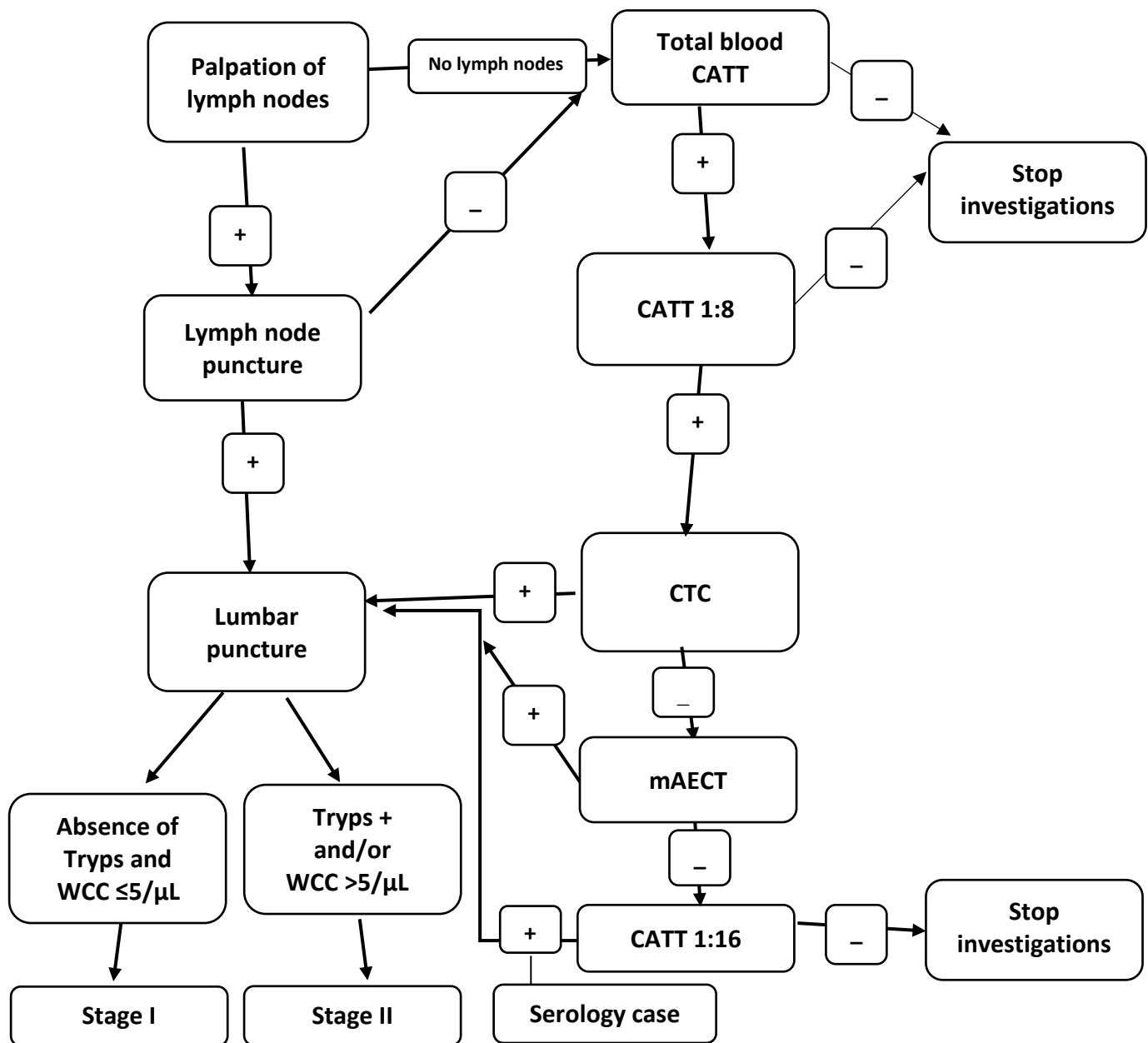
5.5 Diagnostic tree for HAT – March 2014



* Pre-Catt lymph-node palpation only >12 years

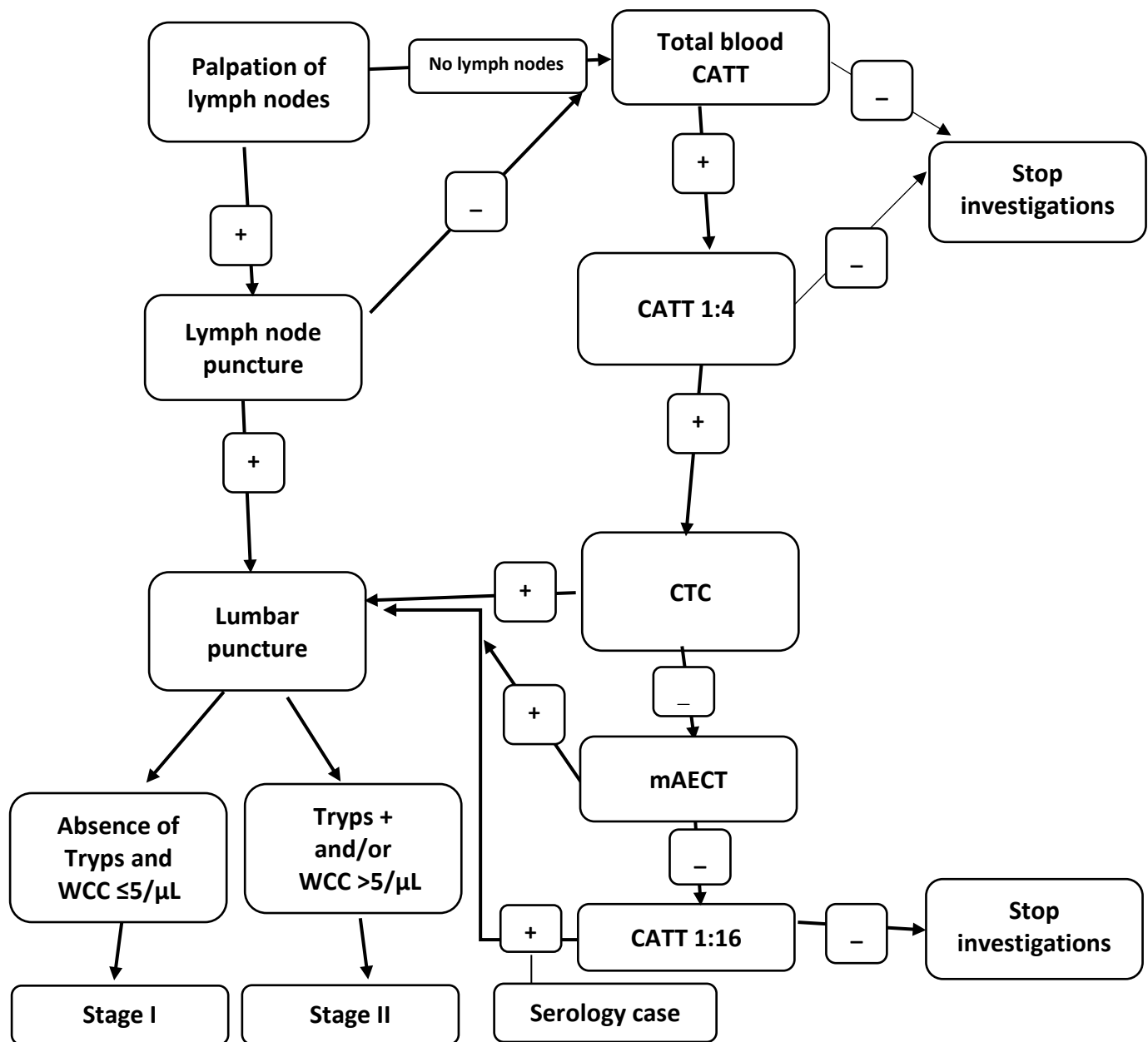
** CTC negative or UI (uninterpretable) when microfilaria present

5.6 Proposed diagnostic tree for an exploratory mission



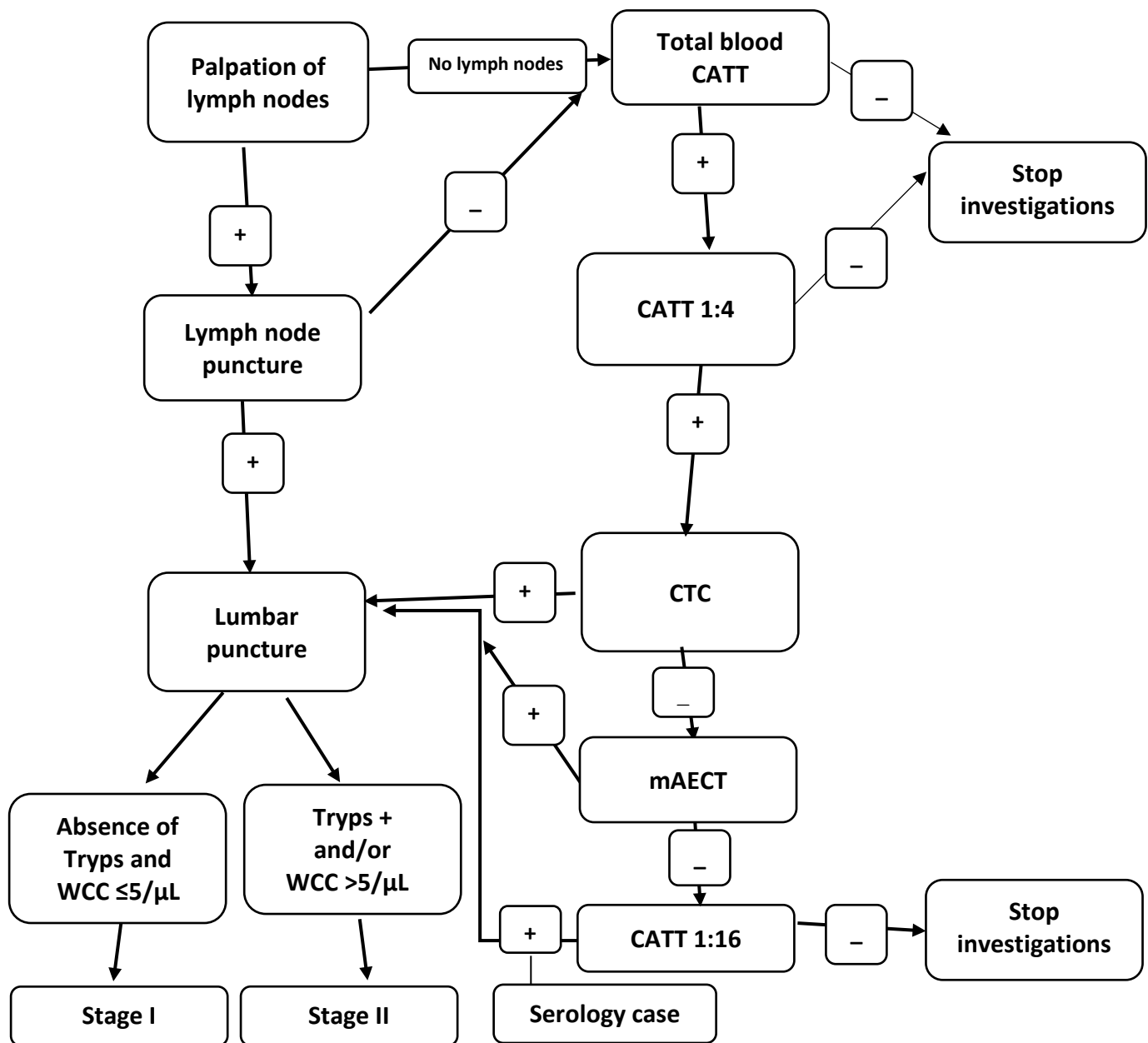
- Lymph-node palpation must be done in all cases (not just positive blood CATTs) and lymph from swollen lymph nodes must be examined for the presence of trypanosomes.
- Total blood CATT must be done in all cases. The results must be recorded with an indication of agglutination appearance (+, ++, or +++).
- (Dubious) blood \pm CATTs, where the agglutination is barely perceptible, must be considered negative.
- Instead of a CATT 1:4, a CATT 1:8 dilution seems more appropriate for an exploratory mission. It allows for focussing parasitology tests on more-suspect individuals than positive CATT 1:4s.
- When the CATT 1:8 is positive, the CTC needs to be done on 2 capillary tubes, using clean, appropriate counting chambers. An X16 eyepiece would make readings easier than one rated at X10.
- When available, a mAECT (preferably buffy coat) must be used as a confirmation test instead of the CTC.
- Individuals showing symptoms suggestive of HAT must be examined, even when the blood CATT is negative.

5.7 Proposed diagnostic tree for HAT - passive screening



- Lymph-node palpation must be done in all cases (not just positive blood CATTs) and swollen lymph nodes must be punctured and the lymph examined for the presence of trypanosomes.
- Where CATT equipment and reagents are available, a blood CATT must be done and the results recorded, showing the appearance of the agglutination (+, ++, or +++). Dubious blood CATTs, where the agglutination is barely perceptible, must be considered negative.
- When the blood CATT is positive, a CATT 1:4 should be done. This dilution reveals a greater number of suspected cases than a CATT 1:8, since the number of false negatives with CATT 1:8 is higher.
- When the CATT 1:4 is positive, the CTC needs to be done on 2 capillary tubes, using clean, appropriate counting chambers. An X16 eyepiece would make readings easier than one rated at X10.
- When the CTC is negative, a mAECT (preferably buffy coat) must be done.
- In instances where there is sufficient mAECT-related equipment available, this test should be done straightaway, without the CTC.
- Individuals showing symptoms suggestive of HAT must be examined, even if the blood CATT is negative.

5.8 Proposed diagnostic tree for HAT - active screening



- Lymph-node palpation must be done in all cases (not just positive blood CATTs) and swollen lymph nodes must be examined for the presence of trypanosomes.
- The blood CATT must be done and the result recorded, indicating the appearance of the agglutination (+, ++, or +++). Dubious blood CATTs, where the agglutination is barely perceptible, must be considered negative. When the blood CATT is positive, a CATT 1:4 must be done.
- When the CATT 1:4 is positive, the CTC needs to be done on 2 capillary tubes, using clean, appropriate counting chambers. An X16 eyepiece would make readings easier than one rated at X10.
- When the CTC is negative, a mAECT (preferably buffy coat) must be done.
- In instances where there is sufficient mAECT equipment available and there are sufficient numbers of staff to perform it (because it takes longer than the CTC), this test should be done straightaway, without waiting for a CTC.
- If all previous tests are negative, a CATT 1:16 must be done.
- In cases where there is a positive CATT 1:16 and the parasitology tests are negative on the day of the screening, if possible, these tests should be repeated the next day.
- Positive CATT 1:16s where the parasitology tests are negative must be considered new serological cases.
- Individuals showing symptoms suggestive of HAT must be examined, even if the blood CATT is negative.

5.9 Graphs, tables, and sample questionnaires

Table 4

Compilation of data obtained from the HAT exploratory mission
Dingila and Poko Health Areas, December 2009

Sites screened	Screened	M	F	Moved	CATT+	LNPs done	LNP+	CTC+	Stage 1	Stage 2
Dingila, Codénord district	100	48	52	11	7	2	0	3	3	0
Tobola	110	27	83	1	6	1	0	3	2	1
Bambesa, Bolungwa district	100	54	46	4	21	10	1	3	3	1
Dembia, Zongia district	80	40	40	0	9	4	1	3	4	0
Sopi, Bobuda	50	23	27	0	12	1	0	3	3	0
Amadi, Kin district: Centre	110	30	80	29	33	1	0	9	7	2
Amadi, Ndedule village	80	31	49	3	16	2	0	2	2	0
TOTAL	630	253	377	48	104	21	2	26	24	4

Table 5

HAT Screening (2014) in the Ganga – Dingila nord Area

Laboratory TEST New Cases	First Quarter 2014			Second Quarter 2014			Total for 2014		
	No. of tests done	No. of tests positive and/or WCC >5/mm ³ or tryp positive	% of tests positive	No. of tests done	No. of tests positive and/or WCC >5/mm ³ or tryp positive	% of tests positive	No. of tests done	No. of tests positive and/or WCC >5/mm ³ or tryp positive	% of tests positive
Total blood CATT	5834	162	2.78%	7838	143	1.82%	Already an impact 13672	305	2.23%
CATT 1:4	158	103	65.19%	142	95	66.90%	300	198	66.00%
LNP	14	0	0.00%	3	0	0.00%	17	0	0.00%
CTC	103	29	28.16%	95	0	0.00%	198	29	14.65%
mAECT	74	5	6.76%	95	2	2.11%	169	7	4.14%
CATT 1:16	4	2	50.00%	93	23	24.73%	97	25	25.77%
LP	27	12	44.44%	21	0	0.0%	48	12	25.00%
Stage unknown (LP refused)		9	25.00%		3	12.00%		12	19.67%
Suspect		53	0.91%		73	0.93%	0	126	0.92%

The difference between the results from the first and second quarters is enormous.

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