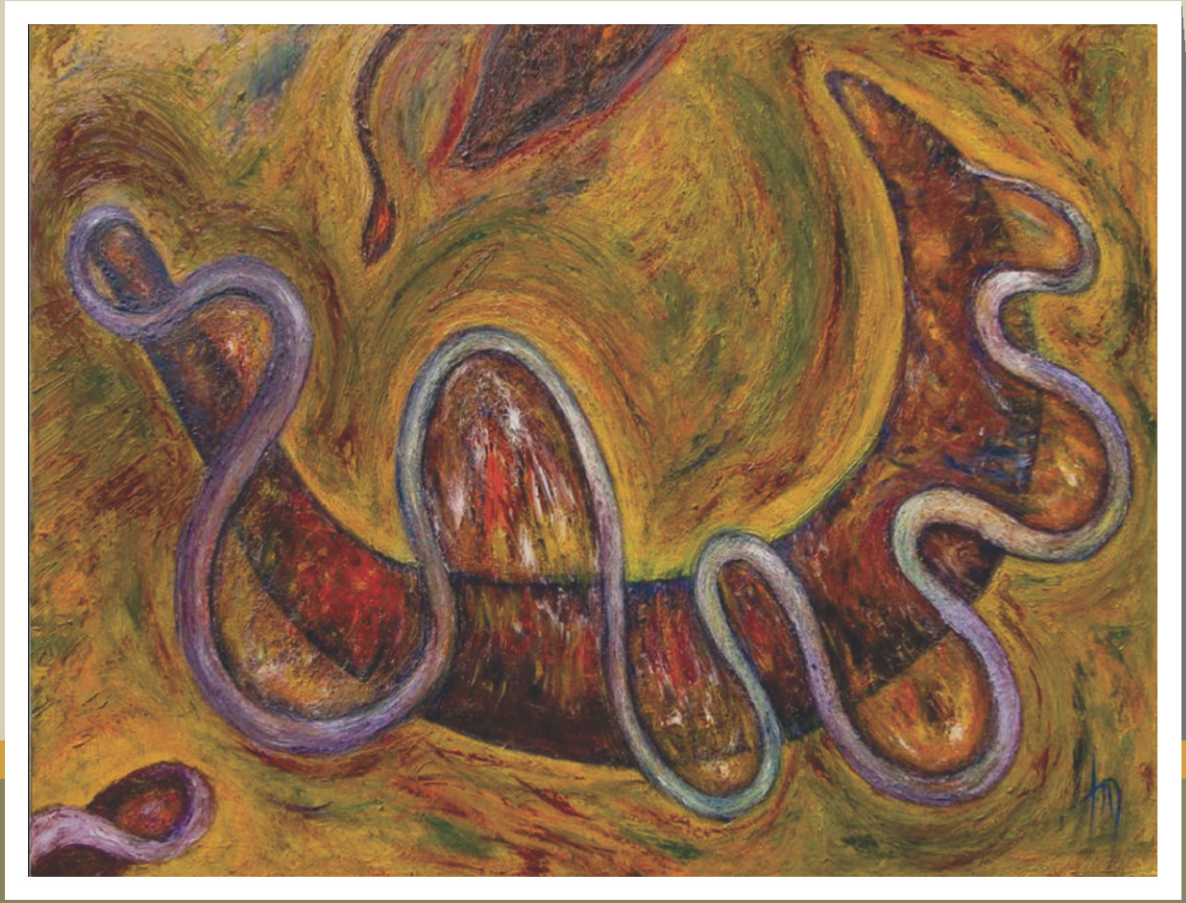
Report of the fourth WHO stakeholders meeting on gambiense and rhodesiense human African trypanosomiasis elimination



Virtual meeting, 1–3 June 2021

World Health Organization

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ISBN 978-92-4004504-0 (electronic version)
ISBN 978-92-4004505-7 (print version)

Suggested citation. Report of the fourth WHO stakeholders meeting on gambiense and rhodesiense human African trypanosomiasis elimination, Virtual meeting, 1–3 June 2021. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Cover page: Illustration from the original "Mala sangre" by Nestor Favre-Mossier, 2007

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Abbreviations and acronyms

AAT	animal African trypanosomiasis
BMGF	Bill & Melinda Gates Foundation
CATT	card agglutination test for trypanosomiasis
CIRAD	Centre de coopération internationale en recherche agronomique pour le développement (Agricultural Research Centre for International Development)
CIRDES	Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (International Centre for Research and Development of Livestock in the subhumid zone)
COCTU	Coordinating Office for Control of Trypanosomiasis in Uganda
CSF	cerebrospinal fluid
DBS	dried blood spot
DiTECT-HAT	diagnostic tools for HAT elimination and clinical trials
DNDi	Drugs for Neglected Diseases initiative
DTAG	WHO Diagnostic Technical Advisory Group
EDCTP	European and Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
FAO	Food and Agriculture Organization of the United Nations
FIND	Foundation for Innovative New Diagnostics
HAT	human African trypanosomiasis
g-HAT	human African trypanosomiasis due to *T. b. gambiense*
r-HAT	human African trypanosomiasis due to *T. b. rhodesiense*
HAT-e-TAG	Technical Advisory Group for HAT elimination
HAT MEPP	HAT modelling and economic predictions for policy
HUG	Hôpitaux universitaires de Genève (Geneva University Hospitals)
ICAReB	Clinical Investigation and Access to Research Bio-resources
IHMT	Institute of Hygiene and Tropical Medicine, Lisbon
INRB	Institut National de Recherche Biomédicale (National Institute for Biomedical Research), Kinshasa
INSP	Institut National de Santé Publique, Côte d'Ivoire
IPR	Institut Pierre Richet, Bouake
IRD	Institut de Recherche pour le Développement (National Research Institute for Development)

ITM	Institute of Tropical Medicine, Antwerp
ITT	intention to treat
LAMP	loop-mediated isothermal amplification
LSTM	Liverpool School of Tropical Medicine
mITT	modified intent to treat
MSF	Médecins Sans Frontières (Doctors Without Borders)
NECT	nifurtimox–eflornithine combination therapy
NSSCP	national sleeping sickness control programme (PNLTHA in French)
NTD	neglected tropical disease
PAAT	Programme Against African Trypanosomiasis
PASS	post-authorization safety study
PATTEC	Pan-African Tsetse and Trypanosomiasis Eradication Campaign
PHP	public health problem
PK/PD	pharmacokinetics/pharmacodynamics
PNLTHA	Programme National de lutte contre la trypanosomiase humaine africaine (NSSCP in English)
PP	per-protocol
PV	pharmacovigilance
RDT	rapid diagnostic test
SL-RNA	spliced leader RNA
STPH	Swiss Tropical and Public Health Institute
TEAE	treatment emergent adverse event
TPP	target product profile
WBC	white blood cell
WHO	World Health Organization

1. Introduction

Since 2000, concerted efforts by national programmes, supported by public–private partnerships, nongovernmental organizations, donors and academia under the auspices and coordination of the World Health Organization (WHO), have produced important achievements in the control of human African trypanosomiasis (HAT). As a consequence, the disease was targeted for elimination as a public health problem by 2020. The Sixty-sixth World Health Assembly endorsed this goal in resolution WHA66.12 on neglected tropical diseases, adopted in 2013.

National sleeping sickness control programmes (NSSCPs) are core to progressing control of the disease and in adapting to the different epidemiological situations. The involvement of different partners, as well as the support and trust of long-term donors, has been crucial for the achievements. Almost 20 years of partnership among WHO, Sanofi and Bayer have enabled WHO to strengthen and sustain financial, technical and material support for the implementation of control activities in countries where HAT is endemic. The long-term support from the Government of Belgium in the Democratic Republic of the Congo has also been essential.

WHO has now convened the fourth stakeholders meeting on the elimination of gambiense HAT (g-HAT) and rhodesiense HAT (r-HAT), for the first time as a joint meeting held virtually in June 2021. The previous meetings on g-HAT in 2014 *(1,2)*, 2016 *(3)*, and 2018, *(4,5)* as well as on r-HAT in 2015, *(6,7)* 2017 *(8)* and 2019 *(9)* reinforced the partnership and commitment for HAT elimination and structured the mechanisms of collaboration within the WHO network for HAT elimination. The network includes NSSCPs, groups developing new tools, international and nongovernmental organizations involved in disease control, and donors.

An outstanding reduction in the number of HAT cases has been achieved, reaching the global threshold targeted for the elimination of HAT as a public health problem three years in advance, in 2017. Accordingly, the area at risk has been importantly reduced as well.

The new road map for neglected tropical diseases 2021–2030 with the target to interrupt the transmission of g-HAT requires the strengthened and sustained efforts of all stakeholders, national authorities and partners. It will take disproportionally high efforts and innovative strategies to find the last cases of g-HAT. Given the limited resources and other competing public health priorities, this is a challenge that requires our joint commitment.

2. Meeting objectives

The objectives of the meeting were:

- to keep up the commitment of national authorities and technical and financial partners to WHO's objectives for HAT;
- to sustain and strengthen the network for collaboration and coordination among stakeholders;
- to review progress towards the elimination of HAT as a public health problem and to share achievements, challenges and perspectives among countries and implementing partners;
- to assess the status of critical technical aspects in research, development and implementation of therapeutic and diagnostic tools, epidemiology and vector control; and
- to discuss strategies for reinforcing control and surveillance of HAT in regard to the targets of the new road map.

3. Opening remarks

Dr Jose Ramon Franco Minguell, Medical Officer, HAT control and surveillance programme, WHO Department of Control of Neglected Tropical Diseases (WHO/NTD), welcomed all participants, reminding them that last year's stakeholders meeting had to be cancelled due to the COVID-19 pandemic, and that in 2021, this was a joint meeting for g-HAT and r-HAT. The participants were introduced and organizational notes concerning the online format were provided.

Dr Alexandre Tiendrebeogo, NTD Team Leader, WHO Regional Office for Africa, on behalf of Dr Matshidiso Moeti, WHO Regional Director for Africa, opened the meeting and welcomed all participants. He recalled the significant progress that has been made towards eliminating HAT as a public health problem. He pointed out the challenges ahead on the way to the interruption of transmission of g-HAT in 2030, such as limited resources and the COVID-19 pandemic. He highlighted the important role of all stakeholders and thanked all the partners whose commitment is highly appreciated.

Dr Mwelecele Ntuli Malecela, Director, WHO/NTD, emphasized the importance of this meeting. She highlighted that for the third consecutive year the number of HAT cases reported was below 1000, and she congratulated Togo and Côte d'Ivoire for the validation of elimination of HAT as a public health problem. She stressed the reduction of NTD activities due to the COVID-19 pandemic, particularly in care provision and mass drug administration. WHO has issued guidance on how to continue essential services safely. She reminded the meeting of the new NTD road map 2021–2030 with the target to interrupt the transmission of g-HAT. For this important challenge, coordinated work among partners and health authorities of endemic countries will be crucial. Integration of activities in peripheral health care systems, expanding multisectoral action, strong national ownership, and the availability and affordability of new tools are required. In response to the difficulties in diagnostics, WHO has established a diagnostic technical advisory group for NTDs to advise on diagnostics for control programmes, design target product profiles for priority diagnostics and explore ways to ensure access to the needed diagnostic tests. She appreciated the great support of all partners and donors and asked them to maintain their efforts, which are producing relevant results. Dr Malecela concluded her remarks by noting that the achievements of HAT elimination should be seen also in the broader goal of providing universal health coverage for the "bottom billion" affected by NTDs.

The meeting was chaired by Professor Michael Barrett, University of Glasgow. The meeting agenda is attached as Annex 1 and the list of participants as Annex 2.

4. Situation report of gambiense and rhodesiense human African trypanosomiasis

The situation report was presented by the representatives of NSSCPs at the stakeholders meeting in three regional groups of countries, namely: West Africa, Central Africa (both with g-HAT), and East Africa (r-HAT).

4.1 West Africa (gambiense HAT)

The West African g-HAT endemic countries can be grouped according to their **surveillance activities** as:

- countries without surveillance and information: the Gambia and Guinea-Bissau;
- countries without surveillance but occasional assessment activities: Liberia, Niger, Senegal and Sierra Leone;
- countries that have moved from active surveillance to passive surveillance: Benin, Burkina Faso, Ghana, Mali, Nigeria, Togo; and
- countries conducting both active and passive surveillance: Côte d'Ivoire and Guinea.

The current HAT situation was presented for nine countries: Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Liberia, Mali, Nigeria and Togo.

Guinea has the biggest HAT burden in this group, and therefore leads the trend in the region (Figures 4.1.1–4.1.2). The Ebola virus disease epidemic forced the complete interruption of HAT surveillance and control in Guinea and impeded access to diagnosis and treatment at that time. Consequently, the number of reported cases decreased in 2014 and 2015. The resumption of active screening led to an increase in the number of cases detected in 2016 and 2017. Côte d'Ivoire continues to report a low number of cases. In 2019–2020 the number of reported cases decreased despite continued active screening efforts. Active and passive screening activities, as well as information on treatment, are shown in Tables 4.1.1–4.1.2 cumulatively for the West Africa region.

Figure 4.1.1. Distribution of g-HAT cases (red) in the West Africa region and locations where no cases were detected in active screening (green), 2016–2020

Figure 4.1.2. Numbers of g-HAT cases declared by countries in the West Africa region, 2011–2020

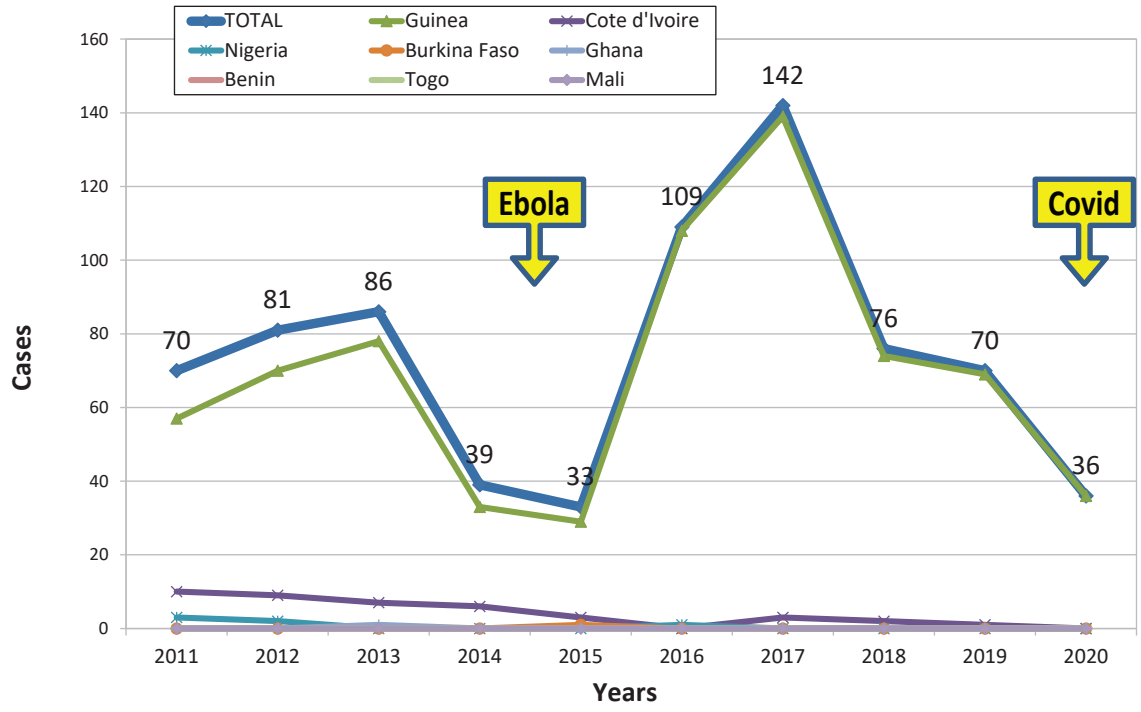


Table 4.1.1. Surveillance with active screening and number of HAT cases detected in the West Africa region, 2016–2020

Active screening	2016	2017	2018	2019	2020
No. of countries with active screening	3	3	2	2	2
Population screened	10 976	25 419	35 763	21 165	20 962
Cases detected by active screening	67	93	42	41	15
Cases detected by passive screening	40	50	34	29	21
Total cases detected	107	142	76	70	36

Table 4.1.2. Number of HAT cases treated in the West Africa region, 2016–2020

Treatment of cases	2016	2017	2018	2019	2020
Treated cases	104	143	76	70	36
(% of detected cases)	97%	101%	100%	100%	100%

Two out of eight countries practice systematic **vector control** against HAT (Côte d'Ivoire, Guinea) with the use of insecticide-treated tiny targets. In both countries there is an awareness of the populations with a strong involvement of the communities. Difficulties in vector control are the lack of funding, lack of expertise at country level, lack of commitment of partners and the focus on research use only in some countries.

The working group of West African countries pointed out the following **difficulties and challenges**:

- The COVID-19 pandemic disrupted planned activities (absence of supervision, cessation of active screenings and training of staff);
- Low funding with an absolute lack of funding for certain planned activities (e.g. supervision of sentinel sites);
- Lack of supervision for various causes resulted in a halt of activities in surveillance sites;
- Insufficient staff assigned to HAT programmes;
- Administrative problems (change of HAT focal points and other health staff);
- Decrease or loss of competence of staff (e.g. retirement, lack of training);
- Fluctuation of trained staff in health facilities;
- Delay in the registration of fexinidazole;
- Shortage of rapid screening tests;
- Low reporting of serological suspects for parasitological testing; and
- Insecurity (Mali).

4.2 Central Africa (gambiense HAT)

The Central Africa group comprised 10 countries: Angola, Cameroon, Central African Republic, Chad, Democratic Republic of the Congo, Equatorial Guinea, Gabon, Republic of the Congo, Uganda and South Sudan.

Figure 4.2.1 shows the geographical distribution of reported g-HAT cases in 2016–2020.

Overall, the numbers of cases in this region have decreased significantly from 2001 cases in 2016 to 529 cases in 2020. Democratic Republic of the Congo has the biggest HAT burden in this group, and therefore leads the trend in the region (Figures 4.2.1–4.2.3)

Figure 4.2.1. Distribution of g-HAT cases in the Central Africa region (red), 2016–2020; the locations of active screenings without cases detected are indicated in green

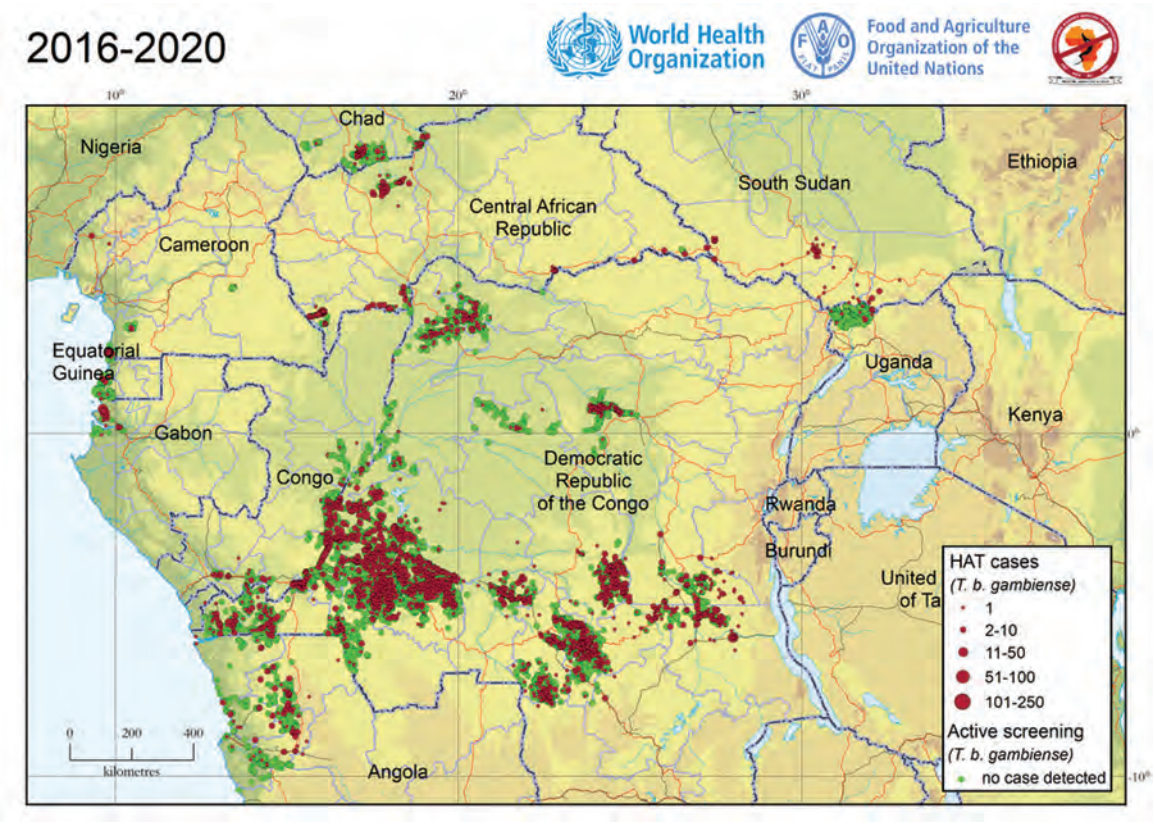


Figure 4.2.2. Numbers of g-HAT cases declared by countries in the Central Africa region (excluding Democratic Republic of the Congo), 2011–2020

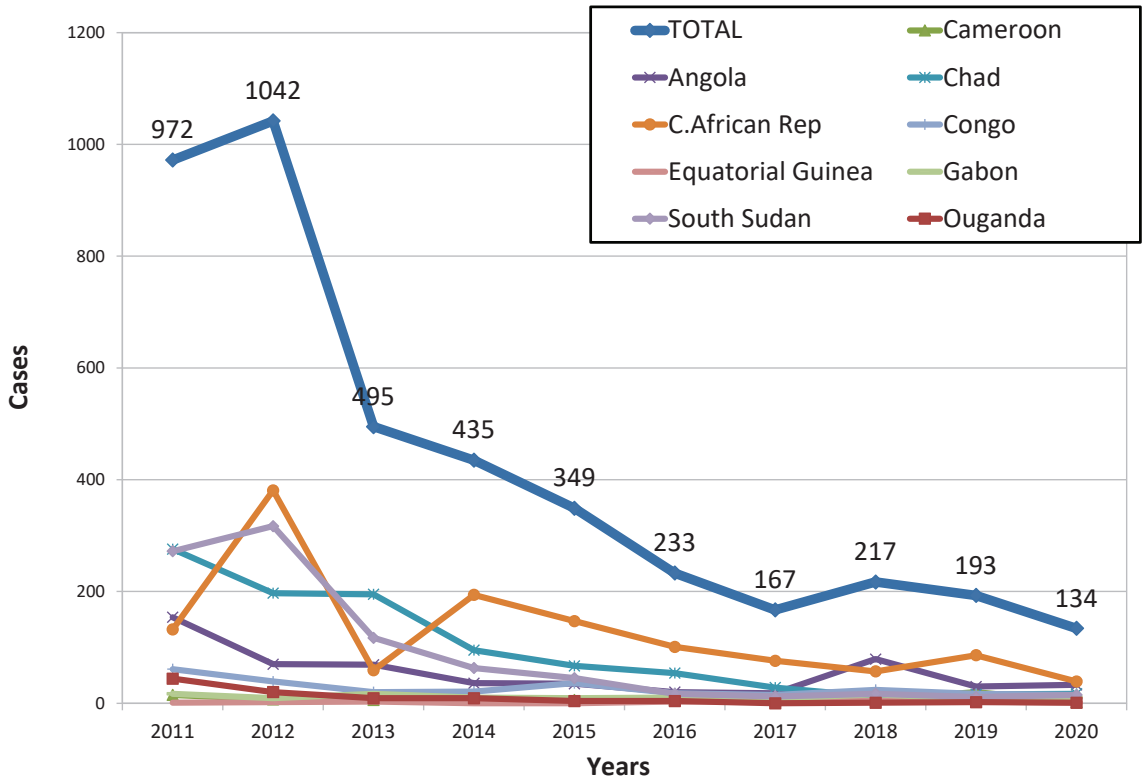


Figure 4.2.3. Total number of g-HAT cases declared by Democratic Republic of the Congo, 2011–2020

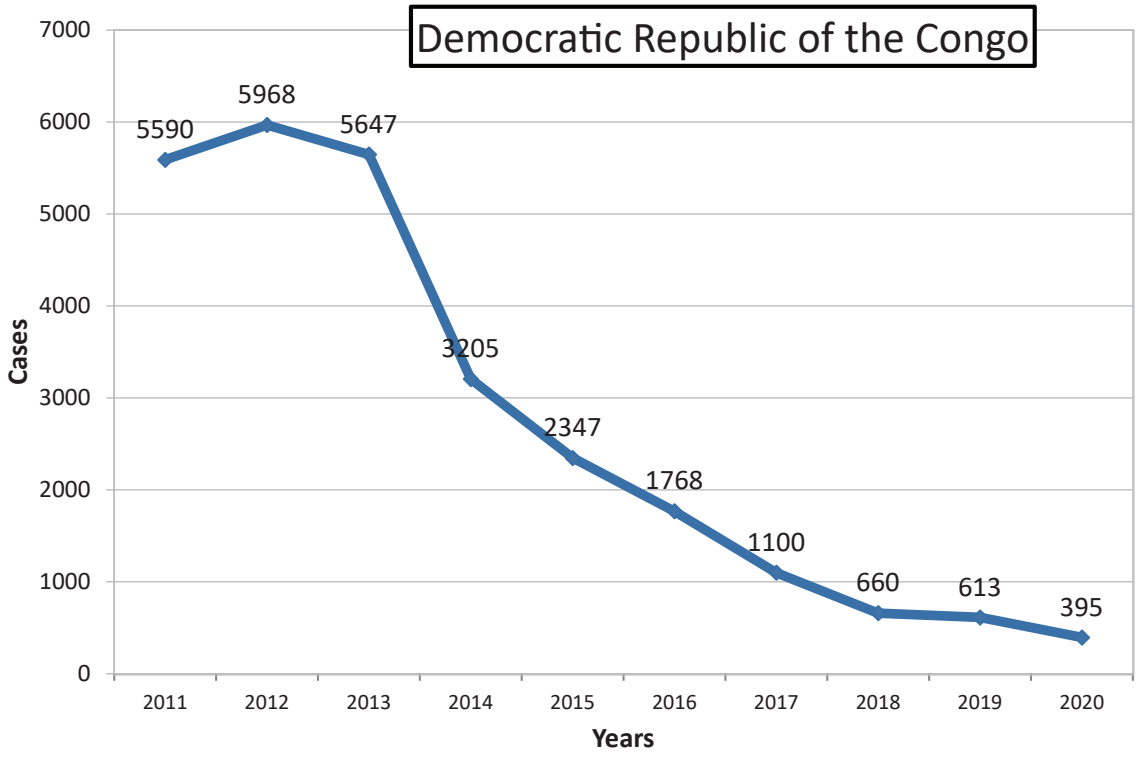


Figure 4.2.4 and Table 4.2.1 summarize active and passive screening activities. As a result of the COVID-19 pandemic, the number of countries conducting active screening and the number of people actively screened declined in 2020. Accordingly, the proportion of passively detected cases increased. Table 4.2.2 provides information on treatment for the Central Africa region from 2016 to 2020.

Table 4.2.1. Surveillance with active screening and number of HAT cases detected in the Central Africa region, 2016–2020

	2016	2017	2018	2019	2020
No. of countries with active screening	10	10	9	9	7
Population screened by active screening	2 337 660	2 258 177	2 663 093	2 826 735	1 624 957
Cases detected by active screening	1148	576	452	457	227
Cases detected by passive screening	853	691	425	349	302
Total cases detected	2001	1267	877	806	529

Table 4.2.2. Number of HAT cases treated in the Central Africa region, 2016–2020

Treatment of cases	2016	2017	2018	2019	2020
Treated cases	2001	1266	877	806	529
(% of detected cases)	100%	100%	100%	100%	100%

Five of the 10 countries practice **vector control** against HAT systematically (Angola, Chad, Democratic Republic of the Congo, Gabon and Uganda). The strategy used is mainly based on the use of insecticide-treated tiny targets but also other strategies (traditional traps and ground spraying in Angola). There is an effort to involve local health structures (Democratic Republic of the Congo, Uganda) and affected communities (Angola, Chad, Democratic Republic of the Congo, Uganda). Difficulties in vector control are lacking or insufficient funding, lack of expertise in some countries and lack of cross-border synergy of activities in some endemic zones.

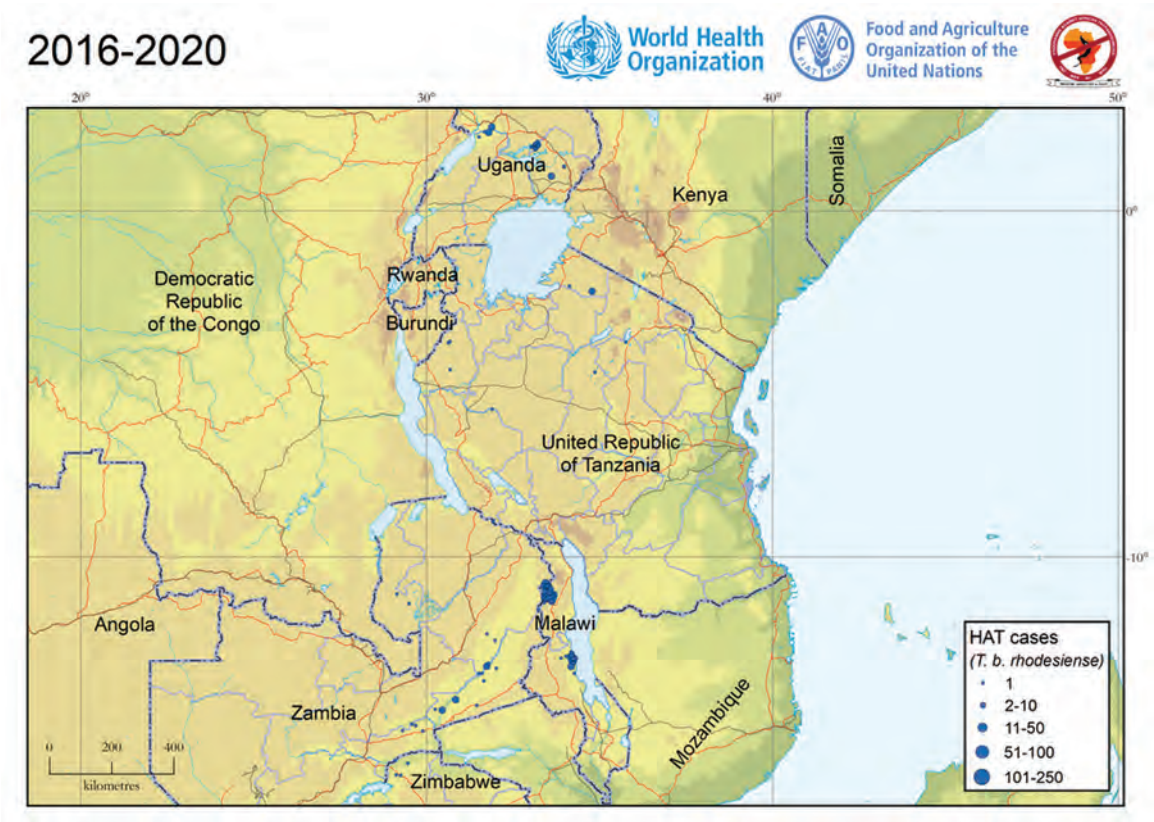
The working group of Central African countries identified the following **difficulties and challenges**:

- Difficulties related to COVID-19: stop of active screenings for several months and decline in passive screenings;
- Insufficient State funding and delays in receiving and mobilizing external funds (WHO and other donors). This may lead to active testing being carried out at an inappropriate time;
- Insufficient budget: difficulties in obtaining funds in a context of decreasing case numbers
- Dependence on partners' priority activities;
- Low population participation in active screening when prevalence is low;
- Difficulty in making reactive screening operational;
- Difficulty in integrating passive screening into health services;
- Insufficient number of well-trained personnel due to retirement of experienced staff and staff turnover;
- Old equipment and materials;
- Logistical problems with no or very old vehicles;
- Weak inter-sectoral collaboration of stakeholders in the fight against HAT; and
- Unforeseen impact of social crises (e.g. insecurity).

4.3 East Africa (rhodesiense HAT)

Seven countries are endemic for r-HAT: Kenya, Malawi, Rwanda, Uganda, United Republic of Tanzania, Zambia and Zimbabwe. Figure 4.3.1 shows the geographical distribution of reported r-HAT cases in 2016–2020.

Figure 4.3.1. Distribution of r-HAT cases (blue), 2016–2020



In the past 10 years (2011–2020), 86% of all cases were reported from Malawi and Uganda. In 2019 and 2020, there was a significant increase in the number of cases due to an outbreak in Malawi starting in late 2019 and calming down by March 2020. This increase was in stark contrast to that of the other countries and to the decreasing trend of previous years. (Figures 4.3.1–4.3.2). This outbreak could have been linked to extraordinarily high temperatures and a parallel outbreak of foot-and-mouth disease in domestic animals causing food shortages in the population, which led to more hunting for food. The number of tsetse flies increased with detection in unusual zones, and tsetse–human contact increased due to these factors combined. Of the 821 r-HAT cases reported during 2011–2020 (Table 4.3.1), 68% were already in stage 2. The case-fatality rate increased from 3.7% in 2016 to 9.2% in 2020 (Table 4.3.2).

Figure 4.3.2. Numbers of r-HAT cases declared by Kenya, Malawi, Rwanda, Uganda, United Republic of Tanzania, Zambia and Zimbabwe, 2011–2020

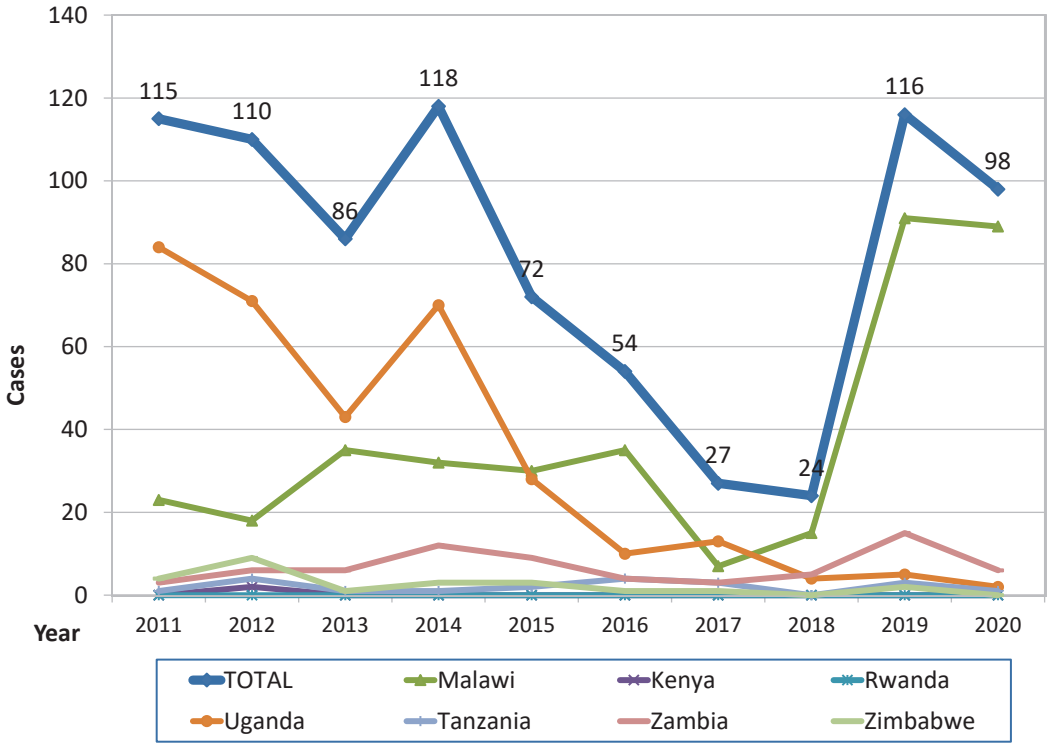


Figure 4.3.3. Distribution of r-HAT cases by country, 2011–2020 (above) and 2019–2020 (below)

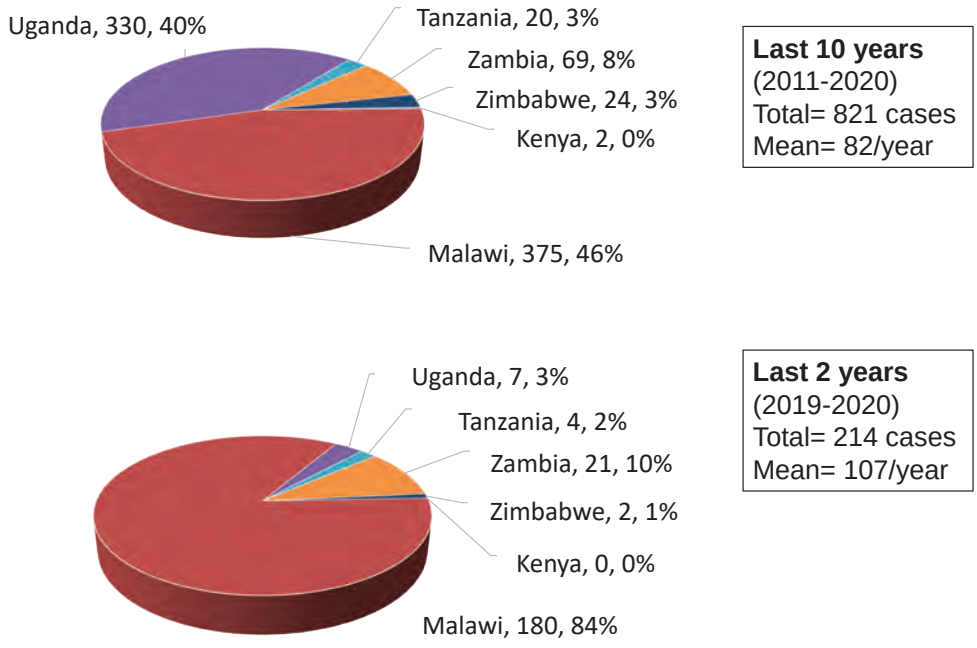


Table 4.3.1. r-HAT cases by disease stage, 2011–2020

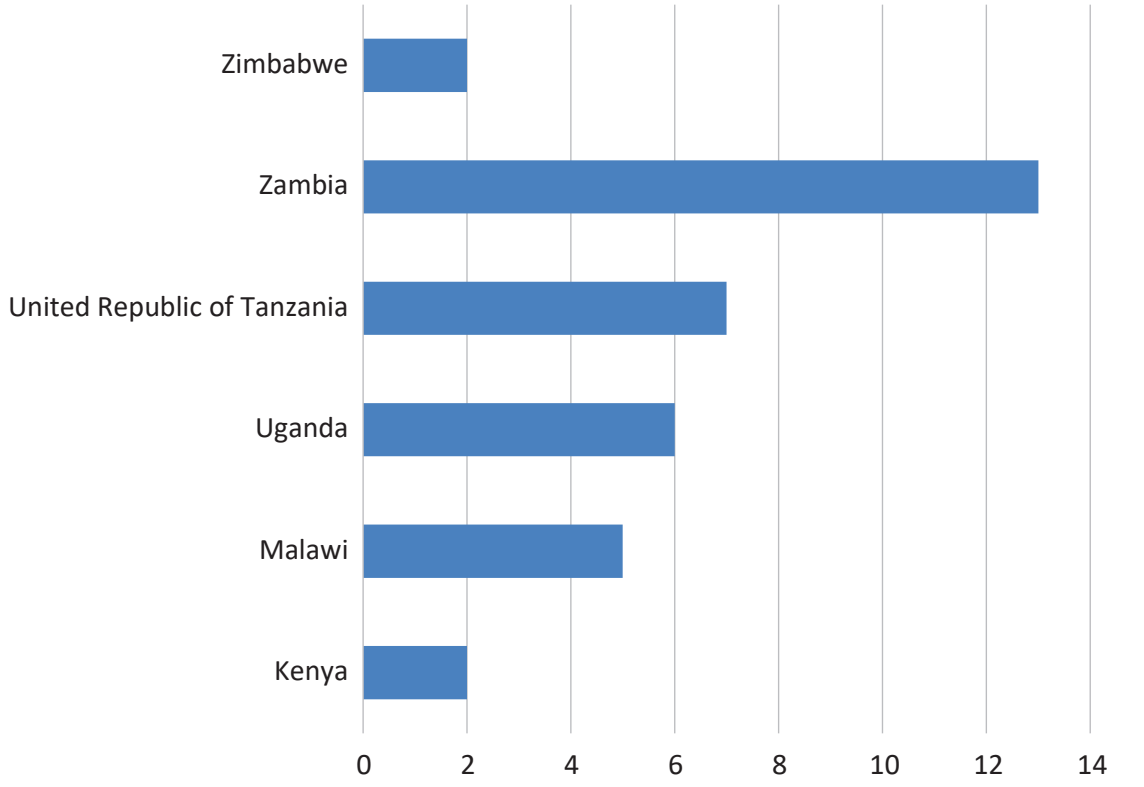
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Stage 1	31	39	17	22	27	15	4	14	46	33	248
Stage 2	83	69	64	94	45	39	22	10	66	65	557
Stage unknown	1	2	6	2	0	0	1	0	4	0	16
Total	115	110	87	118	72	54	27	24	116	98	821

Table 4.3.2. Cases of r-HAT treated, with number of deaths and case-fatality rate, 20162020

Treatment of cases	2016	2017	2018	2019	2020
Treated cases	54	27	24	116	98
% of detected cases	100%	100%	100%	100%	100%
Deaths	2	1	2	7	9
Case-fatality rate	3.7%	3.7%	8.3%	6.0%	9.2%

During the period 2011–2020, 35 cases with r-HAT were reported from non-disease endemic countries. The country exporting more r-HAT cases was Zambia (13). Other countries exporting r-HAT cases were the United Republic of Tanzania (7), Uganda (6), Malawi (5), Zimbabwe (2) and Kenya (2) (Figure 4.3.4). Most r-HAT cases were diagnosed in South Africa (11), a frequent destination for medical evacuation flights from south and east African countries, but also in India (3), Netherlands (3), United States of America (3), Belgium (2), Germany (2), Sweden (2), United Kingdom of Great Britain and Northern Ireland (2), Argentina (1), Canada (1), China (1), France (1), Italy (1), Norway (1) and Spain (1).

Figure 4.3.4. Cases of r-HAT exported by country, 2011–2020



All seven r-HAT endemic countries are using **vector control** to varying degrees. Methods used are the deployment of insecticide-treated targets and traditional traps, ground spraying, spraying of tourist vehicles (national parks), and spraying and treatment of animals. Challenges for vector control are the lack of funding, the insufficient expertise at the country level and the lack of commitment by partners.

The working group of East African countries identified the following **difficulties and challenges**:

- COVID-19 disrupted community activities, drug delivery, supervisory visits and support from the national level;
- The outbreak in 2019–2020 in Malawi that provoked a sharp increase in workload;
- Inadequate funding from the government;
- Few partners interested in supporting the national control programmes;
- Insufficient utility vehicles for the national control programmes;
- Diminishing capacity of health workforce for HAT diagnosis (e.g. through competing priorities, retirement) and insufficient training for health staff in active foci and referral hospitals;
- Weak multisectoral coordination;
- Due to the widespread use of malaria rapid diagnostic tests (RDTs), r-HAT cases are not detected microscopically;
- Lack of a quality assurance programme for r-HAT laboratory diagnosis.

5. Update of the epidemiological situation

In 2012, WHO established the goal to eliminate HAT (g-HAT and r-HAT) as a public health problem by 2020. Beyond that, the goal for g-HAT is to interrupt transmission (sustainable elimination) by 2030.

The **primary indicators** are:

- the number of cases reported per year; and
- the area at risk reporting ≥ 1 case/10 000 people per year, calculated considering a period of five years.

The **secondary indicators** are to assess other aspects including the quality and intensity of activities, namely:

- the geographical extent of the disease;
- the populations at different levels of risk; and
- the proportion of the population at risk covered by control and surveillance.

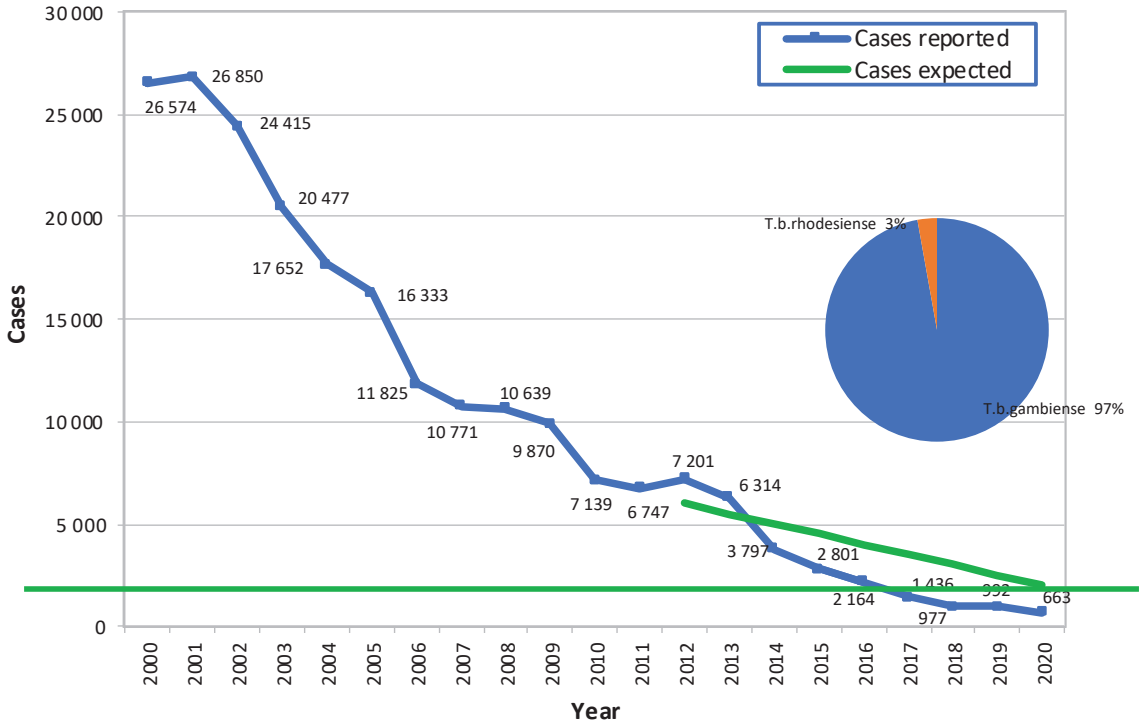
The **global target** for elimination of HAT as a public health problem by 2020 is defined as follows:

- < 2000 cases reported annually at continental level; and
- 90% reduction of the total area at risk reporting ≥ 1 case/10 000 people per year from the 2004 baseline level.

5.1 Reported cases

The **number of HAT cases reported** annually reduced by 98% from 26 574 in 2000 to 663 cases in 2020 (Figure 5.1.1). Most cases (97%) were g-HAT (r-HAT 3%); however, the proportion of r-HAT is increasing. In 2017, for the first time, < 2000 cases were reported, so this target has sufficiently been reached.

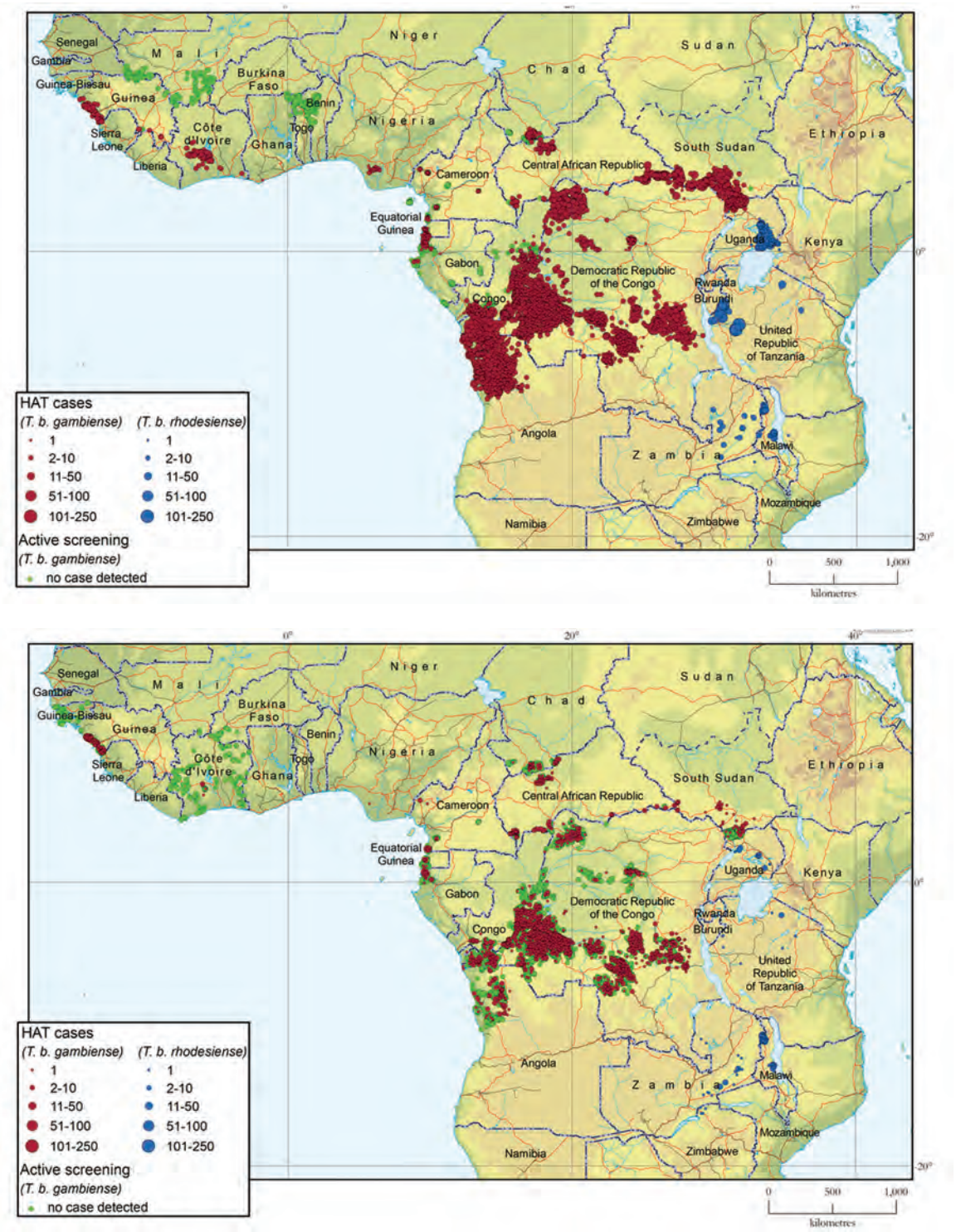
Figure 5.1.1. Progression towards HAT elimination: numbers of cases reported (blue line) in 2000–2020 and benchmark (green line) of the numbers of cases targeted for 2012–2020



5.2 Geographical distribution of cases

Cases of HAT have been mapped at the village level in the HAT Atlas database since 2000. Figure 5.2.1 shows the distribution of cases cumulated by 5-year periods comparing the initial period 2000–2004 with the period 2016–2020. The evolution of the distribution shows the reduction in those areas presenting cases.

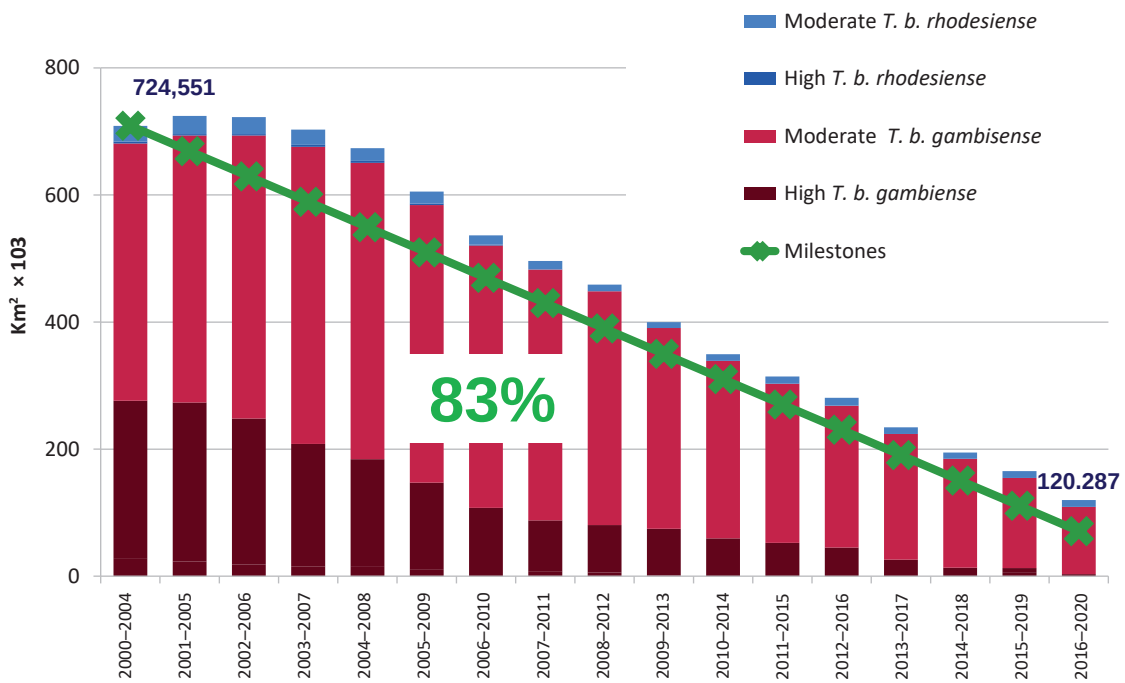
Figure 5.2.1. Geographical distribution of HAT cases (g-HAT in red, r-HAT in blue), cumulated by 5-year periods; the locations of active screenings without cases detected are indicated in green



5.3 Areas at risk

Figure 5.3.1 shows the total area at risk reporting ≥ 1 case/10 000 people per year (g-HAT in red, r-HAT in blue) and the associated milestones from 2000 to 2020. The area in all risk categories showed a marked and steady reduction by 83% taking the mean of the 2016–2020 period.

Figure 5.3.1. Total area at risk (very high, high and moderate) for g-HAT (red) and r-HAT (blue) reporting ≥ 1 case/10 000 people per year, 2000–2020; the green line is the set milestone



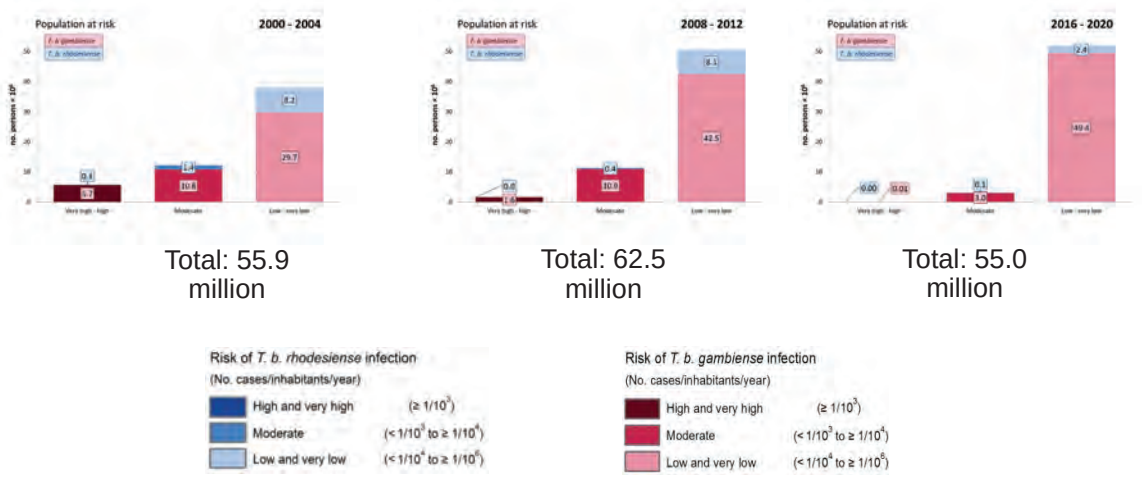
Areas at risk importantly reduced, from 724 551 to 120 287 km^2 (mean of the 2016–2020 period). Nevertheless, this important reduction (83%) is below the target of 90% reduction from 2000–2004 baseline levels. High and very high-risk areas have been extremely reduced (98.8%) with only very few km^2 remaining.

This target was originally defined as < 1 new reported case per 10 000 inhabitants/year in at least 90% of foci. As foci are not objectively measurable and as the area at risk of HAT can be better measured in a standardized way via Geographical Information Systems tools, the HAT-e-TAG refined this indicator. The 90% target was transferred from the initial to the refined indicator. It has also to be considered that the last area at risk shown in this graph is estimated for the period 2016–2020 (mean) and therefore strongly influenced by higher values 5 years ago. It is expected that the targeted 90% reduction of the total area at risk reporting ≥ 1 case/10 000 people per year calculated as overlapping 5-year periods will be reached in 1–2 years.

5.4 Population at risk

During 2000–2004, 55.9 million people were estimated to be at risk of infection (Figure 5.4.1), of which 5.8 million were at very high and high risk, and 12.2 million at moderate risk. Therefore, 18 million people lived in areas where g-HAT was still considered a public health problem. Compared with the former 5-year periods, substantial numbers of people have shifted from higher risk to lower risk categories nowadays. During 2016–2020, still 55 million people were estimated to be at risk of infection. However, a dramatic reduction was achieved in the very high and high-risk categories, which decreased to 0.2 million people; 3.1 million people were at moderate risk in this period; and 51.8 million people were at low or very low risk, which is not considered as a public health problem. When interpreting the data, a general increase in the population must be considered.

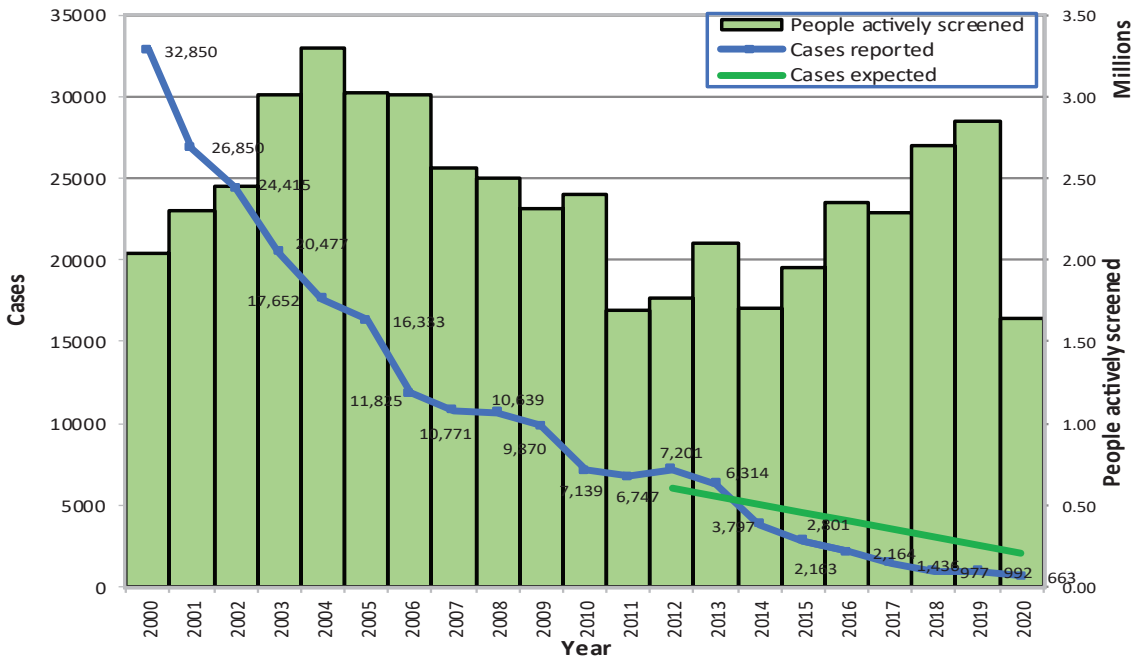
Figure 5.4.1. Population at risk of g-HAT (red) and r-HAT (blue), by level of risk in 2000–2004, 2008–2012 and 2016–2020



5.5 Coverage of population at risk

The sustained decrease in the numbers of reported cases is not a consequence of decreasing surveillance activities: rather, the numbers of people screened have been maintained at high levels (Figure 5.5.1). In 2019, nearly 3 million people were actively screened for HAT through concerted efforts of the countries, with Democratic Republic of the Congo as a major contributor. The marked reduction in 2020 is explained by the impact of the COVID-19 pandemic. The preliminary data of 2021 (not shown) indicate a recovery in the number of people actively screened.

Figure 5.5.1. Number of people screened and number of reported cases, globally; the green line is the benchmark of numbers of cases targeted from 2012 to 2020



The number of health facilities with capacity to screen (passively), diagnose and treat HAT has increased annually, thereby improving access to diagnosis and treatment. In 2013, 732 fixed health facilities provided diagnosis of HAT and 530 provided any treatment for HAT. In 2019, 1438 fixed health facilities provided diagnosis and 719 provided any treatment for HAT (Figure 5.5.2). Surveys are conducted biannually. The 2021 survey (not yet finalized) is confirming this trend. Through the increased diagnostic capacity, the epidemiological knowledge is better than ever before.

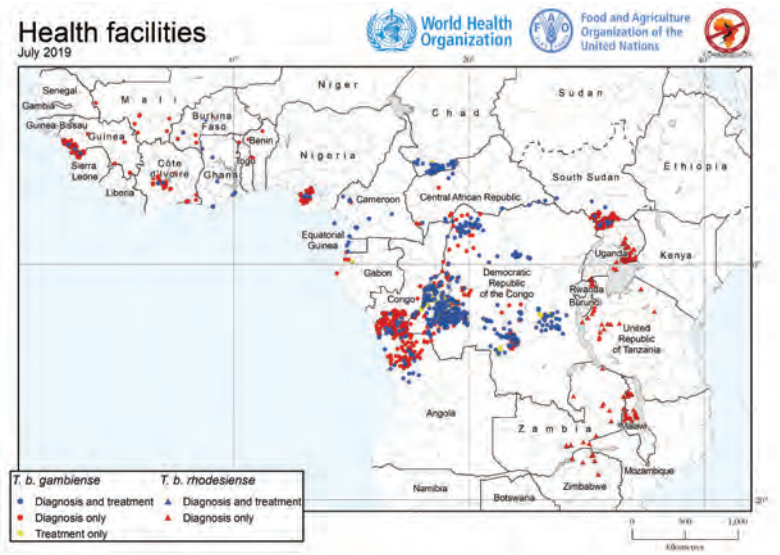
Figure 5.5.2. Health facilities providing g-HAT (dots) and r-HAT (triangles) diagnosis and treatment in 2019; red indicates only diagnostic capacity, blue diagnostic and treatment capacity

2013

732 diagnosis facilities
530 treatment facilities

2019

1 438 diagnosis facilities
719 treatment facilities



*2021 – Update survey in progress

5.6 Impact of COVID-19 on HAT activities

According to a WHO pulse survey conducted in 2020–2021 on continuity of essential health services during the COVID-19 pandemic, the most frequently disrupted services were those for mental health and NTDs. Some 76% of countries have postponed one or more planned NTD activity, mainly training/capacity-building, large-scale preventive chemotherapy campaigns, population screening/surveillance for active case-finding, advocacy and resource mobilization.

For HAT, a major impact was the interruption of active screening activities in all the endemic countries (for a duration of 3–12 months). Furthermore, health resources were diverted to COVID-19 control and management, with a consequent reduction of HAT passive screening (to varying extents). Trainings, including on the new treatment guideline, had to be cancelled and supervisions were disrupted. Vector control activities were reduced (supervision and setting of new traps and targets). Important logistical problems were linked to transport (e.g. of drugs) due to the reduction of flights and the prioritization of resources for COVID-19.

Measures to mitigate the consequences have been taken. WHO provided guidance and the NSSCPs adapted their activities (e.g. digital meetings, active screening and sensitization with face masks).

In the discussion it was pointed out that an interruption of active screening for one year can be subsequently caught up well, also with the help of the WHO HAT Atlas, indicating which villages have been missed.

5.7 Conclusions

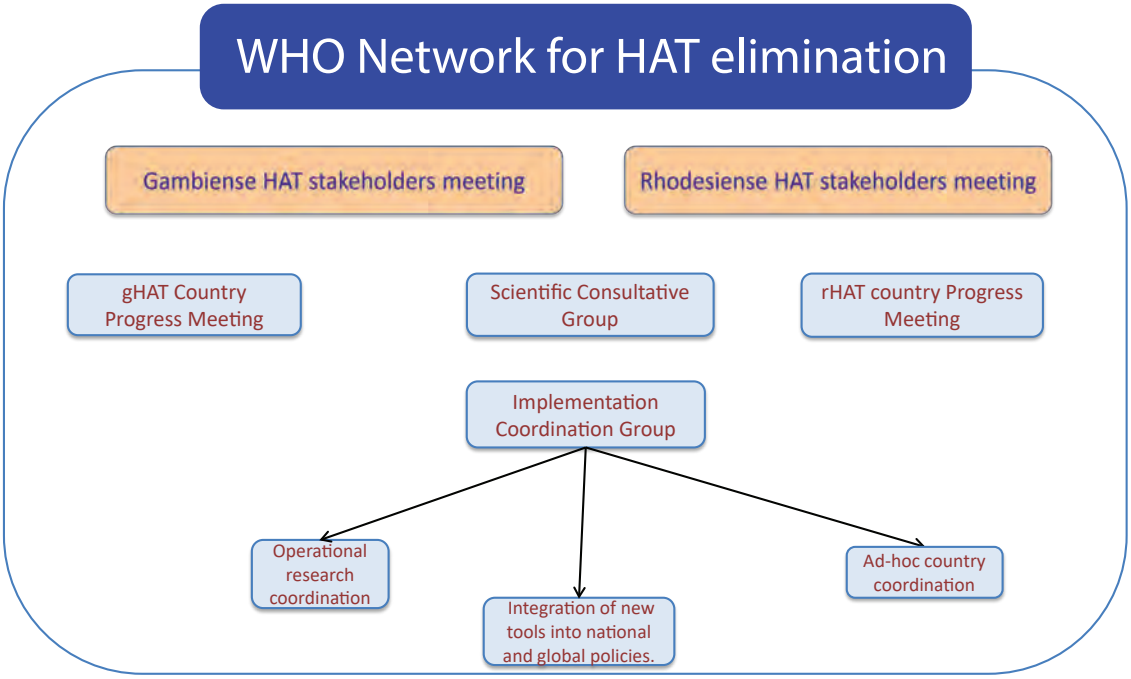
An outstanding reduction in the number of cases has been achieved, below the targeted figure. The coverage of the population at risk by control activities has been maintained, with an increase in passive coverage but a decrease in active screening due to the pandemic situation. The area at risk has been importantly reduced, but slightly below the target. Therefore, the targets identified for elimination of HAT as a public health problem have not been fully achieved; it is expected that this goal will be reached in the next 1–2 years. There are still 55 million people at risk of HAT but only 3 million are at moderate risk, and only 0.2 million at high or very high risk. The progress in HAT control has been remarkable but, strictly speaking, the elimination of HAT as a public health problem is not yet reached. The COVID-19 pandemic had a significant negative impact on the process of HAT elimination; adaptive strategies limited its impact (e.g. virtual meetings, adapted active screening, reinforcement of passive screening). The situation of r-HAT is less well known and the risk for r-HAT epidemics is always present.

Finally, all stakeholders can be congratulated for the achievement. The new targets have now to be addressed for 2030.

6. Report of the WHO network for HAT elimination 2019–2020

In order to coordinate the different stakeholders involved in the HAT elimination process and to strengthen and sustain efforts, WHO launched the network for HAT elimination in 2014 (Figure 6.1).

Figure 6.1. Configuration of the WHO Network for HAT elimination



In the past 2 years, the different groups and subgroups of the network conducted various activities.

- **Stakeholder meetings**
  - 3rd rhodesiense HAT stakeholders meeting in Geneva in April 2019;
  - 4th gambiense HAT stakeholders meeting planned for April 2020 was cancelled due to the COVID-19 pandemic; and
  - for the first time, a joint stakeholders meeting for g-HAT and r-HAT, as a virtual event in June 2021.
- **Annual country coordination meetings**
  - for g-HAT in Abidjan in February 2019, and as a virtual event in June 2020 and February 2021;
  - for r-HAT in Geneva in April 2019, and as a virtual event in February 2021.
- **Ad-hoc country coordination**
  - Democratic Republic of the Congo (PNLTHA partners meeting): Kinshasa, January 2019; Liverpool, September 2019; Antwerp, January 2020; virtual event March 2021;
  - Benin – Togo: Grand Popo, February 2020;

- Guinea: Conakry, December 2019;
- Uganda: Kampala, April 2019;
- South Sudan – Uganda: June 2019; and
- Chad: November 2019.

- **Scientific Consultative Groups**
  - Technical Advisory Group for HAT elimination (HAT-e-TAG): 3rd meeting (Geneva, November 2019) and 4th meeting as virtual event in December 2020; and
  - "Ad hoc" Guideline Development Group: advice on the extended use of acoziborole for g-HAT, virtual event, September 2020.
- **Integration of new treatment tools into national and global policies subgroup**
  - Update on access to new oral drugs for HAT (Geneva, January 2019);
  - Possible uses of a single dose oral drug in g-HAT elimination (Geneva, December 2019);
  - Update on acoziborole development and integration. Next steps and timing (May 2021, virtual).
- **HAT-DTAG subgroup**
  - Terms of reference and methods for developing use cases and TPPs (May 2020, virtual); and
  - Discussion use cases and TPP for a test for r-HAT usable in peripheral health facilities (September 2020, virtual).

Moreover, two new groups have been constituted:

- **Sociocultural perspectives in HAT elimination** (planned meeting in May 2020 postponed to July 2021) (jointly with IHTM Lisbon).
- **Role of vector control in the elimination of g-HAT** (planned meeting in June 2020 postponed to Sept 2021) (jointly with the Food and Agriculture Organization of the United Nations; FAO).

The coordination of the different technical partners and NSSCPs is a high priority for WHO. The HAT elimination network continues actively at different levels as a very useful tool for coordination. NSSCPs play a central role in efforts to eliminate HAT. The HAT elimination Technical Advisory Group (HAT-e-TAG) is a key element to advise on efforts and strategies for HAT elimination. Meetings are held annually on the invitation of WHO.

7. Validation of elimination of HAT as a public health problem at country level

A country could be considered as having eliminated HAT as a public health problem (PHP) when dedicated medical activities and other epidemiological evidence have shown that there are < 1 case/10 000 people, in all the health districts of the country over the previous 5-year period. Countries meeting these criteria can request the validation of elimination as a PHP. A validation dossier has to be prepared and submitted to WHO, documenting the elimination of HAT as a PHP. A reviewing validation team (with a minimum of four experts) is constituted to evaluate the completeness, accuracy and reliability of the country dossier. The reviewing validation team ascertains the likelihood that HAT is no longer a public health problem in the country and that the criteria established for this purpose are met. The validation team assesses whether the surveillance system is adequate and the data can be considered reliable. The WHO secretariat coordinates that process and produces the final report, which is agreed on. The final report is submitted to the WHO Regional Office for Africa and is endorsed by its Regional Director. The Director-General of WHO then sends a letter of notification to the Ministry of Health, and the information is published in the *Weekly Epidemiological Record* and the Global Health Observatory. A reassessment is foreseen after 5 years.

Table 7.1 categorizes the eligibility of the HAT endemic countries – according to national indicators and control/surveillance activities – to request the validation of elimination as a PHP. The countries are grouped in five categories:

- elimination still not reached (red);
- elimination reached but surveillance insufficient (orange);
- elimination reached and ready to submit for validation (yellow);
- elimination reached and dossier submitted for validation (green);
- post-validation surveillance (white).

Elimination of HAT as a PHP has been validated in two countries, which entered the post-validation surveillance phase (as of May 2021): Côte d'Ivoire and Togo. It is expected that some other countries will be validated this year (Benin, Equatorial Guinea, Ghana, Rwanda and Uganda (g-HAT)). Countries are encouraged to advance preparation of the validation dossier. Support is limited, which complicates the validation process for some countries.

Table 7.1. Eligibility of HAT endemic countries for claiming the validation of elimination as a PHP, according to the epidemiological situation and activities in control and surveillance

Elimination as PHP still not reached	Elimination as PHP reached but surveillance insufficient	Elimination as PHP reached and ready to submit for validation	Elimination reached and submitted for validation	Post Validation Surveillance
Angola, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Gabon, Guinea, Malawi, South Sudan	Botswana, Burundi, Eswatini, Ethiopia, Gambia, Guinea-Bissau, Liberia, Mozambique, Namibia, Niger, Nigeria, Senegal, Sierra Leone, United Republic of Tanzania, Uganda (T.b.r), Zambia, Zimbabwe	Burkina Faso Cameroon Ghana Kenya Mali	Benin Equatorial Guinea Rwanda Uganda (T.b.g)	 Togo Côte d'Ivoire

Update on May 2021

8. Updated g-HAT treatment guidelines: implementation and pharmacovigilance of fexinidazole

8.1 New WHO interim guidelines for the treatment of g-HAT

In late 2018, the new oral drug fexinidazole was approved by the European Medicines Agency under Article 58, a mechanism designed for medicines intended for use outside the European Union. WHO conducted an evidence-based, independent, formal process to define recommendations for each medicine for g-HAT considering the new treatment option with fexinidazole.

Fexinidazole has advantages over the other medicines, but has also limitations:

- Easier administration, less demanding for staff;
- Effective in both stages, but less effective than nifurtimox–eflornithine combination therapy (NECT) in severe stage 2;
- Easier logistics, but requires concomitant food intake (to be absorbed in therapeutic levels);
- Being a 10-day oral course, presents a risk of non-compliance, increased by frequent nausea, vomiting and psychiatric effects; and
- Not approved for children aged < 6 years or body weight < 20 kg.

In August 2019, the new WHO interim guidelines for the treatment of g-HAT were issued *(10)* and new criteria for treatment allocation were defined. The first-choice treatment is determined now by a two-step assessment: the first step is a clinical examination and the second is the cerebrospinal fluid (CSF) examination (lumbar puncture; LP), which is required only for patients with defined clinical symptoms and signs suggestive of severe second stage. Without clinical suspicion of severe second stage, a lumbar puncture can be avoided and fexinidazole preferentially be given in patients aged ≥ 6 years and body weight ≥ 20 kg (Table 8.1). Therewith, lumbar punctures can be avoided in many patients.

Table 8.1. Summary of treatment choices for patients with g-HAT

Age, body weight	Clinical examination	CSF findings	Treatment		
			1st choice	2nd choice	Rescue
< 6 yrs or < 20 kg		≤ 5 WBC/µL, no trypanosomes	pentamidine	-	NECT
		> 5 WBC/µL, or trypanosomes	NECT	eflornithine	NECT-long
≥ 6 yrs and ≥ 20 kg	No suspicion of severe HAT	LP not needed	fexinidazole	– LP needed – Pentamidine (first-stage) or NECT (second-stage)	NECT
	Suspicion of severe HAT	< 100 WBC/µL	fexinidazole	Pentamidine (first-stage) or NECT (second-stage)	NECT
		≥ 100 WBC/µL or failed LP	NECT	fexinidazole	NECT-long or melarsoprol

In case of clinical suspicion of severe second stage, according to the result of the lumbar puncture, fexinidazole is the first-choice treatment in patients with < 100 white blood cells (WBC)/µL CSF and NECT is the first-choice treatment in patients with ≥ 100 WBC/µL CSF or unavailable CSF data.

Patients with age < 6 years or body weight < 20 kg (for whom fexinidazole is not approved) must undergo a lumbar puncture and CSF examination to determine the treatment with pentamidine or NECT (same recommendations as before).

For fexinidazole to be absorbed in therapeutic levels it must be taken in a fed condition. Solid food should be taken within 30 min before the tablets. Each fexinidazole intake must be directly observed by a trained health staff. The correct dosage should be ensured and the 10 days of treatment completed. Hospitalization should be mandatory in case of doubts about adherence to treatment, if food intake is not ensured, in patients with psychiatric disorders or body weight < 35 kg.

In the case of fexinidazole, being a new medicine and taking into account the risk of insufficient compliance, it is recommended that patients are asked to attend for a general examination at 6, 12, 18 and 24 months, or at any time if symptoms reappear. In case of signs or symptoms suggesting a possibility of relapse, laboratory examinations of body fluids are recommended.

The interim character of the new treatment guidelines was pointed out. The guidelines need to be further refined according to the experiences that the countries are currently making.

8.2 Implementation, distribution and pharmacovigilance of fexinidazole

For the **implementation** of fexinidazole, countries must comply with certain requirements:

- Official indication of the adoption of fexinidazole through inclusion in national protocols, or in the National List of Medicines, or through a letter from the Ministry (high level);
- List of sites chosen to use fexinidazole;
- Staff trained in use of fexinidazole, and in pharmacovigilance (PV); and
- Commitment to monitoring PV and data transmission.

As of June 2021, six countries have implemented fexinidazole (Table 8.2.1), and Angola has started official adoption as a seventh country. So far, PV data are provided by three countries.

Table 8.2.1. Situation of fexinidazole implementation as of June 2021

Country	Official adoption	List of sites	Trained staff	Shipped	Pharmaco vigilance
Angola	✓[a]				
Cameroon					
Congo					
Côte d'Ivoire					
Gabon	✓	✓	✓	✓	
Guinea	✓	✓	✓	✓	✓
Guinea Eq.	✓	✓	✓	✓	
Nigeria					
CAR	✓	✓	✓	✓	
DRC	✓	✓	✓	✓	✓
South Sudan					
Chad	✓	✓	✓	✓	✓
Uganda					

Pharmacovigilance of fexinidazole was requested by the European Medicines Agency (EMA) as post-authorization study (PASS). Active, enhanced PV has to be conducted during the initial period of use of fexinidazole in a cohort event monitoring design (non-interventional). The treatment follows exactly the routine national protocol. During a period of 3 years, data of all patients treated with fexinidazole will be collected using simple one-page forms for adverse events, for follow-up, and in case of pregnancy. In case of drug exposure in pregnancy, the pregnancy outcome will be reported, and the child followed up for the first 2 years of life. The data will be transmitted to WHO by the HAT national programme. Data will be also transmitted to the national PV programme (long-term PV). The electronic data base is managed by WHO. As of April 2021, around 120 patients are treated with fexinidazole. So far, the PV data of 79 patients treated at 33 sites in Chad, Democratic Republic of the Congo and Guinea were received by WHO (Table 8.2.2). Adverse events occurred in 72%, without any serious adverse events (AEs), and 5 patients completed the 6-month follow-up.

Table 8.2.2. Initial pharmacovigilance data as of 30 April 2021

Number of sites reporting (Chad, DRC, Guinea)	33
Number of patients reported	79
Sex ratio (M:F)	1.6
Age in yrs. (median, range)	30 y (7–74)
Pregnant women	1
Trypanosomes seen	86% (68/79)
Full dosage given	92% (72/79)
AE during treatment	72% (57/79)
Serious AE	0
Follow up reports (6 months)	5

The **distribution** of HAT drugs in the elimination context is challenging. Less patients will be treated at more sites with now six drugs. The amount of required drugs is low or very low, but production is greater than need, due to a minimum batch size. Many facilities are treating few or no patients, but medicines must be accessible. Unused medicines need to be destroyed.

As an adaptive response, eflornithine presentation changed from 100 mL to 50 mL vials and with a new production plant smaller batches can be produced. For fexinidazole, stocks are semi-centralized (e.g. at district level) to avoid wastage and will be sent to the peripheral sites when needed for a patient.

In general, logistics of distribution are still cumbersome and expensive. Despite these new challenges, manufacturers have renewed their commitment to donate the needed medicines, and WHO continues to ensure access to them for all cases in whom HAT has been diagnosed.

Perspectives for new treatments could emerge through the ongoing clinical trial on fexinidazole in r-HAT in Malawi and Uganda. For acoziborole, a clinical trial in adults has been completed and a trial in children will start soon. Furthermore, a study protocol is under development to investigate the widened use of acoziborole beyond confirmed HAT cases.

9. Status of development of acoziborole

The Drugs for Neglected Diseases *initiative* (DND*i*) provided an update on the **OXA-02-HAT trial** including the 18-month follow-up (preliminary analysis), a phase II/III multi-centre, open-label, single arm, prospective trial to assess the efficacy and safety of acoziborole in adult patients with g-HAT.

Study population: 260 patients have been screened in 13 sites and 208 have been treated with acoziborole. Each patient was parasitologically confirmed at baseline (video recording of trypanosomes). Most women were in early stage and most men in stage 2. Among these 208 patients, two groups can be distinguished by disease progression:

1. **41 patients in early and intermediate stage**, defined by no trypanosomes in the CSF and ≤ 20 WBC/µL CSF. All patients were followed-up at M6, 12 and 18.
2. **167 patients in stage 2**, defined by trypanosomes in the CSF or > 20 WBC/µL CSF. During the follow up until M18, 4 patients died (not drug-related), 1 patient was lost to follow-up after D11, and in 3 patients rescue treatments were initiated.

In 139 (83.2%) of the stage 2 patients, trypanosomes were detected in the CSF, and 128 (76.6%) stage 2 patients were in severe stage with > 100 WBC/µL CSF. The mean (± SD) WBC count in CSF was 398.8 (±438.4) cells/µL.

Some preliminary results are presented here waiting for the definitive results after final analysis of the data.

The **treatment success rate at 18 months in early and intermediate stage** was:

- 100% (41/41; CI [confidence interval] 95% Jeffreys: 94.1–100) for mITT=ITT=PP

The **treatment success rate at 18 months in stage 2** was:

- 95.2% (159/167; CI 95% Jeffreys: 91.2–97.7) for mITT=ITT=PP
- 98.1% (159/162; CI 95% Jeffreys: 95.1–99.5) for the evaluable patients

The efficacy results at M12 were the same as those at M18. The efficacy results with acoziborole correspond to the best results of studies with NECT (Table 9.1).

Table 9.1. Treatment success rate at 18 months in the DNDi-OXA-02-HAT trial with acoziborole (No. 9) in comparison to other trials with NECT (No. 1–7) and fexinidazole (No. 8)

Study	Success rate (%) at M18	Jeffrey 95% CL
1.Mesu 2017 (Fex004: NECT) (success=124 / 130)	95.4	90.7-98.1
2.Priotto 2006 (success=16 / 17)	94.1	75.6-99.4
3.Checchi 2007 (success=29 / 31)	93.5	80.9-98.6
4.Priotto 2009 (success=135 / 143)	94.4	89.7-97.3
5.Kansiime 2018 (success=50 / 55)	90.9	81.2-96.4
6.Total (success=354 / 376)	94.1	91.4-96.2
7.NECT field (success=582 / 613)	94.9	93.0-96.5
8.Mesu 2017 (Fex004: Fexinidazole) (success=239 / 264)	90.5	86.6-93.6
9.DNDi-OXA-02-HAT (success=159 / 167)	95.2	91.2-97.7

Note: results are presented in ITT populations instead of mITT because results on mITT are not available for all trials.

For information, results on mITT with fexinidazole were: success = 239/262 (91.2%) -95% Jeffrey CI= (87.3–94.2).

A very rapid decline of the mean **WBC count** (Min; Max) per µL **CSF** could be demonstrated in the evaluable patients **during the follow-up** visits: pre-screening: 398.8 (6; 2705); ≥ D11: 106.7 (1; 946); ≥ M6 12.8 (0; 105); ≥ M12: 6.8 (0; 77); ≥ M18: 4.4 (0; 19). A rapid improvement of HAT signs and symptoms was demonstrated for D15.

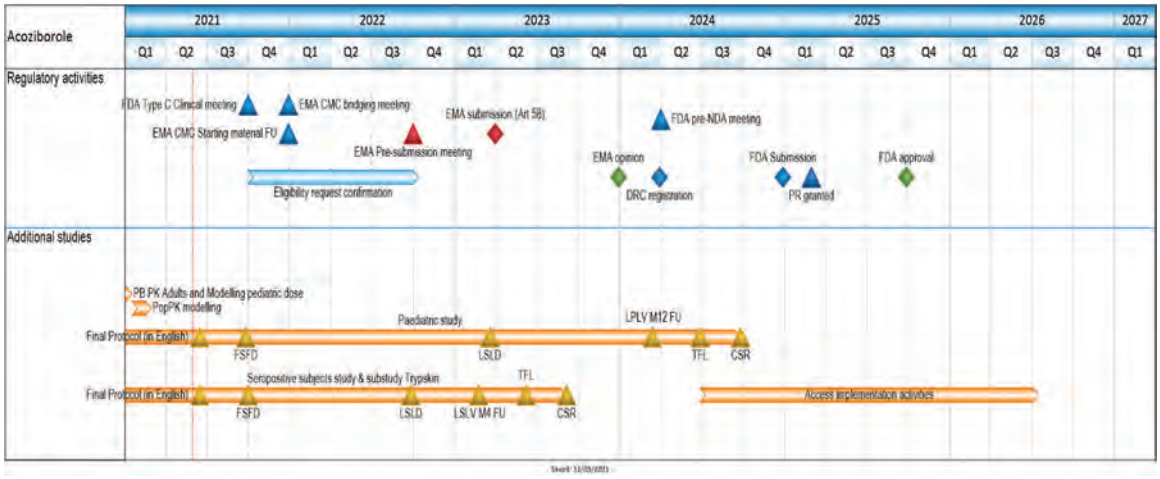
Among the 208 treated patients, 600 **treatment emergent adverse events** (TEAE; 92.7% mild to moderate; 7.3% severe; 4.5% serious) were observed in 155 (74.5%) patients; 38 TEAE (6.3%) in 29 patients (13.9%) were considered as drug related and all were mild to moderate. No severe or serious drug-related TEAE were observed. All 38 drug-related TEAE occurred within D1–D4, mainly on D1.

Four deaths were reported during the study, all of them were considered as not being related to the drug. The 27 serious TEAEs described in 21 patients were all considered not to be related to the drug and all the patients recovered (one with sequel). The serious TEAEs per system organ class were, in descending order of frequency: infections and infestations (e.g. malaria); psychiatric disorders, gastrointestinal disorders, nervous system disorders and others.

The **safety laboratory results** showed no significant changes from baseline in haematology parameters, liver enzyme (ALT, AST) and other biochemistry data. The thyroid function tests (TSH, fT3, fT4) showed no clinically significant abnormal value. The **electrocardiogram** recordings (with central re-readings) detected no out-of-range values. An increase of the heart rate was observed 4 h and 9 h after dosing. No significant change of the QTcF was observed.

The main regulatory activities foreseen in the **development plan** (Figure 9.1) are the pre-submission meeting with EMA planned in Q3 2022, and the submission under Article 58 in Q1 2023. The EMA opinion is expected for Q4 2023. The EMA evaluation timing is based on a “fast track” review of 9 months. A registration of the medicine in Democratic Republic of the Congo is planned in Q1 2024.

Figure 9.1. Acoziborole development plan (best case scenario)



Regarding the paediatric use of acoziborole, the **DNDi-OXA-05-HAT trial**, the study protocol is close to finalization. Study set-up activities are initiated. First patient first dose is planned for Q3 2021. Last patient last follow-up at 12 m is planned in Q1 2024, with the CSR in Q3 2024.

Regarding the **DNDi-OXA-04-HAT trial** for the use of acoziborole in non-parasitologically confirmed cases, the study protocol is finalized, and the start of the study is planned for Q4 2021. The completion of the 4-month follow-up of all patients is planned for Q1 2023 if a recruitment of one year is considered. The study report is envisaged for Q3 2023.

The pharmacokinetics of acoziborole include an absorption rate of 70% without food, a slow rate of absorption (Tmax = 48–72 h) and good distribution in all tissues. Resistance to acoziborole can be selected under pressure in the laboratory. It would be interesting to investigate the genetic background of parasites in relapsed cases.

10. Report of the working group on integration of new tools into national and global policies

The working group on integration of new tools into national and global policies is part of the WHO Network for HAT elimination. The group aims to facilitate the integration of newly developed tools (new drugs, diagnostic tests and algorithms, as well as vector control tools and methodologies) into national and global policies as they become available. It covers regulatory issues where necessary and identifies the needed adaptation and harmonization of policies and strategies together with the countries; it discusses monitoring and evaluation, and it works to develop strategies for ensuring access for populations at risk.

The group is coordinated by the WHO/NTD HAT team and includes various participants: national HAT control programmes, DND*i*, the Foundation for Innovative New Diagnostics (FIND), the Bill & Melinda Gates Foundation (BMGF), Sanofi and Bayer, and several other WHO groups (Prequalification of Medical Products; Regulatory Systems Strengthening; WHO Model List of Essential Medicines; Safety and Vigilance; Innovation, Access and Use; and the Special Programme for Research and Training in Tropical Diseases).

Furthermore, several academic institutions are participating: The Institut de Recherche pour le Développement (IRD), the Swiss Tropical and Public Health Institute (STPH), University of Makerere, University of Glasgow, Institute of Tropical Medicine (ITM) Antwerp, Hôpitaux universitaires de Genève (HUG), Médecins Sans Frontières (MSF), Institute of Hygiene and Tropical Medicine, (IHMT Lisbon). Collaborations are established with EMA, the US Food and Drug Administration and the HAT-e-TAG.

The group has celebrated 11 meetings – 8 on new drugs and 3 on diagnostics – since December 2014.

One focus of the group was on fexinidazole in the treatment of g-HAT, with discussions on clinical trials, access and deployment plans, regulatory procedures, roles and responsibilities. The meeting on 24 January 2019 addressed the access to fexinidazole, taking into account the positive scientific opinion of the EMA. This led to the development of the WHO interim treatment guidelines for g-HAT including fexinidazole.

The clinical trial of fexinidazole for the treatment of r-HAT was first discussed and approved in December 2016. In 2018, the European and Developing Countries Clinical Trials Partnership (EDCTP) approved and funded a clinical trial in Malawi and Uganda. This can be considered as a milestone achievement as the treatment of r-HAT is a particularly neglected aspect of a neglected disease.

Another focus of this group was on acoziborole. Discussion on its use started in June 2015. The pivotal clinical trial (OXA-02) for the treatment of g-HAT started in October 2016. The possible extended use of acoziborole in the context of elimination of g-HAT was explored on 11 December 2019. The current status of the clinical trials, next steps and timelines of acoziborole development and integration in elimination policies were discussed at the eleventh meeting on 25 May 2021. The efficacy and safety results are very promising, but there is need for more safety data including rare adverse events for extended use in seropositive g-HAT patients, need for more safety data in pregnant and lactating women, as well as need for more safety data in paediatric patients and a paediatric formulation.

In recent years, the group has been able to assist the development and deployment of major new tools and the proceeding was mainly according to expected schedule. New tools bring new challenges for adequate integration for the field use, requiring innovative visions and solutions.

11. Diagnostics for HAT

11.1 Advances and perspectives

Laboratory diagnostics in the context of HAT elimination can be applied to individuals with suspected but microscopically unconfirmed g-HAT, in order to (i) increase suspicion or confirm infection (e.g. sentinel sites of WHO); (ii) for a-posteriori confirmation of infection in persons treated without parasitological confirmation (e.g. widened treatment); and (iii) for surveillance of transmission in low-prevalence settings.

High throughput g-HAT testing (simultaneously on a larger number of specimens) can be applied for verification of elimination, post-elimination monitoring, and for the exploration of "blind spots". It can be applied on humans, other vertebrates or tsetse flies.

There are several options of **serological tests**: trypanolysis, immunofluorescence, indirect enzyme-linked immunosorbent assay (ELISA), inhibition ELISA and α-tsetse saliva ELISA (Table 11.1)

Table 11.1. Serological tests for g-HAT

	throughput	antigen N / R	laboratory level	technical skill	DBS	animal reservoir
Trypanolysis	low	N	high	high	yes	no
Immunofluorescence	medium	N	low	medium	yes	no
Indirect ELISA	high	N/R	medium	medium	yes	no
Inhibition ELISA	high	N/R	medium	medium	yes	no
α-tsetse saliva ELISA	high	R	medium	medium	yes	yes

All these tests can be applied on dried blood spot (DBS) samples. The α-tsetse saliva ELISA has been developed recently and still needs validation. The immunofluorescence test has been forgotten for quite a long time, but the availability of LED-based fluorescence microscopes (FIND) opens new perspectives for an update of this test.

Molecular tests on DNA or RNA can be applied on all tissues, including skin. DNA is very stable and taxon-specific. Some tests allow identification at subspecies level. Several protocols exist for the extraction of DNA from dried blood samples, but none can be considered for high throughput testing. RNA is an unstable molecule and therefore a better marker for active infection. RNA has to be stabilized before sent to the reference laboratory. Table 11.2 summarizes new developments in molecular tests.

Table 11.2. New developments in molecular tests for g-HAT

DNA

Institute	Target	Assay	Specificity
ITM, Van Reet	minichromosome TBR	multiplex qPCR	Trypanozoon
ITM, Geerts	minicircle kDNA	qPCR	*T.b. gambiense* I

RNA

Institute	Target	Assay	Specificity
ITM	18S	RT-qPCR	Trypanozoon
ITM	SNP in 60S	RT-qPCR	*T.b. gambiense* I
ITM	TgsGP	RT-qPCR	*T.b. gambiense* I
IRD	SNPs in 6 different genes	RT-qPCR	*T.b. gambiense* I
IP	TgsGP	SHERLOCK*	*T.b. gambiense* I
IP	7SL-RNA	SHERLOCK	Trypanozoon

* Specific High sensitivity Enzymatic Reporter unLocking

All these molecular tests still need **validation**. This is foreseen in **retrospective studies** on stored samples from the DiTECT-HAT study (blood and CSF from patients before and after treatment), from the WHO specimen bank (blood and CSF from patients before treatment), and on tsetse fly specimens at the Liverpool School of Tropical Medicine (LSTM). Furthermore, **prospective studies** are planned: CHARHAT (blood, skin), HAT+ (blood), TRYPELIM (blood), and TRYPSKIN as part of DNDI-OXA-04-HAT (blood, skin).

There are **constraints to transporting high-quality specimens** to reference laboratories, such as the limited infrastructure and equipment at the point of collection, humidity at the collection site, the lack of cold chain and the big distance.

Dried blood spots (DBS) are the classical way to collect samples for reference laboratories. DBS are applicable for serological and molecular diagnosis (also for CSF), are relatively cheap, and have a prolonged stability when protected from ultraviolet light and humidity. With DBS, there is a loss in sensitivity compared to analysis on blood or plasma. The manual punching-out of filter discs also takes time, which is impractical for high throughput testing.

An alternative to DBS are **microfilter plates** in a 96-well format, allowing high throughput testing. The system is compatible with ELISA and iELISA. The compatibility with TL or with DNA detection is not yet known. Disadvantages are the costs of the plates, the risk of misidentification of a sample in a plate and the limited volume of a plate.

Another alternative to DBS are **tubes with stabilization buffer**, which are especially important for molecular diagnosis on RNA. For DNA, the reagents are cheap and stable at ambient temperature. For larger volumes of blood, the PaxGene DNA tubes are preferred, whereby the DNA is concentrated to a very small volume before the extraction process. For RNA, the reagents are expensive and require a cold chain. The DNA/RNA Shield is in use, as well as the PaxGene RNA tube for larger volumes. As a consequence of the diagnostic efforts during the COVID-19 pandemic, it is hoped that better alternatives for RNA detection will become available in the near future.

11.2 Rapid tests for g-HAT: FIND update

HAT RDT projects supported by FIND are:

- **SD BIOLINE HAT** (native antigens) – commercialized in 2013 but currently not available due to manufacturing and quality control issues;
- **Abbott BIOLINE HAT 2.0** (recombinant antigens) – commercially available since April 2021; and
- **HAT/malaria combined RDT** – project put on hold in September 2020 due to other priorities at Abbott.

The first-generation RDTs (**SD BIOLINE HAT**) use two native antigens supplied by ITM (VSG LiTat 1.3 and VSG LiTat 1.5) and are manufactured by Standard Diagnostic, Inc. (SD), now part of Abbott. In total about 2.2 million tests were delivered until 2020. However, this test is currently not available. Multiple interruptions in production occurred due to issues of quality control of native antigens. Abbott is working on a change of control process using antigens in a frozen solution instead of freeze-dried, as suggested by ITM to hopefully help with quality control issues. Due to other priorities at Abbott (including SARS-CoV-2), this process has been progressing very slowly and it is not known when the test will be available again.

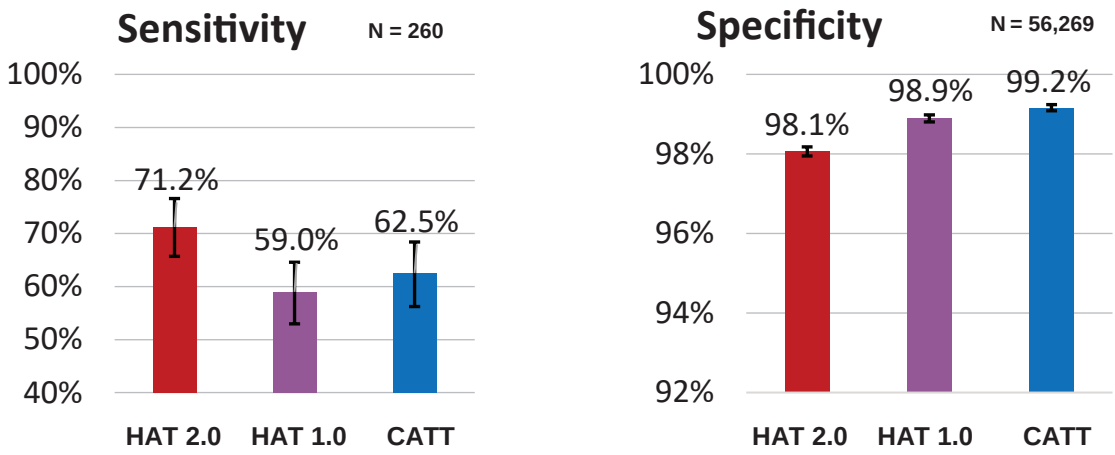
The second generation RDTs (**Abbott BIOLINE HAT 2.0**) uses 2 recombinant antigens (ISG65 and VSG LiTat 1.5) which are produced in-house by Abbott (using *Escherichia coli* and baculovirus expression systems, respectively). The commercialization has been delayed several times, mostly for technical reasons (in particular due to challenges with expression/purification of recombinant antigens). Finally, this test has been commercially available since April 2021 and can be ordered from Abbott (US$ 0.50/test, thanks to a subsidy from BMGF through FIND). This test has also been made available to HAT endemic countries as part of a donation by Abbott, in a total quantity of 450 000 tests over 3 years, being distributed by FIND, WHO and ITM. The diagnostic performance appears to be similar to that of the first-generation SD BIOLINE HAT. Data that are now going to be collected as part of programmatic use in HAT endemic countries will be important to evaluate its performance in field conditions.

There are essentially **three datasets about the test performance:**

First, a prospective clinical study in Democratic Republic of the Congo *(11)* that compared the first (HAT 1.0) and second-generation RDT (HAT 2.0) with the card agglutination test for trypanosomiasis [CATT] (Figure 11.2.1). HAT 2.0 showed a higher sensitivity than HAT 1.0. The specificity of HAT 2.0 (98.1%) was significantly lower than that of HAT 1.0 (98.9%) and of CATT (99.2%).

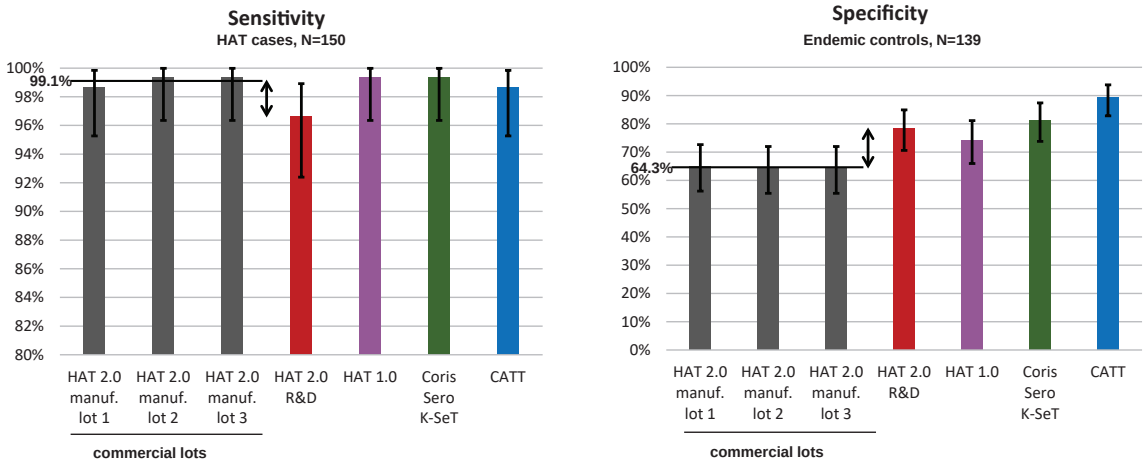
A key limitation of this study was that the HAT 2.0 tests used were produced in SD/Abbott's research and development (R&D) department. The HAT 2.0 that is now commercially available is produced in Abbott's manufacturing department (same product design, but different production scale, equipment, procedures, etc.). This might result in slight differences in test performance.

Figure 11.2.1. Sensitivities and specificities of the first (HAT 1.0) and second-generation RDT (HAT 2.0), and CATT, with sample size (N), in a prospective clinical study in Democratic Republic of the Congo *(13)*



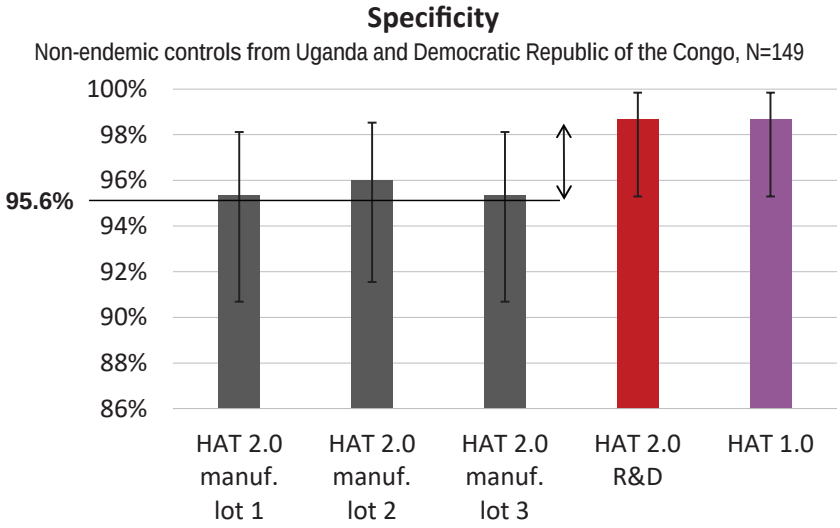
Second, a retrospective study using samples from the WHO HAT specimen bank was conducted in cooperation with ITM in 2020. The three commercialized batches of HAT 2.0 were compared with the HAT 2.0 used for R&D, together with HAT 1.0, the Coris Sero K-Set and CATT (Figure 11.2.2). The sensitivity of all RDTs was very high. The sensitivity of HAT 2.0 was slightly higher than that of HAT 1.0 (not statistically significant). The specificity of all RDTs was unusually low, quite different from specificities reported earlier in the literature. The reasons for that are not clear. This may be related to the use of relatively old samples from WHO's HAT specimen bank from a time of higher HAT endemicity. The persons from whom the control samples were obtained could have been exposed to parasites (even if TL-positive samples were excluded). A lower specificity of the commercialized HAT 2.0 in comparison of HAT 2.0 used in R&D could be potentially of concern (not statistically significant).

Figure 11.2.2. Sensitivities and specificities of three commercialized lots of HAT 2.0 (HAT 2.0. manuf. lot 1–3), the HAT 2.0 used for research and development (HAT 2.0 R&D), HAT 1.0, Coris Sero K-Set and CATT, with sample size (N), in a retrospective study using samples from the WHO HAT specimen bank



Third, a specificity study was conducted at Makerere University using control samples from non-endemic regions in Uganda and Democratic Republic of the Congo, which could mimic the situation in the post-elimination context in a few years. As expected, a much higher specificity of the HAT RDTs was found (Figure 11.2.3). There was again a trend of a lower specificity of the commercialized HAT 2.0 compared to the HAT 2.0 used in R&D (statistically not significant), which should also be kept in consideration in the future.

Figure 11.2.3. Specificities of the three commercialized lots of HAT 2.0 (HAT 2.0 manuf. lot 1–3), the HAT 2.0 used for research and development (HAT 2.0 R&D), the HAT 1.0, with control samples from non-endemic regions in Democratic Republic of the Congo and Uganda



In conclusion, the Abbott BIOLINE HAT 2.0 is available and can be ordered; 90 000 tests were recently supplied to endemic countries as part of Abbott's donation (through FIND and ITM). Its sensitivity is similar to that of the SD BIOLINE HAT 1.0 (according to the retrospective study), and possibly even higher (according to the prospective study). There is some uncertainty around the specificity of the Abbott BIOLINE HAT 2.0, with results suggesting that specificity could be slightly lower than that of the SD BIOLINE HAT. Data on the diagnostic performance of the commercialized Abbott BIOLINE HAT 2.0 from the field using fresh samples are missing. Some information will be collected as part of routine HAT control/elimination activities, but a new formal prospective clinical trial is not planned at this stage. It is unclear when/if the old SD BIOLINE HAT will be available again. However, having two different HAT RDTs produced by the same manufacturer might not be very useful, if the HAT 2.0 performs well.

11.3 Rapid tests for g-HAT: Coris BioConcept update

Coris BioConcept (Belgium) has developed in 2012 the HAT Sero K-Set RDT based on native antigens (LiTat 1.3 and 1.5) which are produced in rodents. Now, Coris BioConcept is developing the **HAT Sero K-Set 2.0** assay based on recombinant antigens. Hosts for production of recombinant proteins are: *E. coli*, *Pichia pastoris*, *Leishmania tarentolae*, *T. brucei brucei*, Insect cells (baculovirus) and Mammalian cells (transient expression). Requirements for use of recombinant antigens are an equal or better performance compared to native antigen-based assays, an animal-free antigen production (sustainability), a decrease of manufacturing cost, and stability of the antigen and the final assay.

Several **prototypes based on recombinant antigens** were defined and developed in an iterative process. The performance of the last three prototypes was evaluated, including stability evaluations. In 329 samples, the sensitivity was low (84%) with the first prototype but high (99%) with the second prototype in the range of the assays based on native antigens. The sensitivity and signal intensity of the third protype could be improved in smaller sets of samples (n=119). yielding an overall sensitivity of 97.5%. The specificity with this sample size appears as good as or higher than the native antigen-based HAT Sero K-set (to be confirmed).

Required **next steps** are a retrospective sensitivity evaluation of the HAT Sero K-Set 2.0 in comparison to native antigen-based assays on a large sample size. Regarding specificity, a prospective field evaluation is envisaged and interest of partners is welcomed.

11.4 The DiTECT-HAT project: first results

The first field results of the Diagnostic Tools for Human African Trypanosomiasis Elimination and Clinical Trials project (abbreviated as DiTECT-HAT) were presented. The objectives of DiTECT-HAT are to evaluate the accuracy and feasibility of new diagnostic tools and to propose algorithms for HAT diagnosis in three contexts: passive case detection in peripheral health centres (WP2); post-elimination surveillance and detection of disease re-emergence (WP3); and early test of cure in therapeutic trials (WP4). Three diagnostic trials corresponding to these objectives are ongoing.

DiTECT-HAT-WP2 – passive case detection (ClinicalTrials.gov Identifier: NCT03356665) addresses the following key questions:

- What clinical symptoms and signs should trigger HAT testing?
- What is the diagnostic performance of RDTs for HAT screening?
- How can serological suspects be tested further?
- What are the best algorithms for HAT diagnosis?

The results from the study sites in Côte d'Ivoire and Guinea were presented but the results from Democratic Republic of the Congo are still under evaluation. Patients with one or more clinical symptoms/signs indicative for HAT were included from August 2017 to January 2020. Three RDTs were conducted: (i) HAT Sero-K-Set (Coris BioConcept), (ii) rHAT SeroStrip (Coris BioConcept) and (iii) SD BIOLINE HAT (Standard Diagnostics). If any RDT was positive, a parasitological examination was performed and DBS on filter paper were sent to the reference laboratory for indirect ELISA/*Tbg*, trypanolysis, quantitative polymerase chain reaction [qPCR] (m18S/TgsGP) and loop-mediated isothermal amplification (LAMP). If any of the tests on filter paper were positive, additional parasitological examinations were performed.

In Côte d'Ivoire, 3433 clinical suspects were included, of whom 97 were positive on RDT (2.8%), and 2 were parasitologically confirmed (0.06%). The participants had mainly weakness, headache and fever. In a multivariable analysis for RDT positivity, convulsions, sleep disturbance, motor disorders, psychiatric problems and/or weight loss were associated with positive RDT. These symptoms and signs should trigger HAT screening. Enlarged lymph nodes was not included in the analysis, as only very few patients presented with enlarged lymph nodes in Côte d'Ivoire.

In Guinea, 2353 clinical suspects were included, of whom 122 were positive on RDT (5.2%) and 48 were parasitologically confirmed (2.04%). The participants had mainly headache and fever. In a multivariable analysis for parasitological confirmed diagnosis, male sex, enlarged lymph nodes, severe itching and/or severe weight loss were associated with a parasitological confirmation. The following combination of symptoms strongly increase the likelihood of being a true patient: lymph nodes and severe itching (OR 413); severe weight loss and motor disorders (OR 2220). All these symptoms and signs should trigger HAT screening. In Guinea, fever as a single criterion should not trigger HAT screening due to a negative association.

Table 11.4.1 demonstrates the diagnostic performance of the RDTs in Côte d'Ivoire and Guinea. The sensitivity of the HAT-Sero-K-Set (100%) and the SD BIOLINE HAT (93.8%) were superior in comparison to the HAT Sero-Strip (59.6%). Regarding specificity, the HAT Sero-Strip performed best (99.3/99.6%); HAT-Sero-K-Set (97.5/97.8%) and SD BIOLINE HAT (98.9%/97.5%) showed similar specificities.

Table 11.4.1. Diagnostic performance of the three HAT RDTs in the study in Côte d'Ivoire (left) and in Guinea (right)

RDT	% Specificity (95% CI)	% PPV (95% CI)
HAT Sero-*K*-Set	97.8 (97.2-98.2)	2.5 (0-9)
rHAT Sero-Strip	99.6 (99.4-99.8)	14 (2-43)
SD Bioline HAT	98.9 (98.5-99.2)	4.9 (1-17)

RDT	% Specificity (95% CI)	% Sensitivity (95% CI)	% PPV (95% CI)	% NPV (95%CI)
HAT Sero-*K*-Set	97.5 (96.8-98.1)	100 (92.4-100)	52 (43-61)	100 (99.8-100)
rHAT Sero-Strip	99.3 (98.9-99.6)	59.6 (45.3-72.4)	64 (49-76)	99.2 (98.7-99.5)
SD Bioline HAT	97.5 (96.7-98.0)	93.8 (83.2-97.9)	48 (39-58)	99.9 (99.6-100.0)

Table 11.4.2 shows the diagnostic performance of trypanolysis, m18s qPCR, LAMP and ELISA/*Tbg* on filter paper with DBS of RDT-positive patients. All tests showed high specificity in both countries (with large confidence intervals limiting the conclusions). The sensitivity showed strong differences, high for trypanolysis (85.3%), moderate for ELISA/*Tbg*, (67.6%) and low for the molecular tests (LAMP 36.4%, m18s qPCR 44.1%). The positive predictive value (PPV) was markedly increased if another diagnostic test on filter paper followed the RDT.

Table 11.4.2. Diagnostic performance of trypanolysis, m18s qPCR, LAMP and ELISA/Tbg on filter paper with DBS of RDT-positive patients from Côte d'Ivoire (left) and Guinea (right)

	% Specificity (95% CI)	% PPV (95% CI)
Trypanolysis	94.4 (87.4-98.1)	29 (4-71)
m18S qPCR	93.3 (85.7-97.5)	25 (4-89)
LAMP	98.9 (93.9-99.9)	67 (9-99)
ELISA/*Tbg*	98.9 (93.9-99.9)	67 (9-99)

	% Specificity (95% CI)	% Sensitivity (95% CI)	% PPV (95% CI)	% NPV (95%CI)
Trypanolysis	92.9 (81.0-97.5)	85.3 (69.9-93.6)	91 (76-97)	89 (76.0-95.0)
m18S qPCR	97.7 (87.9-99.9)	44.1 (28.9-60.5)	94 (72-100)	70 (56-79)
LAMP	93.0 (81.4-97.6)	36.4 (22.2-53.4)	80 (55-93)	66 (53-76)
ELISA/*Tbg*	95.3 (84.5-99.2)	67.6 (50.8-80.9)	92 (75-99)	79 (66-88)

DiTECT-HAT-WP3 – post-elimination monitoring (ClinicalTrials.gov Identifier: NCT04099628) addresses the question of which methods can be used for surveillance and to detect re-emergence of HAT in an eliminated focus. The results from Burkina Faso are presented here; the results from Côte d'Ivoire and Democratic Republic of the Congo are still under evaluation.

Door-to-door visits were conducted in low to zero prevalence areas in Burkina Faso from October 2019 to July 2020. Three RDTs were performed on every permanent inhabitant: HAT Sero-K-Set (Coris BioConcept), rHAT SeroStrip (Coris BioConcept), SD Bioline HAT (Standard Diagnostics), as well as four tests on DBS: indirect ELISA/*Tbg*, trypanolysis, qPCR (m18S/TgsGP), LAMP. If any of these tests were positive, the patient was revisited for parasitological examinations.

The first results were obtained from South-West Burkina Faso (Batié). Some 5883 individuals were included, of whom 842 were positive on RDT (14.3%). None could be parasitologically confirmed. The specificity was highest for the rHAT Sero-Strip (99.1%, 95% CI 98.9–99.4), followed by the SD Bioline HAT (96.7%, 95% CI 96.2–97.1) and the HAT Sero-K-Set (93.0%, 95% CI 92.4–93.7). The specificity of the HAT Sero-K-Set was lower than in passive screenings in Côte d'Ivoire and Guinea, which may be associated with a high prevalence of animal African trypanosomiasis (AAT) and extensive tsetse fly contact in this region of Burkina Faso.

ELISA/*Tbg* and trypanolysis were performed on the specimens of 816 RDT-positive patients. For the ELISA/*Tbg*, the high specificity observed elsewhere was confirmed (99.1%, 95% CI 98.5–99.7). Trypanolysis reached a specificity of 100% (95% CI 99.5–100).

In conclusion, among the laboratory tests the trypanolysis appears to be superior considering sensitivity and specificity. However, trypanolysis is only available in a limited number of laboratories. The ELISA/*Tbg* is more universally available and appears to be the second-best option.

DiTECT-HAT-WP4 – early test of cure (ClinicalTrials.gov Identifier: NCT03112655) addresses the question of how to detect relapses earlier and without lumbar puncture. This trial was conducted in Democratic Republic of the Congo in association with the acoziborole clinical trial (DNDi-OXA-02-HAT). Some 97 patients were included from February 2017 to March 2019. Samples were collected before treatment, and on day 11, month 3, 6, 12 and 18. Two parameters were analysed to assess the accuracy of treatment outcome in therapeutic trials: the detection of neopterin in CSF and the detection of spliced leader (SL)-RNA in blood and CSF.

So far only the pretreatment results are available. Neopterin was hardly detectable in CSF and the potential of neopterin to indicate neurological involvement could not be confirmed. The WBC count in CSF was much more discriminating between stage 1 and 2.

The method for the detection of SL-RNA in blood and CSF was improved, including an internal extraction control and performing in parallel "noRT"-qPCR for genomic DNA contamination. In blood, the sensitivity of SL-RNA (95.8%) was remarkably higher than parasitological examination of both blood and lymph nodes (80.4%) (Table 11.4.3). The detection of SL-RNA in the blood may be a good and less invasive marker for the diagnosis of relapse. In the CSF, the detection of SL-RNA was feasible, which was shown for the first time. The sensitivity of SL-RNA detection in the CSF was comparable to the modified single centrifugation technique.

Table 11.4.3. Sensitivity of SL-RNA detection in comparison to parasitological detection methods in the blood and lymph nodes, as well as in the CSF

	Parasitology % sensitivity (95% CI)	SL-RNA % sensitivity (95% CI)	*p*
Blood & lymph	80.4 (71.1-87.8)	95.8 (89.8-98.8)	0.007
CSF	71.1 (61.0-79.9)	76.0 (66.2-84.1)	0.2

In perspective, the missing analyses of WP2 and WP3 will be conducted. A latent class analysis will follow with the six different groups of WP2 and WP3, considering that parasitology is not 100% sensitive, Furthermore, a cost–effectiveness analysis is ongoing to define the most appropriate test algorithm and the best "test and treat" strategy for the different countries and different prevalence. For WP4, the neopterin, 5-hydroxytryptophan and SL-RNA analysis will be continued during the post therapeutic follow-up. An evaluation of more sensitive RNA targets will be also conducted.

The analyses were realized with the support of the NSSCPs, the DiTECT-HAT partners and personnel (PNLTHA Guinea, PNLTHA RDC, INRB, CIRDES Burkina Faso, Institut National de Santé Publique Côte d'Ivoire (INSP), ITM, University of Liverpool, IRD), in collaboration with DND*i* and funded under the EDCTP.

11.5 Report from the WHO Diagnostic Technical Advisory Group HAT subgroup

Since 2014, under the WHO Network for HAT elimination, diagnostics experts have been convening to analyse needs and coordinate efforts. In 2019, WHO/NTD created the WHO Diagnostic Technical Advisory Group (DTAG) to establish a harmonized approach, and to identify and prioritize diagnostic needs for all NTDs. Several subgroups were formed for specific diseases: (i) skin-NTDs, (ii) HAT, (iii) onchocerciasis, (iv) lymphatic filariasis, (v) soil-transmitted helminthiases and (vi) schistosomiasis; as well as subgroups on cross-cutting topics: (i) surveillance and surveillance platforms, (ii) improving the quality of microscopy and clinical diagnosis, and (iii) manufacturing and regulatory pathways. The subgroups have specific terms of reference, consist of 6–12 members for a period of up to 3 years, and may invite individual experts.

The groups follow a standard WHO procedure to develop WHO target product profiles (TPPs) for preventives, therapeutics, diagnostics or medical devices. The core process is an analysis of the diagnostic landscape to determine unmet public health needs and needs of TPPs according to public health priority. Use-cases for the missing health products are built, as well as TPPs following the standard procedures.

The landscape of serological, microscopical and molecular HAT diagnostics is summarized in Table 11.5.1.

Table 11.5.1. Landscape of HAT diagnostics

Serology
• **CATT** – screening of Tbg. Community
• **RDT** (SD Bioline, Coris Sero-K-SeT) – screening, community and point-of-care
• **Immune trypanolysis (TL)** – referral test for surveillance, dried blood spots; cumbersome (reference laboratories)
• **ELISA** – test for surveillance (reference laboratories)
Microscopy (parasitological confirmation)
• **Microscopy** of body fluids – low sensitivity
• **mAECT** and **HCT** (Woo) – higher sensitivity but resource-intensive
Molecular methods
• **PCR; LAMP** – reinforce suspicion, lack of accuracy for confirmation (PCR– reference laboratories; LAMP – district hospitals)

Several **gaps** for HAT diagnostics have been recognized: simpler confirmatory tests for g-HAT that can be used in peripheral sites; more sensitive and specific g-HAT serological test allowing cheaper screenings; high throughput testing on DBS for surveillance in low prevalence or post-elimination settings and for verification of elimination; algorithm combining different tests to improve specificity; a test of cure to reduce long-term follow-up and reliance on the lumbar puncture; ensured production and affordability of existing tests; and a serological test for r-HAT for screening.

The following **use-cases** were defined as **priorities**:

- Test for r-HAT usable in peripheral health facilities (TPP completed);
- Diagnostic tool to identify individuals with suspected but microscopically unconfirmed g-HAT infection, to receive widened treatment (TPP started);
- Individual test to assess g-HAT in low prevalence settings (TPP planned);
- High throughput g-HAT test for verification of elimination (TPP planned).

A template for **HAT TPPs** was adopted as a working document. For TPP Nr 1 on r-HAT, a version 0.1 was produced by group discussion, consolidated via distance consultation (version 1.0), and posted on the WHO website for public consultation for 28 days. The final version is currently submitted for Executive Clearance for publication. For TPP Nr 2 on g-HAT, a version 0.0 draft is currently circulating for distance consultation and group discussion is planned for mid-June (consensus building and version 0.1).

TPP Nr 1 (test for r-HAT diagnosis usable in peripheral health facilities) defines the following **technical scope**:

- Ideally, an antigen detection test in a simple format (RDT), but it could also be a molecular test detecting DNA or RNA, or a microscopy-free test detecting the presence of trypanosomes;
- To provide immediate results for taking therapeutic decisions, but, if not possible, a screening test to be followed by confirmatory microscopic examination (parasitaemia is usually high);
- In the current context, confirmation is mandatory, but in future with a safe medicine allowing for widened treatment, a screening test to identify individuals to be treated would be desirable.

And the following **medical needs**:

- Currently, the diagnosis of r-HAT is based on the microscopic confirmation of trypanosomes, requiring microscope, centrifuges, electricity source and trained laboratory technicians;
- A simple test for r-HAT would facilitate the control and surveillance of the disease: faster prescription of a treatment and capturing more information on the occurrence of r-HAT transmission;
- It would be important that the test can be performed at the location where people seek malaria diagnosis.

TPP Nr 2 (a g-HAT test identifying individuals to receive widened treatment) is under development and defines the following **technical scope:**

- It could be a non-parasitological method, or a parasitological method of high sensitivity but simple enough to be applicable at the point-of care level;
- This tool could be in any format, as long as it is simple and requiring minimal specialized training.

And the following **medical needs:**

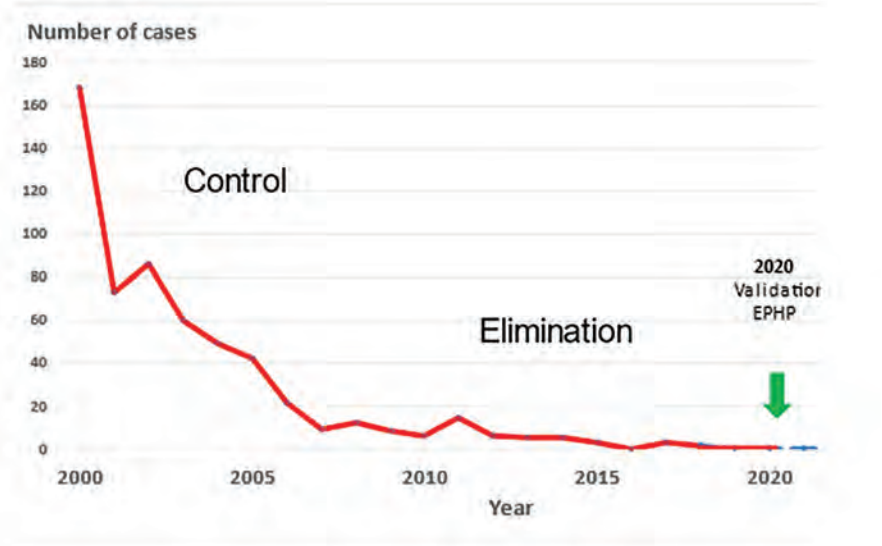
- With the possible advent of a safe, effective and simpler treatment it would be conceivable to widen the criteria of eligibility for treatment, to include individuals without parasite confirmation but with a degree of suspicion of harbouring it (widened treatment);
- Infected individuals for whom the current diagnostic methods fail would benefit;
- The parasite reservoirs would be further reduced.

12. Innovations in surveillance and control

12.1 Case-finding in the elimination context

The experience of Côte d'Ivoire was presented as example of adaptations of case-finding in an epidemiological scenario changing from control to elimination (Figure 12.1.1). Fewer than 10 cases per year have been reported since 2009, with only 8 cases in total during 2015–2019. In 2020, HAT elimination as a PHP in Côte d'Ivoire was validated by WHO.

Figure 12.1.1. Number of g-HAT cases reported in Côte d'Ivoire, 2000–2020



This **epidemiological transition** requires an adaption of strategies. With decreasing HAT prevalence, active mass screening is less cost effective. Moreover, with decreasing prevalence, the population no longer perceives HAT as a threat and is less participating in active screenings. Regarding passive surveillance, integration of the laboratory tests in the health facilities remains a challenge and population coverage is limited. As patients are diagnosed mainly in second stage they serve as reservoir for ongoing transmission also for a longer time.

The question remains how to diagnose the last cases. **Seropositive individuals** may be infected and can function as an ongoing reservoir. They should be targeted in control strategies. In Côte d'Ivoire the definition of seropositivity was adapted and is nowadays defined as CATT plasma ≥ ¼ and/or RDT positive, parasitology negative, and trypanolysis positive. Seropositive subjects are followed up annually until the parasitology becomes positive or serology negative (CATT plasma/RDT, trypanolysis).

In 2019, trypanosomes were detected in a seropositive individual who was followed up for 20 years without symptoms. This exceptional case illustrates the potential role of residual reservoirs of trypanosomes. In this regard the TrypaDerm project aims at understanding the significance of skin parasites as an anatomical reservoir for HAT.

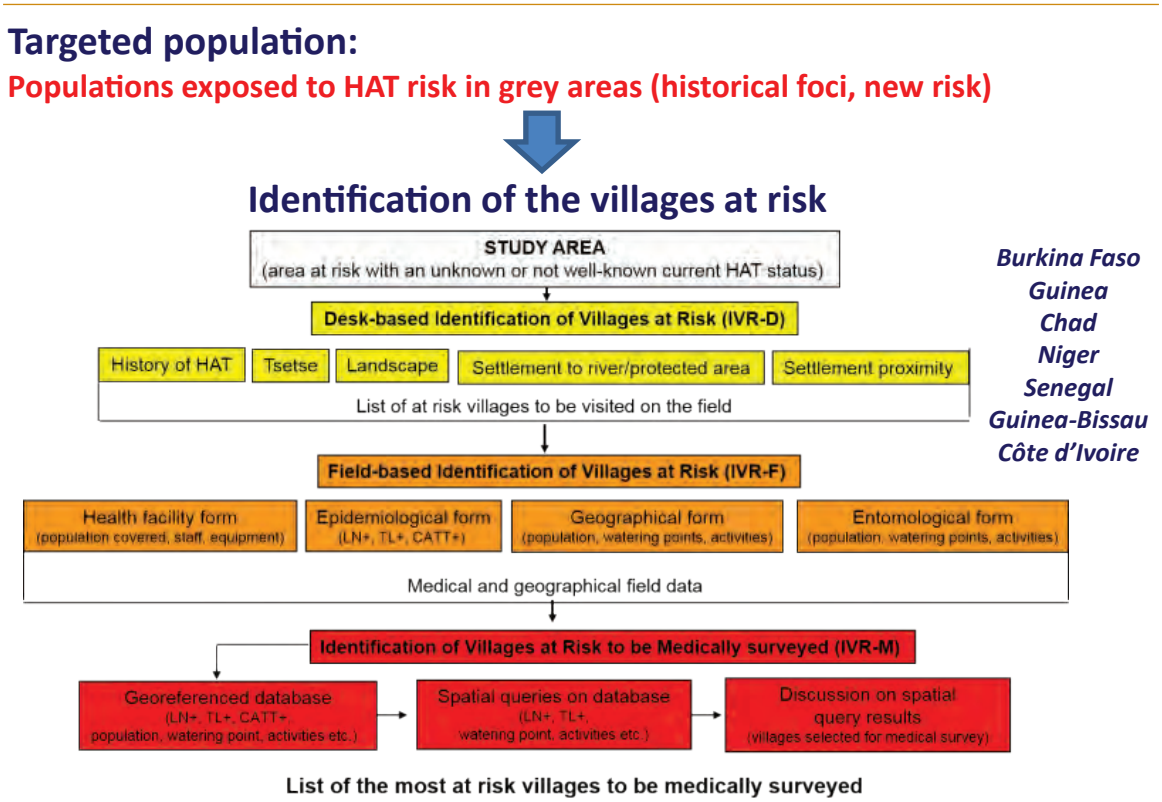
Another population at risk for HAT are subjects sharing the same living places as confirmed HAT cases and seropositives. After the identification of the living places, a **spatial follow-up** of the population sharing these places will be conducted. This approach was developed in Forécariah (Guinea) *(12)*, in Gouéra (Burkina-Faso) *(13)* and in Bonon (Côte d'Ivoire).

An alternative active screening strategy consists of visiting former patients at their home and testing the people living in their close neighborhood (**targeted door-to-door strategy, TDD).** The TDD appears more effective than classical active screening to detect cases in a low prevalence context, where very localized transmission cycles may persist.

Another approach is to identify new populations with **HAT risk due to human mobility**, where passive surveillance to identify an emergence of HAT should be implemented.

There is often no recent HAT data from grey areas (historical foci, areas with new risk), which are essential in the context of elimination. A method in three steps was developed for **targeting the population at risk** considering historical and contemporary data, as well as other epidemiological, geographical and entomological information (Figure 12.1.2). Villages at risk will be identified for medical surveillance. This strategy has been implemented in several countries in West Africa (Burkina Faso, Guinea, Chad, Niger, Senegal, Guinea-Bissau, Côte d'Ivoire).

Figure 12.1.2. A 3-step method for targeting the population at risk for HAT



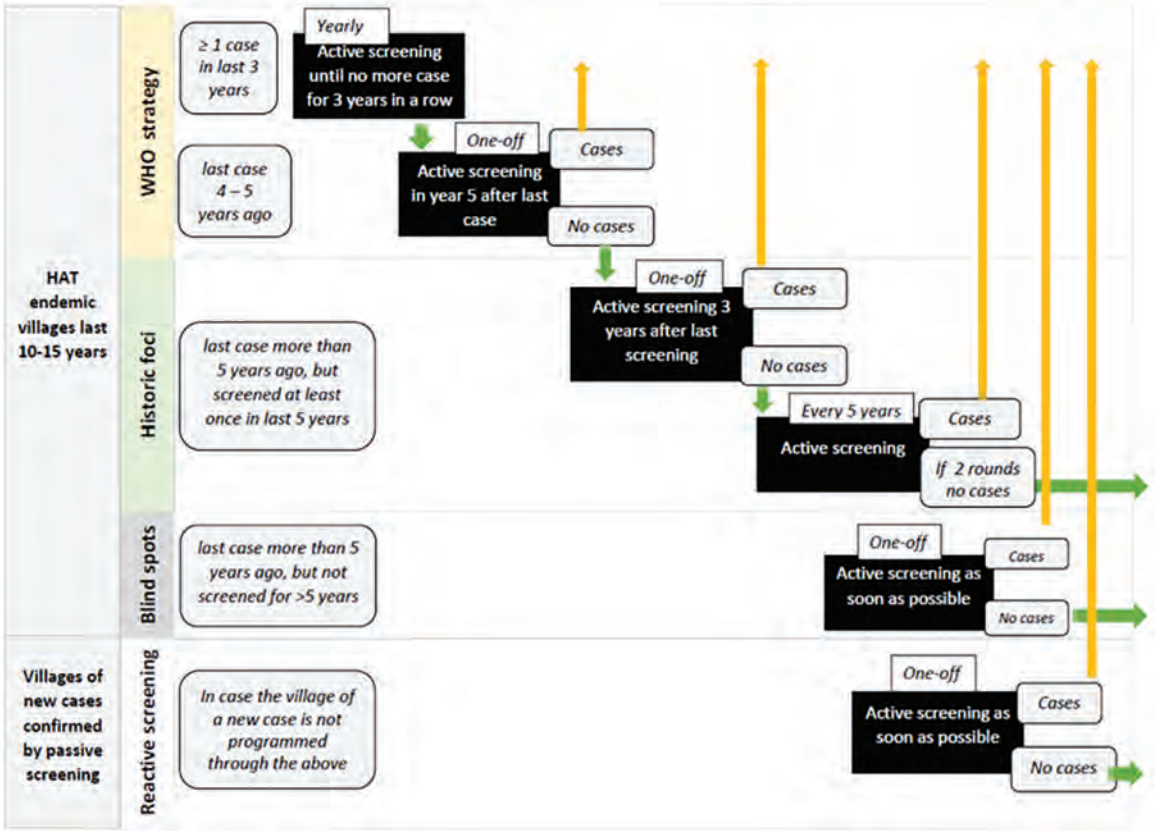
In total, 8 HAT cases were identified in Côte d'Ivoire from 2015 to 2019. The follow-up of seropositives was particularly effective, with 2 HAT cases identified among 97 seropositives who were followed-up annually during this period. No further cases were identified with the other targeted active screening methods. In summary, all these methods contribute important information for the validation of g-HAT as a PHP and for the verification of zero transmission.

12.2 Different contexts, different methods: some snapshots from Democratic Republic of the Congo

The experience in Democratic Republic of the Congo about adapting strategies in different contexts was presented.

In the past 5 years (2016–2020), 189 health districts reported HAT cases in Democratic Republic of the Congo. The number of cases is continuously decreasing. Most of the active screening teams detect < 1 case per 10 000 people screened. Based on WHO guidance, the PNLTHA has shifted focus from traditional active screening (complementing passive screening) to a diverse range of active screening methods and decisional criteria (Figure 12.2.1). The health care utilization rate in primary and secondary health care remains very low, which underlines the importance of active screening measures. The strategy will be adapted to the epidemiological situation including also historic foci, blind spots and reactive screening. Reactive screening means active screening in villages reporting cases by passive screening, that are not yet targeted. One-off active screening rounds allow to decide about further measures according to the results. Investments are made in quality assurance of passive screening.

Figure 12.2.1. Criteria for active screening in Democratic Republic of the Congo according to HAT endemicity in the villages



The adaptations of the PNLTHA in response to the local epidemiological situation were illustrated with examples. In Equateur Sud/Nord and Bandundu Nord, mini-mobile teams were created, exploring historic foci and blind spots (on motorbikes and pirogues), and performing reactive screening, as less resources were required for regular active screening. Macro/micro-planning was implemented via TryElim.org and quality assurance by video control in Bandundu Nord. In Kasai Occidental, the epidemiological situation is different due to political instability. The number of confirmed cases remains high with 3.3 cases per 10 000 people in 2020. As a response, one mini-mobile team was added to three large mobile teams, to start reactive screening with easier access to remote areas. A challenge on the road of elimination is seen in very remote

areas bordering Central African Republic and South Sudan, and in the Maniema-Katanga area, where access is limited due to insecurity. If a "test and treat" strategy becomes available, these areas should be considered (with a-posteriori confirmation), to enable access for the population to treatment and not to endanger the mobile teams with repeated visits.

For screening and surveillance there is no "magic bullet", as there are several contextual challenges. Guidance for passive case-finding and for surveillance of historic foci may be further specified. A combination of approaches, that are tailored and flexible, as well as further operational and epidemiological research are required.

12.3 Using the WHO HAT Atlas to plan active screening activities

Active screening is very effective when prevalence is high, but its effectiveness decreases with decreasing prevalence. Active screening can detect cases early, reducing the presence of human reservoirs. As it requires significant resources, it is important to maximize the performance of the mobile units and to target villages at higher risk. Active screening should also respond to passively diagnosed cases.

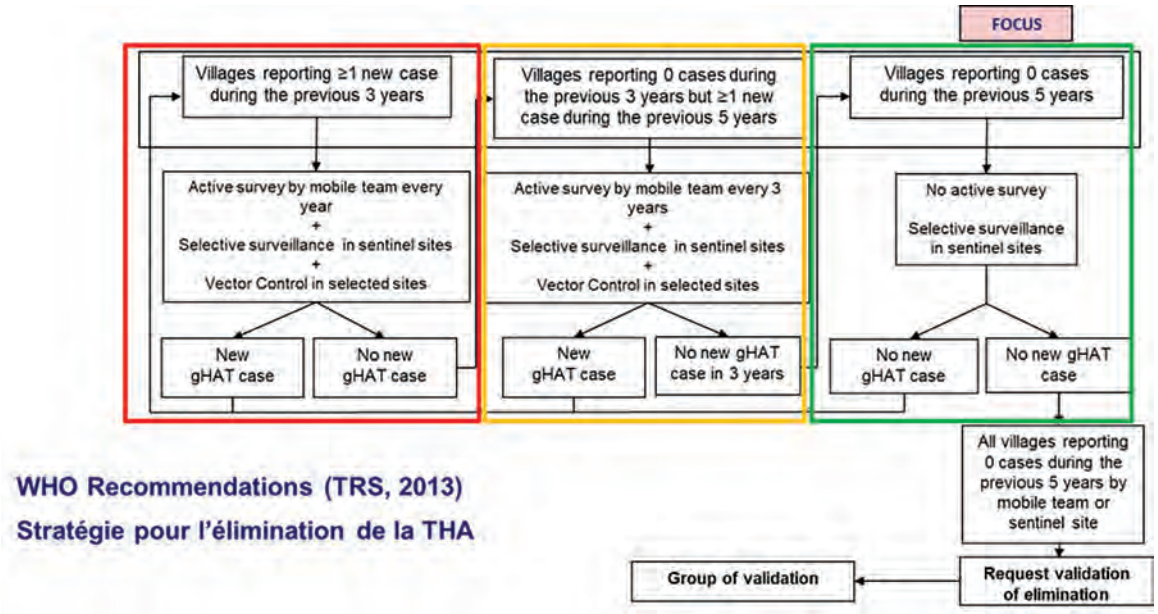
The HAT Atlas is a tool that can be used to select villages for programming control activities. This tool has been in use during PNLTHA annual planning workshops in Democratic Republic of the Congo since 2018.

The planning of activities includes:

- the identification of villages to be screened;
- the capacity assessment of the local HAT coordinators and their mobile units to screen these villages;
- an adjustment of the list of villages scheduled according to capacity; and
- the planning of itineraries.

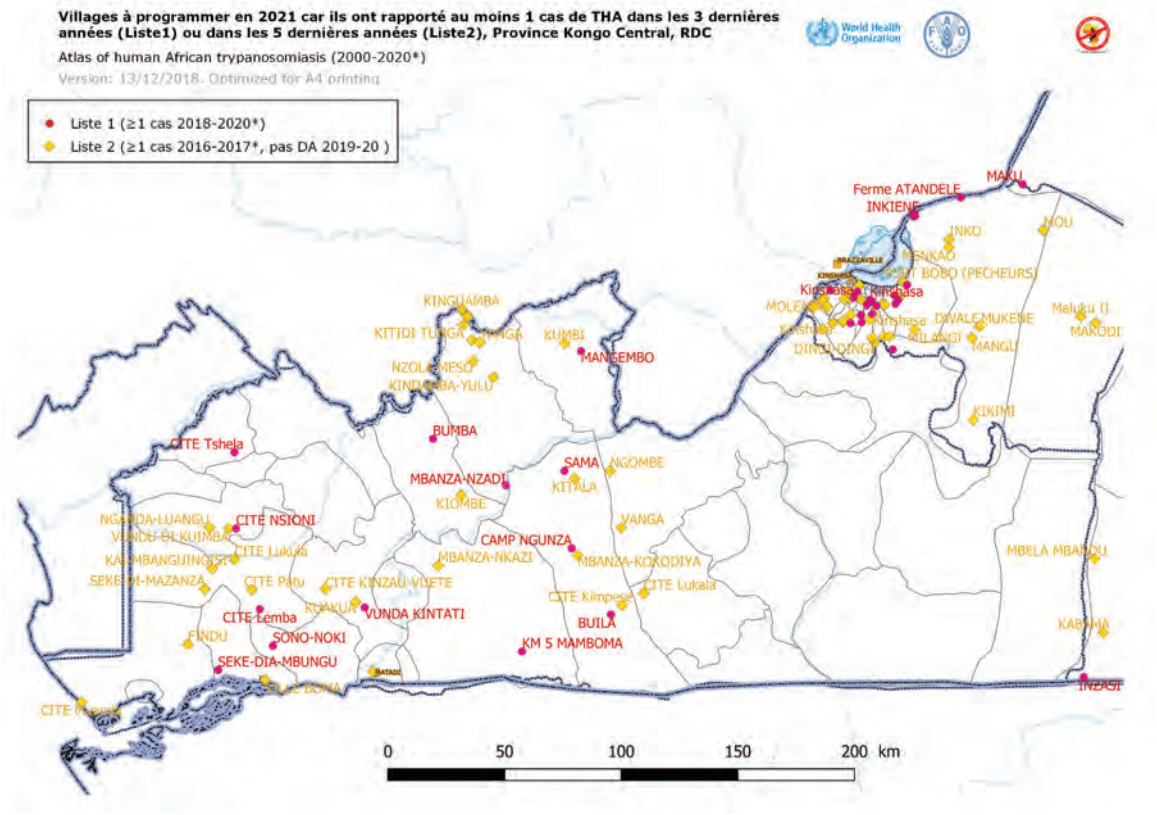
The villages to be visited and the corresponding control measures are defined in three categories according to the local epidemiological situation (Figure 12.3.1).

Figure 12.3.1. Three different scenarios at village level with corresponding control activities according to WHO recommendations



With the HAT Atlas, maps and lists (spreadsheet format) of villages can be created by priority group (Figure 12.3.2).

Figure 12.3.2. Example map of Province Kongo Central, Democratic Republic of the Congo, showing the planning of villages to be actively screened (red = higher priority, yellow = lower priority)



Regarding the **capacity assessment** of the local HAT coordinators and their mobile units, it is planned that one mobile unit screens 250–300 people per day or around 6000 people per itinerary. The village population data (partially incomplete) from the Atlas are therefore key for the capacity assessment, which is carried out by the PNLTHA.

If the mobile units do not have the capacity to screen all of these villages, certain villages will be prioritized according to the number of cases screened in recent years, the distance from passive and/or active screening sites, 5 km and 10 km buffers around active and passive screening sites and the geographical accessibility.

If the mobile units have the capacity to screen more villages, additional villages will be selected according to the proximity to a village that has reported cases in the past 3 years and depending on whether a village has been missed for screening in previous years.

The **planning of itineraries** requires the practical knowledge of the terrain. The HAT Atlas provides information about the roads, the watercourses, the topography, the zones de santé and more. This information helps to regroup the planned villages in a monthly itinerary.

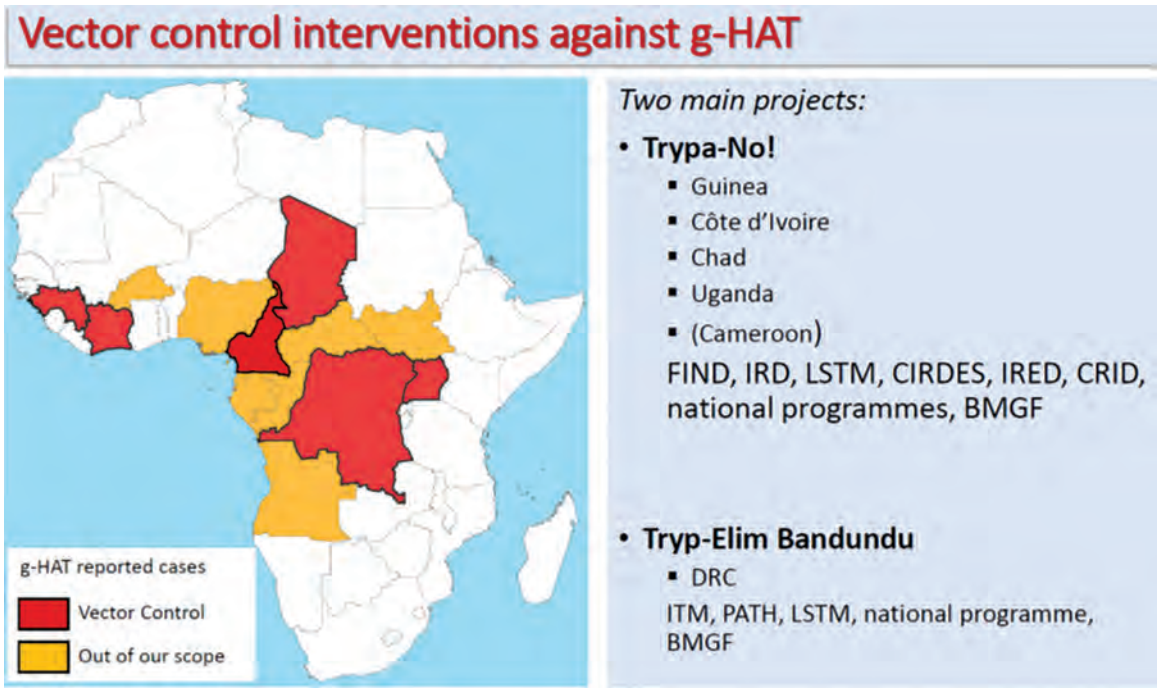
13. Vector control

The aim of vector control is to decrease the transmission of the disease by increasing the vector's mortality (reducing the number of infectious bites). The reduction of *Glossina* spp. vectors will have an impact on the transmission of both HAT and AAT.

The two main projects in vector control were presented (Figure 13.1):

- the **"Trypa-No!"** partnership project, which is performed across Chad, Côte d'Ivoire, Guinea and Uganda; and
- the **"Tryp-Elim"** project developed throughout the former Bandundu Province in Democratic Republic of the Congo.

Figure 13.1. Countries in red have implemented vector control activities through the two main projects "Trypa-No!" and "Tryp-Elim"



Both projects are mainly based on the use of low-tech "**tiny targets**" (small insecticide-impregnated fabric screens, attractive to tsetse flies) for vector control.

The **main activities** include top-down interventions by capacity strengthening of national programmes, the preselection of sites using geographical information systems, pre-intervention entomological surveys and baseline catch data, target deployment along rivers (about 20 targets per km), and entomological evaluation at selected sentinel sites. The sensitization is conducted together with the communities and complementary community-based interventions are conducted (e.g. in Democratic Republic of the Congo and Guinea). For data management, mobile digital applications (Apps) and dashboards are used.

Figure 13.2 displays the targeted protected population (i.e. the population considered to have a reduced risk of HAT transmission due to vector control activities) and the areas covered in each country.

Figure 13.2. The protected population (population that has a reduced risk of HAT transmission) due to vector control activities

Project	Country	Foci	Population protected	Area covered (km^2)
TrypElim	DRC	Bandundu, Bolobo South, Bulungu, Kwamouth East, Kwamouth Noth, Masi Manimba, Yasa Bonga	2,120,000	6,909
TrypaNo	Chad	Manddoul, Maro	80,000	960
	Côte d'Ivoire	Bonon, Sinfra	170,000	250
	Guinea	Boffa, Dubreka, Forecariah	200,000	1,900
	Uganda	West Nile	1,139,000	3,900
Total			**3,709,000**	**13,919**

Trials in different types of environments were conducted: linear habitat in West Nile focus, Uganda; mangrove forest in Boffa focus, Guinea; and swamp area in Mandoul focus, Chad. In each focus the numbers of tsetse flies decreased dramatically, by 60% to more than 90%. The greatest impact was seen in isolated foci such as the Mandoul focus in Chad, where also a strong decrease of HAT cases directly after the implementation of vector control activities was observed. At each site, the annual incidence of cases declined with a combination of vector control and medical control activities.

During the **Ebola virus disease outbreak** in Guinea, HAT active screening activities were postponed or impaired. However, tsetse control using tiny targets could be maintained in the Boffa focus, where a pilot project had been launched in 2012. While the disruption of screening activities over 2 years led to a dramatic increase of HAT prevalence, HAT remained under control in areas with tsetse targets.

During the **COVID-19 pandemic**, one round of the entomological evaluation was suspended in Chad and Côte d'Ivoire. In general, the pandemic only caused minor delays of surveillance activities. Vector control activities could be well conducted. In Democratic Republic of the Congo, previous efforts on capacity strengthening allowed the provincial teams to conduct routine activities with remote support from the Kinshasa team and LSTM. Vector control activities were also conducted in new areas by the provincial and Kinshasa teams, with remote support from LSTM.

Tiny targets are low-tech, and their use requires only minimal training. Therefore, they are suitable for local use with minimal external support and for community-based interventions. Tiny targets allow large-scale interventions to be implemented at acceptable costs in a combined strategy with medical interventions. The costs of using tiny targets across a range of epidemiological settings are US$ 0.2–1.4 per person protected *(14,15)*.

The deployment of the targets along the rivers requires hard work. Community acceptance is declining in areas where HAT is no longer perceived as a problem. The financial sustainability for the interventions is also a challenge.

Tiny targets are effective against g-HAT, which is transmitted via tsetse flies mainly of the Glossina (G.) palpalis group. The *G. palpalis* vector requires humidity as found in dense riverine habitats and is attracted by small objects. However, tiny targets are **not effective against r-HAT**, which is transmitted via tsetse flies mainly of

the Glossina morsitans group, living in drier and more open areas of woodlands and savannahs. Traditional, larger traps and screens can be deployed for *G. morsitans* vectors. Furthermore, insecticide treated cattle are reducing the abundance of tsetse in farming areas and reducing the risk of r-HAT. Also, simulation models suggest that insecticide-treated cattle reduce the transmission of *T. b. rhodesiense* and *T. congolense*.

A simulation model has been developed to test whether recent **increases in temperature** in the Mana Pools National Park of the Zambezi Valley of Zimbabwe could account for the simultaneous decline of tsetse flies *(16)*. The model suggests that the increase in temperature may explain the observed decrease of tsetse flies. It provides a first step in linking temperature to trypanosomiasis risk. Conversely, new disease foci may emerge with the relocation of flies in higher, previously cooler regions.

In future, vector control and vector data can play different roles according to the context. A scale-down is possible in countries where interruption of transmission has been unequivocally demonstrated, while maintaining capacity for reactive vector control in case of resurgence. A scale-up is required in countries with active foci (e.g. in some areas of Democratic Republic of the Congo). Transboundary interventions are important and difficult to realize. A One Health approach is required, measuring the benefits of g-HAT vector control for AAT (in g-HAT areas where there is livestock and AAT), and also for r-HAT. The possible availability of acoziborole treatment in the future may influence the role of vector control.

New tools/technologies needed are updated maps and data sets of tsetse fly presence/absence to help countries build their elimination dossiers. Mathematical models and statistics are needed for assessing tsetse absence, as well as markers of tsetse fly–human contact. Markers to unequivocally identify *T. b. gambiense* in tsetse flies (and animal reservoirs) are required. Attracting devices should be made of biodegradable materials.

Until new tools are developed, vector control should be applied continuously in the field, since it is the only prevention measure for this deadly and stigmatizing disease.

14. Statements of HAT stakeholders

Belgium Government

Pieter Vermaerke recalled the long tradition of Belgium in the support of HAT control, especially in Democratic Republic of the Congo. In 2017, on the fifth anniversary of the London declaration, the Government of Belgium announced that it would take the lead in supporting HAT control together with the BMGF. He welcomed the significant progress that has been made towards eliminating HAT as a public health problem. Belgium remains ready to invest in activities on the way to the interruption of transmission of g-HAT in 2030. The elimination of HAT is getting the support of the new Belgium government. At the official launch of the WHO NTD road map 2021–2030, Belgium Prime Minister De Croo renewed the Government's commitment to lead on the HAT agenda. Subsequently, Belgium engaged in an exchange with the BMGF to continue the partnership. As endemic countries are facing multiple health challenges, resources have to be allocated efficiently. There are expectations in the rationalization process in Democratic Republic of the Congo, with integration of activities in the primary health care system for sustainability. Belgium also committed to the development of HAT diagnostics and availability in endemic countries. The new European legislation on diagnostics (in May 2022) and its impact on control of NTDs was addressed. He invited stakeholders to share ideas to avoid a possible negative impact of the more stringent requirements and to continue the success of HAT control.

Sanofi

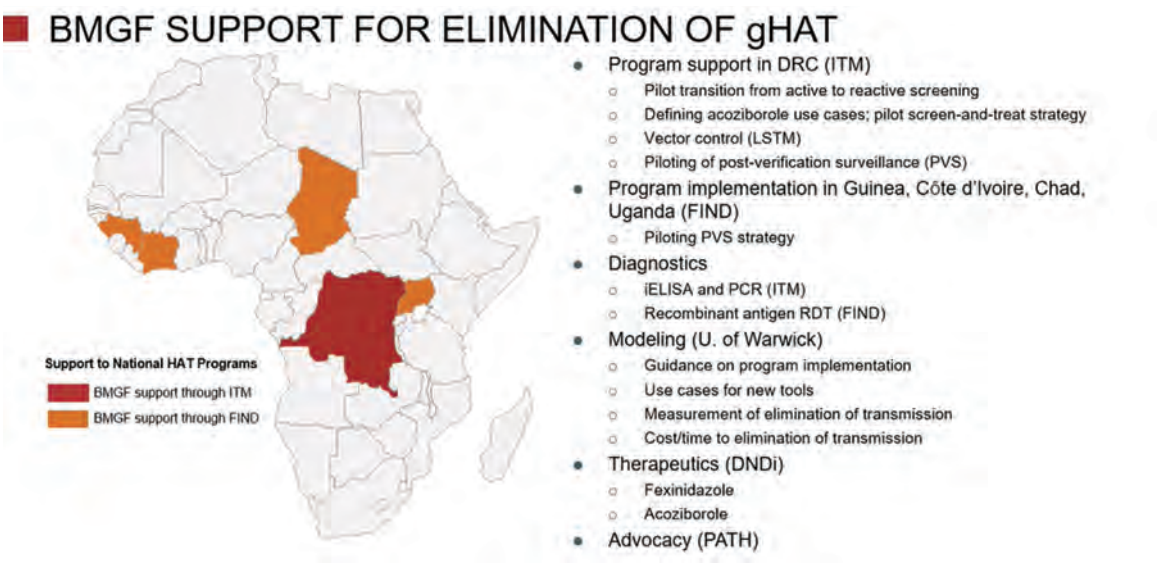
Philippe Neau pointed out the close cooperation with WHO in HAT control for 20 years. At the end of 2020, Sanofi signed a renewed partnership agreement with WHO for 5 additional years to support the goal of sustainable elimination of HAT by 2030. In the long cooperation with DND*i*, fexinidazole as an oral treatment was successfully developed and made available for endemic countries. Furthermore, acoziborole as a single dose oral treatment was developed. The results of the pivotal trial are very encouraging and acoziborole may become a game changer for the sustainable elimination of HAT. Under the new Chief Executive Officer of Sanofi, Paul Hudson, the sustainable elimination of HAT is a key flagship for Sanofi's social responsibility and will be supported in the long term.

Bayer

Ulrich-Dietmar Madeja recalled the start of the partnership with WHO in 2002, at a time when high numbers of patients were infected with HAT. The engagement of Bayer started already in the 1920s when suramin as the first effective treatment for HAT was invented, which is still an essential medicine after almost 100 years. The introduction of NECT was a major breakthrough and Bayer has been able to extend its support with the donation of nifurtimox. Together with the donation of eflornithine by Sanofi it was possible to provide treatment kits in order to reach the most remote and poor settings. Beyond the donation of medicine, Bayer follows an integrated approach, also supporting a range of activities like mobile intervention teams in Democratic Republic of the Congo or financial support for the WHO HAT programme. Experiences were gained on the challenging production of suramin in small quantities and Bayer has committed to produce it for as long as it is needed.

Bill & Melinda Gates Foundation

Rachel Bronzan thanked the many partners with special recognition of the important partnership with the Belgian government on HAT elimination in Democratic Republic of the Congo in particular. The figure shows the BMGF support for the elimination of g-HAT.



In Q3 2021, a g-HAT strategy review with the foundation co-chairs will take place to determine the level of future funding. The exit of the UK Foreign and Commonwealth Development Office is clearly impacting global NTD community funding. The impact on foundation support for g-HAT is currently unknown, but hopefully recent historic funding levels for g-HAT elimination will be retained.

Coris BioConcept

Pascal Mertens commented also on the planned new European regulation on in vitro diagnostics, requiring the registration of diagnostic assays to notified bodies. Currently there are only four notified bodies in Europe, which are very occupied with COVID-19 demands. The registration of new tests or maintaining the CE mark of existing tests could cause long delays and therefore add costs. The status of CE marking should be considered for diagnostics on NTDs and HAT. The European Commission could consider that CE marking is not required for NTD diagnostics. For companies such as Coris BioConcept, it is very important to have more visibility on the future regulation of NTD diagnostic assays. Coris is committed to continue developing and providing HAT diagnostics. Regarding rapid tests based on recombinant antigens, the assays will be provided to partners who would like to evaluate them, and their interest is very welcome.

Vestergaard

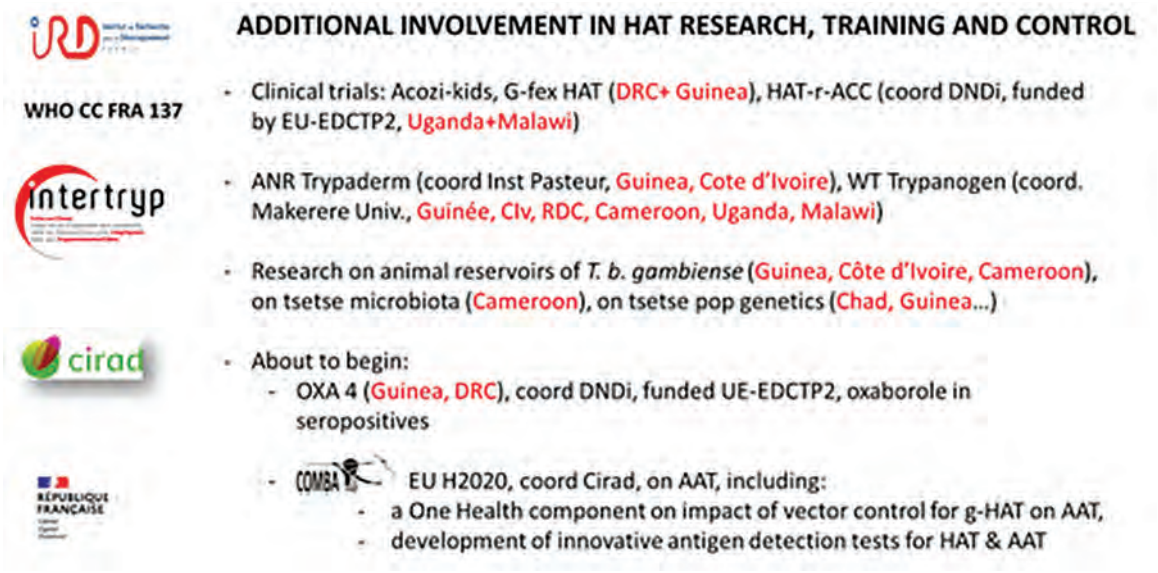
Melinda Hadi pointed out that there is a sense of pride to be the industrial partner for the innovative tiny targets in HAT control. There is a successful collaboration with the LSTM, IRD and other partners. Vestergaard is one of the manufacturers of long-lasting insecticidal nets for malaria prevention and tiny targets build on the same technology. In 2017, Vestergaard pledged to donate tiny targets and the company works closely with the HAT stakeholders for the elimination of g-HAT as a public health problem. Vestergaard renews and continues its commitment alongside the WHO NTD road map. In 2020, over 150 000 tiny targets were donated for the "Trypa-No!" partnership in Uganda, Chad, Guinea, Côte d'Ivoire and the "Tryp-Elim project" in Democratic Republic of the Congo. Vestergaard anticipates the same donation level for 2021 and remains committed to provide tiny targets until HAT is eliminated.

Institute of Tropical Medicine Antwerp

Epco Hasker emphasized that the ITM will continue its support for HAT elimination in the coming years, with both research and implementation of control activities. HAT control is entering a new phase requiring an adaption of activities to a changing epidemiological reality. New tools will become available to respond to this. He pointed out the tremendous progress towards HAT elimination as a PHP in Democratic Republic of the Congo. Even if the vast majority of serological suspects will not be true cases, having a non-toxic oral single dose treatment available within the coming years gives the perspective of presumptive treatment. Emphasis will shift from annual screening of endemic villages to more ad hoc reactive screening when a HAT case is diagnosed. Quality assurance will become even more a key issue, as available resources will have to be used highly efficiently. Historic foci will need to be monitored aiming to screen a maximum variety of villages requiring different screening algorithms. An inhibition ELISA and several new PCR methods have been developed that can be performed in remote laboratories. These tests are still undergoing evaluation and further improvements will be required. In research, ITM will continue to work on molecular confirmation tests and their field implementation in laboratories in Democratic Republic of the Congo. Another area of increasingly important research is to monitor transmission of *T. b. gambiense* including other potential reservoirs such as animals or asymptomatic humans. The end game of HAT control will be an interesting phase with many challenges. ITM plans to continue its efforts in close collaboration with its partner. So far ITM is mainly engaged in Democratic Republic of the Congo, but ITM is also ready to share the expertise with other countries.

Institut de Recherche pour le Développement

Bruno Bucheton summarized the activities and the continued commitment of IRD in HAT research, training and control together with its partners (Figure).



Pan-African Tsetse and Trypanosomiasis Eradication Campaign

Gift Wiseman Wanda reported on behalf of the AU-PATTEC. The AU-PATTEC wishes to commend the WHO HAT team for organizing the fourth WHO meeting of stakeholders on elimination of HAT. The meeting comes at a time when the whole world is still battling the COVID-19 pandemic, which has affected service delivery in almost all sectors. Disease control efforts in both the public and animal health sectors have been negatively impacted. AU-PATTEC is concerned that the achievements made towards the elimination of HAT under the leadership of WHO will no doubt be negatively impacted by the pandemic.

For its part, AU-PATTEC investigated the impact of the pandemic on implementation of the PATTEC initiative. Zoom meetings were organized for 30 tsetse affected countries to assess the impact of the pandemic on tsetse control activities. In addition, a questionnaire was circulated to 38 tsetse and trypanosomiasis affected countries requesting them to detail what was planned, what was implemented and what were the reasons for deviation from the planned activities during 2020. The common finding in all these countries was that field tsetse control activities had virtually stopped due to the pandemic. A few countries, notably Kenya, Ethiopia, Ghana, Kenya, United Republic of Tanzania and Zimbabwe reported a scaled down level of activity with reduced numbers of staff involved at any one time.

AU-PATTEC recognizes the great strides that had been made towards elimination of HAT prior to the pandemic. AU-PATTEC equally recognizes the potential benefit of vector control towards the eventual elimination of HAT. It is against this background that AU-PATTEC appeals to this meeting to come up with a resolution or recommendation on the best strategy to maintain or recover the gains already made towards elimination of HAT in the shortest time possible during and after the pandemic.

Food and Agriculture Organization of the United Nations

Weining Zhao reported on behalf of the FAO that the FAO shares with WHO and the other stakeholders attending this meeting the vision of an African continent free from the burden of trypanosomosis, and where the disease no longer constrains the attainment of the Sustainable Development Goals. FAO is determined to continuously collaborate with WHO, in realization of this vision and to achieve our common final goal.

Since 1997, FAO and WHO have collaborated closely within the framework of the Programme Against African Trypanosomosis (PAAT). In particular, in 2008 the continental atlas of sleeping sickness was launched. Since then, the atlas has become a key tool for monitoring the elimination of HAT, and it is also increasingly used for planning field control activities and for scientific research.

FAO and WHO also collaborate closely to promote One Health within the framework of the FAO–WHO–OIE tripartite. Indeed, the control of AAT has a role to play in the elimination of sleeping sickness, especially for the zoonotic form caused by *T. b. rhodesiense* in eastern and southern Africa.

FAO and PAAT welcome the new WHO road map on NTDs and confirm their commitment to supporting WHO and endemic countries in their efforts to achieve the goal of HAT elimination.

Drugs for Neglected Diseases initiative

Olaf Valverde recalled the progress of the ongoing clinical trials on acoziborole and the perspective that the drug will be available in 2023. He pointed out the projects facilitating access to fexinidazole at different levels in most of the endemic countries, mainly in Angola, Central African Republic, Democratic Republic of the Congo, Guinea and South Sudan. The focus is on training in the use of fexinidazole and on PV, with integration in the post-approval safety study conducted by the NSSCPs, WHO and Sanofi. He reported from a social science study to understand the perceptions and actions of HAT on the community level, which should help the communities to target their interventions. He emphasized the importance of the FEX-07 trial on the efficacy and safety of fexinidazole in patients with r-HAT. The trial is mainly conducted in Malawi and Uganda. It is envisaged to complete the inclusion this year and the clinical trial next year. In Uganda and Malawi, DND*i* is also working together with the NSSCP on communication activities that are targeted at furthering social science studies, which is a new field for DND*i*. These activities for fexinidazole provide a better understanding on the requirements for access, which should be also helpful for acoziborole in the future. DND*i* aims to complete all objectives of the HAT programme before 2026.

Foundation for Innovative New Diagnostics

Sylvain Biéler pointed out the development and implementation of new diagnostics solutions and the support to HAT elimination that was realized by FIND in the past 15 years. FIND is committed to pursuing

this work and is collaborating with various stakeholders, including research institutions, industry, donors, nongovernmental organization, international organizations, and in particular WHO. Two weeks ago, FIND launched its new 3-year strategy which is focused on testing to accelerate universal health coverage and to mitigate health emergencies (currently for testing on COVID-19), exploiting emerging digital innovations, and building product development partnerships focused on diagnostic for TB, malaria, hepatitis C and NTDs. FIND's strategy is closely aligned with the new road map for NTDs launched by WHO. Dr Bill Rodriguez will join FIND as new Chief Executive Officer next month. He worked already with FIND from 2015 to 2017 as chief medical officer, when he was also working closely with the HAT team.

FIND's effort will be focused to ensure that appropriate diagnostic tools are made available to HAT endemic countries, especially regarding RDTs, recognizing the importance of securing reliable production of affordable high-quality products. Furthermore, endemic countries will be supported for laboratory strengthening, training, coordination and implementation, logistics and data management, facilitating cooperation between countries with transborder foci.

More specifically, HAT elimination efforts will be supported in Chad, Côte d'Ivoire, Guinea, Uganda and South Sudan as part of the "Trypa-No!" partnership. Similar activities will be supported in Angola and Democratic Republic of the Congo and are planned in Sierra Leone and Central African Republic in the near future.

FIND acknowledges the immense progress made towards the elimination of HAT and congratulates all stakeholders for the achievement. FIND is proud to be part of it and looks forward to reaching the elimination targets together.

Coordinating Office for Control of Trypanosomiasis in Uganda

Charles Waiswa reported on behalf of the Coordinating Office for Control of Trypanosomiasis in Uganda (COCTU). He shared the experiences of the One Health approach to HAT control that has been followed in Uganda over the past 3 decades. He acknowledged the contribution of the various partners involved and appreciated the joint elimination efforts. The Uganda Trypanosomiasis Control Council has a key role in the elimination efforts. Transboundary issues, such as those on the South Sudan–Uganda border, are especially addressed, as are vector dynamics and the effect of increasing vector numbers on livestock and humans. The information gained is used to react at an early stage and also to involve new stakeholders. The partnerships and the exchange of experiences are greatly appreciated.

ICAReB Platform – Institut Pasteur

Blanca Liliana Perlaza from the ICAReB platform (Clinical Investigation and Access to Research Bio-resources) of the Center for Translational Science, Institut Pasteur, reported on the WHO HAT specimen bank.

In a cooperative framework between WHO and the ICAReB Platform-Institut Pasteur and with the financial support of FIND and Sanofi, a biobank hosting samples from donors of sub-Saharan Africa was constituted to develop and validate new tests for the diagnosis of HAT: it is field-friendly, cost–effective and species-specific.

Fourteen centres from six endemic countries were implicated: 1880 subjects (840 patients, 840 controls and 200 suspects) were enrolled according to the parasite presence, diversity and load using different parasitological and serological tests. All data and specimens (serum, plasma, plasma buffy coat, saliva, urine and CSF) were collected following international standards. The ICAReB team has been involved in the conception and setting up of the biobank: conformity to ethico-regulatory prerequisites, specimen collection, transfer, reception, processing and conservation with associated bio-clinical data under the best quality management and good clinical practice conditions.

In 2020, WHO designated the ICAReB platform as WHO Collaborating Centre for the HAT biobank. We support WHO in: (i) the management of HAT specimen biobanking (aliquoting, storing and distribution of samples),

(ii) the information associated with the specimens with adapted electronic databases, and (iii) in the HAT biobank governance with participation in the deliberations of the Exit Committee of the specimen bank.

Today, 23 000 biospecimens have been collected, with associated data from which nearly 39 000 aliquots have been produced and 9680 samples have been so far distributed to 20 different international research teams working in HAT diagnosis, after approval of the WHO Exit Committee through a material release form.

So far, RDTs, a lateral flow immunodiagnostic test, a biomarker of meningo-encephalitic stage (neopterin), the multiplex serological and RT-PCR tests have been developed while others are under pilot testing. This consolidated collaboration opens perspectives for an optimal use of biobanks in research.

Institut National de Recherche Biomédicale, Kinshasa

Dieudonné Mumba reported on behalf of INRB in Kinshasa. The INRB is a WHO Collaborating Centre and the national reference centre for HAT. INRB offers its services to the PNLTHA and other programmes in the subregion. The HAT diagnostic services include the production and distribution of the mini-anion exchange centrifugation technique (mAECT) with the support of WHO. Another focus is the training of laboratory technicians. Quality assurance of diagnostics is addressed in cooperation with ITM. HAT surveillance is carried out with the trypanolysis test in serological suspects without parasitological confirmation. Research activities are conducted with ITM, IRD, DND*i*, Makerere University, Glasgow University and multiple other partners. The partnerships and the joint efforts in the fight against HAT are much appreciated.

Liverpool School of Tropical Medicine

Andrew Hope reported on the vector control activities with tiny targets and the two consortia "Trypelim Bandundu" and the "Trypa-No! 2" project. Programmes are supported in Cameroon, Democratic Republic of the Congo and Uganda and are also envisaged for South Sudan. Through "Trypelim Bandundu" the PNLTHA in Democratic Republic of the Congo has been supported to scale-up vector control activities in the former province of Bandundu. At the end of this year, activities will have been expanded to about 12 500 km^2 in 11 health zones. This work is supported through a capacity strengthening package, and vector control activities are integrated in the PNLTHA. The project will end at the end of this year. LSTM is committed to continuing the support of the PNLTHA and to facilitating the expansion of vector control activities in Bandundu and other provinces. In the "Trypa-No! 2" project there is a direct cooperation with COCTU in Uganda. Since 2014 there has been large-scale cooperation on vector control. At this stage, interventions are scaled back with maintenance of entomological monitoring. If cases resurge, there is capacity for reactive vector control.

Geostatistical models are being used to develop cost–effective strategies for entomological monitoring, which will be especially useful for the shift from routine to risk-based monitoring in the post-elimination era. It is hoped that activities can be started in South Sudan in future, as there are active foci and as transboundary activities are also important regarding Uganda. In Cameroon, technical support is provided to a research fellow with funds from LSTM, who is implementing vector control activities in a transboundary area with Equatorial Guinea. Contact is also established with the national programme of Equatorial Guinea for visits of the activities in Cameroon.

In all of the countries where vector control is being implemented, LSTM is committed to continuing support efforts with the partners to sustain the progress in the years to come.

Institut Pasteur Paris

Brice Rotureau from the Institut Pasteur in Paris acknowledged the remarkable progress achieved by all stakeholders since the last meeting. The Institut Pasteur has been conducting HAT research since 2008 in direct interaction with WHO, the national control programmes in Côte d'Ivoire, Democratic Republic of the Congo and Guinea, as well as with other partners including IRD, ITM, the University of Glasgow, INRB, CIRDES, IPR and DND*i*.

Three units at the Institut Pasteur are engaged in different aspects of the HAT elimination programme. The group Trypanosome Molecular Biology, led by Lucy Glover, is developing new molecular HAT diagnostics. The Clinical Investigation and Access to Biological Resources platform (ICAReB), led by Marie-Noëlle Ungeheuer, is in charge of the WHO biobank for HAT. The Trypanosome Transmission Group, led by Brice Rotureau and based at the Institut Pasteur in Paris and at the Institut Pasteur in Guinea, is studying the biology and epidemiology of dermal trypanosomes. The presence of trypanosomes in the skin of patients and people free of symptoms has been highlighted by the group, in collaboration with researchers from the TrypaDerm consortium. New diagnostics to detect dermal trypanosomes or molecular assays (SHERLOCK technique) are under development. Currently, the Trypskin study is in preparation together with DND*i* as part of the DNDi-OXA-04-HAT trial for the widened use of acoziborole, funded by BMGF. The Trypskin sub-study includes examination for dermal trypanosomes and new molecular techniques for detection of trypanosomes in the blood and skin. The Institut Pasteur is dedicated to continuing its collaboration and contributing to the joint efforts towards the elimination of HAT.

HAT MEPP project – University of Warwick

Kat Rock reported for the University of Warwick in the UK about the HAT modelling and economic predictions for policy (HAT MEPP) project. The NTD Modelling Consortium brings together modellers working across several NTDs in the WHO road map. Many of the HAT MEPP and NTD Modelling Consortium team members from Warwick university and STPH are present at this meeting. In these two projects, both funded by the BMGF, modellers and health economists have been working alongside national programmes and other researchers to contribute to understanding past, current and future transmission dynamics of g-HAT. Key work focuses on:

- Understanding past transmission of infection including the role of potential animal hosts or asymptomatic human hosts in maintaining or slowing progress. This work is also able to estimate the historic reduction in transmission, which can be hard if active and passive screening coverage has been variable across time.
- Providing predictions of future case reporting and transmission across different geographical locations. The predictions compare continuation of current strategies versus adding available tools to these strategies; the range will be expanded to include alternative combinations of interventions.
- Examining the cost–effectiveness of possible future strategies in order to compare the amount of money it might take to alleviate additional disease burden from both morbidity and mortality. This is particularly saliant as elimination of infectious diseases is notoriously expensive when considering the cost of programmes when very few cases remain.

The HAT MEPP project will continue until 2024 and, in addition to updating and expanding similar studies to the ones described, will broaden focus in the coming year on how it might be able to indirectly measure local elimination of transmission using different types of data.

National Institute for Communicable Diseases Johannesburg

Lucille Blumberg reported for the National Institute for Communicable Diseases including the reference centre for parasitic diseases, based in Johannesburg, South Africa. The Institute is supporting case management and diagnosis of HAT and has built significant expertise over the past 20 years. Mainly travellers, expatriates and soldiers affected by r-HAT have been treated, either returning from endemic areas or referred from other countries without experience in HAT management. The perspective of treating r-HAT with fexinidazole is very much appreciated. Due to the decrease in travel during the COVID pandemic, no cases have been treated in South Africa in the past 15 months. With the resumption of travel, a big problem is raising awareness of r-HAT as part of the differential diagnosis, as r-HAT diagnosis is often missed. The revision of the clinical guidelines is an important task for the next few months.

15. The road map for neglected tropical diseases 2021–2030

In 2012, WHO published its first road map for NTDs, which set targets for 2020. With the first road map, substantial progress in reducing the overall burden of NTDs has been gained. In January 2021, WHO launched a new road map – *Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030 (17)* which builds on the progress of the previous one and places countries at the centre. Intensified cross-cutting approaches are followed and disease-specific targets are set for 2030. It was developed through a global consultative process with different partners, including many of the stakeholders present at this meeting. The road map is aligned with the United Nations Sustainable Development Goals and WHO's Thirteenth General Programme of Work. It was endorsed by the 73rd World Health Assembly in 2020 for implementation by all Member States with technical assistance of WHO. Progress will be monitored biannually by the World Health Assembly.

The **overarching 2030 global targets** are:

- 90% reduction in people requiring interventions against NTDs;
- 75% reduction in disability-adjusted life years related to NTDs;
- 100 countries having eliminated at least one NTD; and
- 2 NTDs to be eradicated.

The individual diseases are grouped in four categories:

Diseases targeted for eradication: dracunculiasis and yaws.

Diseases targeted for elimination (interruption of transmission): Human African trypanosomiasis (gambiense), leprosy and onchocerciasis.

Diseases targeted for elimination as a public health problem: Chagas disease, human African trypanosomiasis (rhodesiense), leishmaniasis (visceral), lymphatic filariasis, rabies, schistosomiasis, soil-transmitted helminthiases, trachoma.

Diseases targeted for control: Buruli ulcer, dengue, echinococcosis, foodborne trematodiases, leishmaniasis (cutaneous), mycetoma, chromoblastomycosis and other deep mycosis, scabies and other ectoparasitoses, snakebite envenoming, and taeniasis and cysticercosis.

In the first road map, the defined goal for g-HAT and r-HAT was identical: the elimination of HAT as a public health problem by 2020. In the new road map, the goals for g-HAT and r-HAT differ:

- gambiense HAT: "to interrupt transmission of g-HAT (sustainable elimination) by 2030"
- rhodesiense HAT: "to keep r-HAT eliminated as a public health problem by 2030".

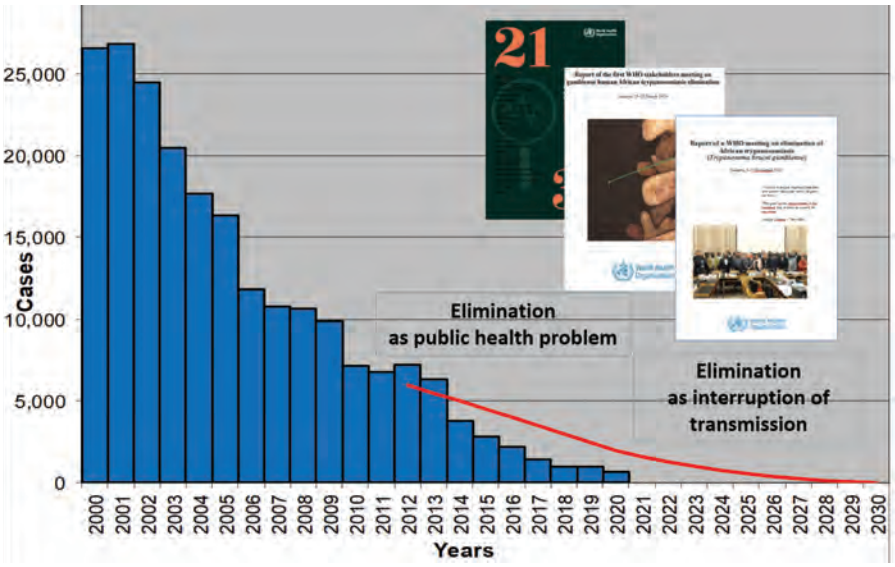
The indicators and the global targets set by 2030 are specified in Table 15.1.

Table 15.1. WHO indicators and 2030 global targets for g-HAT and r-HAT

INDICATOR	GLOBAL TARGET
Human African trypanosomiasis (gambiense)	
Number of gHAT cases reported	0 cases
Number of countries verified for interruption of transmission	15 countries (62%)
Human African trypanosomiasis (rhodesiense)	
Number of countries validated for elimination as a public health problem (defined as <1 case/10,000 people/year, in each health district of the country averaged over the previous five-year period)	8 countries (61%)
Areas with ≥1 HAT case per 10 000 people per year (average of 5 years)	0 km²

Figure 15.1 illustrates the declining number of HAT cases since 2000, together with the benchmark that was set for elimination as a public health problem and for elimination as interruption of transmission. Even if the remaining number of cases is low, it must be considered that it takes huge efforts to find the last cases and that without intervention a new resurgence could be expected.

Figure 15.1. Numbers of cases reported in 2000–2020 (blue bars) and benchmark (red line) set for elimination of HAT as a PHP (2012–2020) and for elimination of HAT as interruption of transmission (2021–2030)



The following points were discussed as **main challenges for elimination:**

- To build **resilience and adaptation to unexpected events** (e.g. social disturbances or epidemics);
- To increase **ownership and commitment of national authorities** from endemic countries of the elimination process;
- To advance in the **sustainable integration of HAT control and surveillance activities** in the weak general health services with unskilled staff, lack of resources and low attendance rates. Reinforcement of the peripheral health system is necessary;
- To face the **progressive loss of expertise in NSSCPs**, with lack of replacement. The reduction in prevalence makes it difficult to gain experience. Training for the transition of HAT expertise from specialized HAT programmes into national health systems is needed;

- To maintain **coordination between stakeholders** with different agendas, in order to avoid overlapping and disruption and to synergize efforts for sustainable elimination;
- To continue trials for a **safe and efficient single oral dose for both stages** (e.g. acoziborole), that would facilitate integration of treatment into primary health system and adapted strategies. At the same time better **tools for diagnosis and treatment** are needed for **r-HAT;**
- To develop **tools for monitoring the elimination** of HAT and post-elimination surveillance (e.g. high-throughput tests, remote testing with DBS) to detect disease reemergence/reintroduction (sustainability);
- Access to treatment is guaranteed, but there is a need to ensure **access to screening and diagnostic tools** for the population at risk. There is a worrisome lack of funding mechanisms to support availability of diagnostic tools, including the production of tests;
- To clarify the **epidemiological role of human carriers and animal reservoirs** in maintaining transmission and re-emergence of g-HAT;
- To integrate interventions between zoonotic and anthroponotic trypanosomiasis (One Health approach); and
- Financial support (Belgian Government, Sanofi, Bayer, BMGF and others) is guaranteed for next 2–5 years but an extension of **funding for long-term support** (to avoid donor fatigue) is required to sustain the current gains and to reach the elimination goals in 2030.

16. Country involvement in the elimination of HAT: lessons learnt

The national control programmes have played a key role in achieving the enormous reduction of HAT cases since 2000.

As of May 2021, HAT elimination as a PHP has been validated in Togo and Côte d'Ivoire, which entered the post-validation surveillance phase. Benin, Equatorial Guinea, Ghana, Rwanda and Uganda (g-HAT) are expected to be validated soon (see table 7.1).

The endemic countries are supported by WHO, as well as public and private partners.

The following **lessons learnt** were discussed. The endemic countries started from different epidemiological situations, but all have the same criteria for elimination. Over time the control strategies have been adapted according to the individual epidemiological situation in the country (different case-finding strategies see sections 12.1 and 12.2, with or without vector control). The success of HAT control depends on the ownership of the national control programmes, paired with the political will to achieve elimination. Other important factors are compliance with established strategies and criteria, scientific and technical support from partners, financial support to WHO, to pertinent projects and actors, and to countries, and technical support to countries by experts.

HAT-endemic countries are facing the following **difficulties and constraints**:

- socio-political instability in some countries;
- insufficient resources and State funding;
- fluctuation of trained personnel;
- lassitude of some staff to continue surveillance due to the rarity of cases;
- COVID-19 and other epidemic-prone diseases or other health risks with more visible impact; and
- major difficulties in preparing the dossier to be submitted for claiming the validation of elimination as a PHP, regarding documentation, lack of time and lack of competence.

In **conclusion**, real ownership of the national control programmes is required, with an ongoing involvement of the political authorities. Support of WHO and all partners is needed to raise awareness among policy-makers that major efforts are still needed in the fight against HAT and that local resources need to be strengthened.

Gratitude, congratulations and encouragement were expressed to all stakeholders: national control programmes, as well as technical and financial partners.

17. HAT elimination Technical Advisory Group

In 2016, the HAT elimination Technical Advisory Group (HAT-e-TAG) was convened to assist WHO in defining the criteria and procedures for assessing HAT elimination. The 2020 target (i.e. elimination as a PHP) needs **validation** per country. The 2030 target (zero transmission of g-HAT) needs country **verification**. For that, the country status is assessed against objective criteria and the achievement is recorded in a formal manner.

The HAT-e-TAG reviews the indicators to assess HAT elimination, establishes templates for national dossiers of validation/verification and establishes the procedures to review the national dossiers. Furthermore, procedures for post-elimination surveillance and revision of the national status are defined. The process is periodically reviewed, according to scientific advances and tools.

The HAT-e-TAG is the main technical consultative body for WHO concerning HAT elimination. The group consists of fixed members and invited advisors, who meet annually on the invitation of WHO complemented with remote collaboration in between.

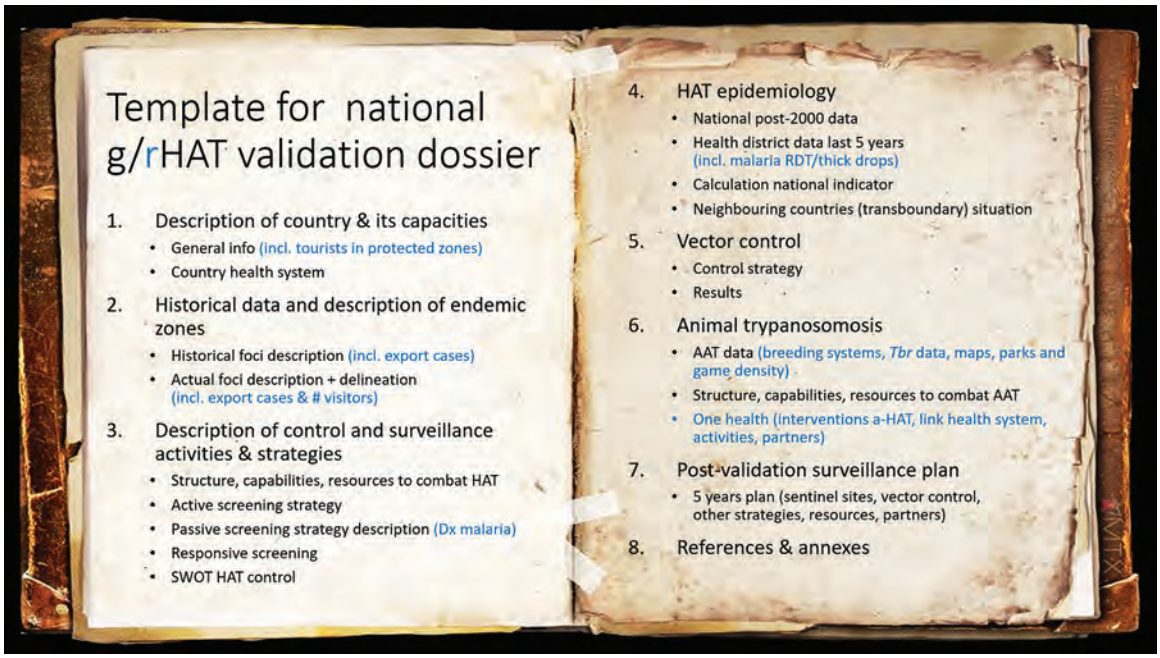
17.1 Validation and verification of elimination

It is important to understand the two terms of validation and verification. They are also applied in the new road map with the 2030 targets. For g-HAT one indicator is the number of countries verified for interruption of transmission; and for r-HAT the number of countries validated for elimination as a PHP.

A main outcome of the first HAT-e-TAG meeting in 2016 was the refinement of the second primary indicator for the global elimination of HAT as a PHP, defined as a 90% reduction of the area at risk reporting ≥ 1 case/10 000 people per year. During the second HAT-e-TAG meeting in 2017, this global indicator was adapted to national-level indicators, defined as < 1 case/10 000 people in all health districts, averaged over the previous 5-year period, together with indicators on systematic HAT surveillance.

For **validation**, templates for national **dossiers** were developed documenting the elimination of HAT as a PHP. The dossier for g-HAT and r-HAT comprises 8 chapters that are summarized in Figure 17.1.1. Chapter 7 – post validation surveillance plan – is a key chapter that requires a 5- year plan explaining activities to maintain elimination and to reach zero transmission (sentinel sites, vector control, other strategies, resources, partners). Initial validation dossiers submitted by Togo and a draft submitted by Cameroon were assessed during the third HAT-e-TAG meeting in 2018.

Figure 17.1.1. Validation dossier documenting the elimination of HAT as a PHP; dossier for g-HAT (text in black) and adapted version for r-HAT (with additional text in blue)



With the **lessons learnt** from the initial submissions, the validation process was further improved during the third and fourth HAT-e-TAG meetings (2018 and 2019). All eligible countries were encouraged to submit a dossier. Support for drafting the validation dossier is provided by the WHO team or HAT-e-TAG members. The administrative process was streamlined and guidance for the validator team to harmonize the assessment was established. Some adapted criteria for tsetse-free countries should be incorporated. For post-validation surveillance, a short annual report is requested and every 5 years the status will be re-assessed. The re-assessment is based on a simplified "update" dossier including a further 5-year surveillance plan, with focus on interruption of transmission for g-HAT.

The **verification** process was a focus of the third to fifth HAT-e-TAG meetings (2018–2020) with two directions of work. First, the strategies for g-HAT "interruption of transmission", combining new approaches for treatment, diagnostics, and vector control and considering integration in the health systems; all in a framework of decreasing expertise, uncertain funding, limited country ownership, and unexpected events. Second, the definition of indicators, targets and milestones for interruption of g-HAT transmission.

Regarding the global HAT elimination indicators, zero reported cases and the verification of interruption of transmission in 15 countries are targeted for 2030. These **global indicators** need to be **adapted to national indicators** in line with the 2030 road map and in line with the national verification dossier. Validation is not a mandatory requirement before verification. Indicators (primary, secondary, mandatory, optional) need to be further developed.

17.2 Possible strategies of widened treatment for gambiense HAT

"Treating HAT is eliminating HAT" was already known early in the fight against HAT and mass treatments were effectively used in the past to tackle the main reservoir of g-HAT in humans. Gambiense HAT is difficult to diagnose. Populations are screened on epidemiological and/or clinical suspicion. Serological suspects undergo parasitological examinations to confirm HAT diagnosis. Globally, around 4% of seropositives may be parasitological confirmed. However, cases are being missed (e.g. due to imperfect diagnostics, lack of human resources) constituting the residual reservoir. There remains the old question: should we treat all seropositives? The main problem in this regard is the toxicity especially of second stage drugs and the complex administration (injectables, directly-observed treatment, required food intake, long course).

Acoziborole as a new oral drug is in development. It has a very long half-life and is taken in a single dose (adult dose: 3 tablets at once in a fasting condition). Phase III trials are completed, and safety and efficacy data are promising. The very good safety results of acoziborole so far are in strong contrast to all other HAT treatments, which puts us in a unique situation for innovative treatment strategies.

Five **scenarios for the wider use of acoziborole** were discussed and analysed by the HAT-e-TAG in November 2019:

- Treatment of confirmed g-HAT cases;
- Treatment of confirmed g-HAT cases and serosuspects;
- Treatment of g-HAT serosuspects without parasitology;
- Collective use in well-defined populations at risk; and
- Mass administration in endemic areas.

For each of the five scenarios noted above it is necessary to ponder the benefit–risk ratio, considering the individual benefit and the benefit for the community, and considering the feasibility and the implications for monitoring the disease situation. The main requirement is the safety of the drug.

The **target product profile (TPP)** for a widened treatment was developed by HAT-e-TAG for different scenarios. Table 17.2.1 displays selected items of an ideal and an acceptable TPP.

Table 17.2.1. TPP (ideal and acceptable profile, selected items) for widened treatment

Characteristics	Ideal profile	Acceptable profile	Comments / Questions
Target population	All population (no subgroups excluded)	Adults including pregnant / lactating women, children >5 years old.	In extended use, if there was need to exclude young children, it's still feasible.
Safety	Safe in presence of any coexisting pathology or condition. No drug interaction with commonly used medicines.	Few and identifiable conditions where exclusion is recommended (contraindications).	If too many criteria need to be applied, it complicates implementation in wide use.
Need for monitoring adverse events	No need for monitoring	Need to monitor for 1-2 days	The monitoring could be done by health staff in ambulatory
Setting of administration	Anywhere, including out of health structures (given by health staff)	In health structures, given by health staff	

A TTP for safety was developed by HAT-e-TAG (Table 17.2.2). The more the treatment would be widened, the more safety data would be needed. For example, treatment of g-HAT suspects without parasitological examination (scenario 3) – which is currently under discussion – would require strong safety data with larger studies detecting uncommon (1/100 to 1/1000) adverse events, safety data in pregnancy and in children of all ages (at least in children ≥ 5 years old).

The difference of scenario 2 (serosuspects) and scenario 3 (serosuspects without parasitology) for the widened treatment with acoziborole is the absence of parasitological testing in scenario 3. Even if the population to be treated will be the same, there is an enormous difference in feasibility and for the implementation of new strategies. Conversely, the epidemiological information on whether real transmission is taking place (indicated by the presence of parasite) is lost. For scenario 3, significant overtreatment would be accepted, under the prerequisite of a safe drug.

At the same time, seropositivity is not yet precisely defined. Studies about serological tests and the combination of tests are ongoing. At some point a clear definition of seropositivity will be required.

Table 17.2.2. TPP regarding safety for widened treatment

Use of medicine	TPP safety (benefit – risk ratio)
1. Treating confirmed g-HAT cases	Comparable to current treatments (pentamidine, NECT, fexinidazole)
2. Treating confirmed g-HAT cases + suspects	- More robust safety data, on larger cohorts (e.g. from pharmacovigilance) - Safety data in pregnancy - Safety data in children (ideally all ages, but at least in >5 yrs.)
3. Treatment of g-HAT suspects without parasitological exams	Strong safety data - Larger studies detecting uncommon (1/100 to 1/1,000) AE - Safety data in pregnancy - Safe in children (ideally all ages, but at least in >5 yrs.)
4. Collective use in well-defined populations	Requires larger studies and specific studies to complete safety knowledge - Rare adverse events (1/1,000 to 1/10,000) studied and characterized - Good safety in pregnancy - Safe in children (ideally all ages, but at least in >5 y/o) - No interactions, with other drugs or pathogens, causing toxicity or threatening efficacy of other drugs
5. Mass administration in endemic areas	- Proven very low toxicity - No attributable SAE - Very rare adverse events (< 1/10,000) studied and characterized - No toxicity in children exposed in utero - No threat in pregnancy - Safe in children and elderly - No drug interactions causing toxicity or threatening efficacy of other drugs

For the **development of the clinical trial protocol** (DNDi-OXA-04-HAT trial) for the use of acoziborole in non-parasitologically confirmed cases, DND*i* provided the protocol synopsis in 2020. WHO has constituted an ad hoc consultative expert panel that met in September 2020. The expert panel reviewed the documents provided and gave technical advice regarding a possible future consideration in the WHO guidelines. DND*i* adapted the protocol design. After a follow-up meeting in May 2021, further adjustments were suggested.

As next steps, the start of a clinical trial is required to generate mainly safety data that may support the strategy of treating seropositive individuals with acoziborole. Afterwards, the WHO Guideline Development Group could consider new guidelines on HAT treatment. The current guidelines are considered as interim. The next guidelines could include treatment with fexinidazole in r-HAT and acoziborole treatment in adults, children and seropositive individuals. The timeframe will depend on the availability of evidence and on regulatory procedures.

17.3 Further innovative strategies

Within the framework of widened treatment there are diagnostic implications. TPPs for diagnostics have to be developed, as well as optimized diagnostic algorithms to increase HAT suspicion and to improve the benefit–risk ratio of the treatment of seropositive individuals. Higher positive predictive values may result by combining clinical signs and/or screening tests and/or DBS remote testing. Guidelines for post-therapeutic follow-up are required, in particular if seropositives are getting treated. The concept of surveillance and monitoring of HAT elimination must be reconsidered, when the epidemiological information on confirmed HAT presence is lost, while a certain level of seropositivity will exist. There is a need to identify and develop elimination verification tools for population surveys, population monitoring, and xenomonitoring, including high-throughput remote testing. With innovations, vector control should better target transmission areas and human–tsetse contact points. Vector control should be associated with other control tools, e.g. reactive vector control to complete reactive screening.

18. Integrating new tools on the way to elimination: adapting strategies

Elimination, also referred to as **interruption of transmission**, is the reduction to an incidence of zero infections caused by a specific pathogen, in a defined geographical area, with minimal risk of reintroduction, and as a result of deliberate efforts; continued actions to prevent re-establishment of transmission may be required *(18)*. The process of documenting elimination of transmission is called **verification**.

Control strategies can target the **human reservoir**, the **vector** or the **animal reservoir**. All three approaches are subject to limitations and adapted strategies are necessary (Tables 18.1–18.2).

Table 18.1. Limitations of HAT control by case detection with possible alternative approaches

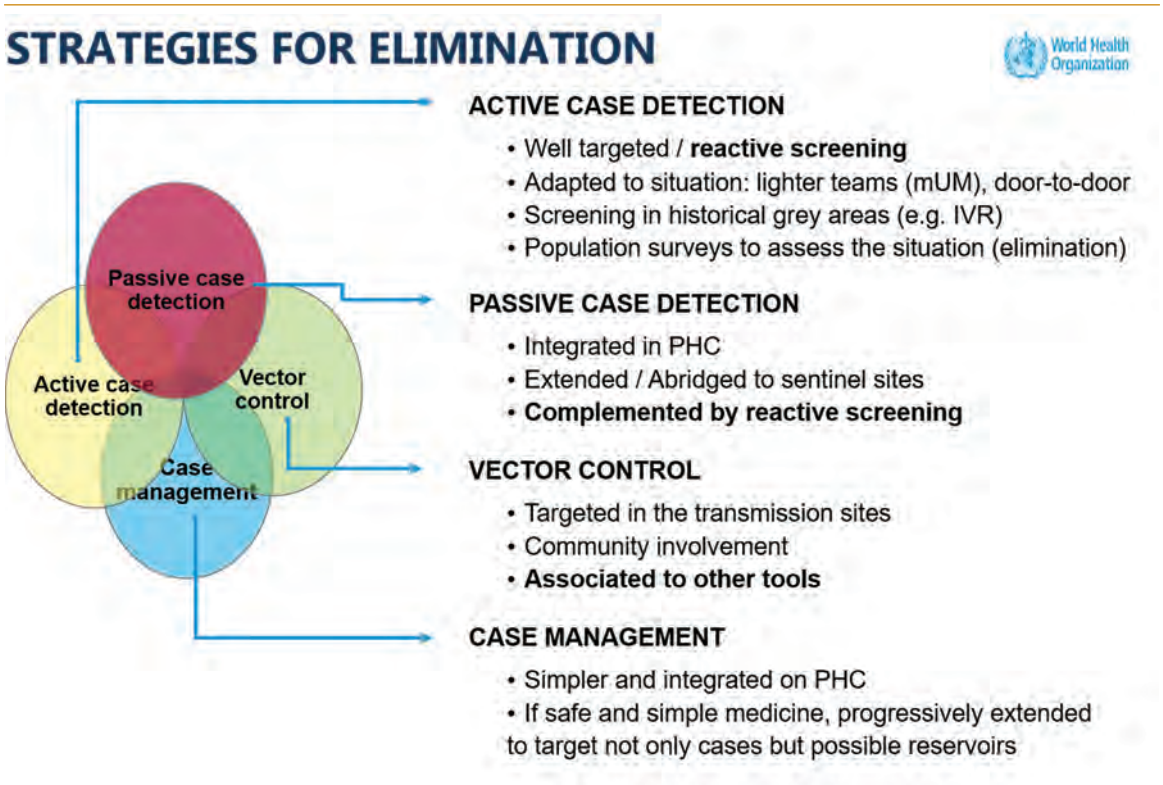
Limitations	Alternatives
Limitations of confirmation diagnostic: - **Limited sensitivity of tests**: Some infected people (screened) are not detected by parasitology - Parasitological tests **cumbersome** (need of trained staff and devices)	- Simpler, more sensitive and specific tests - If a very **safe and simple-use medicine** is available, simpler and more sensitive but less specific tests could be used (treating serosuspects):
Population at risk is not fully screened - When prevalence is low, participation of population at risk is low - AS has low efficacy in low prevalence areas - Difficulties to integrate passive screening in PHC - Limited access to health services	- Reinforcing passive screening including targeted reactive screening - Persistence of intervention over time - Simpler diagnostic tests - Adapted approaches (e.g. door-to-door) - Community awareness - Reinforce PHC and access to health system

Table 18.2. Limitations of HAT control regarding the vector and the animal reservoir with possible alternative approaches

Limitations	Alternatives
Vector extended in vast areas	Targeted VC in sites contact host – vector
Biology of vector is different in different ecological settings	Adapted to local conditions
VC is expensive and requires high expertise	Introduce cheaper methods Training of staff Community involvement
Not enough knowledge about role played by animal reservoirs	More research is needed One health approach (treating animals ?, protecting them (e.g. net impregnated fences)?

Current interventions – case detection (active and passive), case management and vector control – are effective but need to be progressively **adapted to new epidemiological settings** of low and very low prevalence and **integrated in primary health care (PHC) health systems** to ensure sustainability (Figure 18.1).

Figure 18.1. Possible adaptions of active and passive case detection, case management and vector control to new epidemiological settings of low and very low prevalence



Integration of HAT control and surveillance activities in general health care services is a must, but a vertical approach to planning, monitoring and technical advice has to be maintained. Widened treatment based on diagnostics with a lower specificity could be considered if safer treatments become available.

The **ownership of national control programmes** should be reinforced. If HAT is no longer perceived as a PHP, national authorities and donors must be sensitized to maintain the commitment and funding.

To prove the absence of cases for the verification of elimination is a difficult task ("*Absence of evidence is not evidence of absence*"). Evidence of absence of transmission (zero cases) must be obtained despite all limitations. The HAT-e-TAG is working on the definition of indicators to assess HAT elimination and on innovative strategies and templates for national dossiers of validation/verification.

A clear **case definition** of HAT is needed. The question of what real cases are becomes even more complex if treatment of seropositives without parasitological diagnostics is introduced. Real cases need to be identified to signal that transmission is ongoing and whether control measures are justified and should be maintained. Other complementary diagnostics available for remote testing could be used to obtain this information. Case definitions must also take into account that a newly diagnosed case may indicate an old infection acquired years ago; imported and transboundary cases must also be considered.

The **absence of cases** can be assessed with

- maintained **integrated passive case detection coupled with reactive screening**: the intensity, coverage, diagnostic methods and duration of application have to be defined.

- **dedicated population surveys**: attention should be given to the definition of target groups, sample size, diagnostic tools, periodicity, remote testing, high throughput testing; and
- **active screening in populations in well-defined areas**: the definition of coverage, diagnostic tools and periodicity need consideration.

Costs and feasibility must be taken into account and quality control must be ensured.

Other **complementary tools and indicators** for elimination concern the assessment of

- the **absence of tsetse flies**: the question arises whether in this case elimination can be assumed and how to demonstrate the absence of tsetse flies;
- the presence or absence of *T. b. gambiense* **in tsetse flies (xenomonitoring)**: clarification is needed on its relevance, on the diagnostic methods (sensitivity, specificity for subspecies) and on sample size; and
- the presence or absence of *T. b. gambiense* **in domestic and wild animals**: its relevance and the performance of diagnostic methods need assessment.

Availability of diagnostic methods, sampling methods and costs play an important role.

The **main tools required for verification** of elimination are:

- simple screening tests: these are already available and further optimization would be desirable;
- simple methods to refer the samples at low cost: DBS and microplates are possible tools; methods should not depend on cold chain;
- reliable remote tests to identify cases including the capacities for performing the tests: the trypanolysis test is available, but tests that are easier to perform are needed; and
- high-throughput tests for analysing large amounts of samples: currently it takes a very long time until results become available.

Finally, we must bear in mind that interruption of transmission is not an irreversible status. The possibility of re-emergence/reintroduction (e.g. from animal reservoirs, or hidden human reservoirs) will remain. Post-elimination surveillance at reasonable cost will be needed.

19. Conclusions

1. Great success has continued across National Sleeping Sickness Control Programmes towards elimination of the disease. The stakeholders participating in the meeting expressed unanimous enthusiasm to continue supporting the endeavour and working towards the elimination of HAT. Only 663 cases were reported in 2020. Togo and Cote d'Ivoire were validated for elimination of HAT as public health problem in 2020, following submission and evaluation of the dossier outlining progress and the status of HAT in each country. Benin, Equatorial Guinea, Ghana, Rwanda and Uganda have all submitted dossiers for review. WHO and other partners can support countries in producing their dossier.
2. COVID-19 has impacted activities in a number of countries in 2020–2021, particularly in diminishing some surveillance activities, vector control programmes and training of personnel. Therefore, case-finding has been impacted and it is probable that cases were missed due to the pandemic, although the extent to which this happened is difficult to quantify.
3. Progress towards integrating HAT surveillance and control into primary health care systems needs to be reinforced (WHO and other stakeholders will advise on implementation). However, attention must be paid to retaining specialized skills associated with HAT management, as a loss of experienced and highly trained personnel from national programmes is accompanying the decline in case numbers. National programmes should transform to focus more on training and supervisory roles in disease control and surveillance, quality assurance and intervention as HAT embeds within primary health care. National ownership of the HAT elimination goals is needed to ensure sustainability
4. Further integration between programmes to control HAT and AAT in a One Health approach is desirable where appropriate, alongside continued cooperation among WHO, OIE and FAO.
5. The recent approval of fexinidazole for g-HAT provides the first fully oral drug. Trials are under way for fexinidazole use against r-HAT too. Moreover, a single dose oral drug, acoziborole, has also completed phase III trials for use against g-HAT. Data from the trials, while still under analysis, look very promising. The possibility of "test and treat" with use of a safe and easily applied drug such as acoziborole on a simple serological positive test may become possible, but sufficient evidence on safety is required.
6. New diagnostic tools, including molecular tests, are under development, and may meet the need for remote testing and high throughput. Second-generation serological rapid tests are now available and in use. As data on their specificity and sensitivity are limited, the performance of this new generation of tests should be closely monitored. Parasitological confirmation remains necessary for the time being. The decline in the use of microscopy in many diagnostic settings in endemic countries thus presents a problem, especially in r-HAT foci where no serological test exists.
7. New legislation raising quality control requirements for diagnostics could hamper the production of tools used in HAT interventions. It should be monitored, and we may need to find alternatives if detrimental to control programmes: for example, new European legislation on CE marking for diagnostic risks increasing development and production costs beyond those compatible with use for low prevalence NTDs such as HAT.
8. Innovative approaches to case-finding including door-to-door surveys and reactive screening can help to increase the efficacy of case-finding. Moreover, attention to the asymptomatic human reservoir and animal reservoirs is still required. The dermal infections need further studies.
9. Integrated with other control methods, vector control interventions have proven effective in reducing transmission, e.g. tiny targets against riverine tsetse flies (palpalis group) in g-HAT foci. For savannah flies

(morsitans group), the main vectors in r-HAT foci, other tools and methods (e.g. larger/standard targets and insecticide treated cattle) can be applied.

10. Substantial work is needed to sustain the current momentum against the disease(s) and advance towards the 2030 goals of verified interruption of transmission of g-HAT and elimination of r-HAT as a public health problem. The WHO Technical advisory group for HAT elimination has been instrumental in defining the criteria and processes to claim and validate elimination as a public health problem. The group has started work on adapting strategies to reach the interruption of transmission of g-HAT and the criteria to verify it, and leads the guidance on this process for national programmes and stakeholders in attaining their elimination goals.

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Annex 1. Agenda

Day 1, 1 June 2021		
14:00–14:30	**Introduction and welcome. Opening** Presentation of the meetings and participants. Addresses from WHO officials	CDS AFRO/ Director NTD/ Coordinator PCT
HAT epidemiological status 2020		
14:30–15:00	**Situation report of gambiense HAT** Update on the epidemiological situation of gambiense-HAT per subregion and country and outstanding remarks from the perspective of national programmes in endemic countries ⊙ West Africa ⊙ Central Africa	National Sleeping Sickness Control Programme (NSSCP) focal points
15:00–15:15	**Situation report of rhodesiense HAT** Update on the epidemiological situation of rhodesiense-HAT per country and outstanding remarks from the perspective of national programmes in endemic countries	National Sleeping Sickness Control Programme (NSSCP) focal points
15:15–15:45	**Global progress in HAT elimination as a public health problem** Update on the global situation of HAT. Status of HAT elimination as a PHP 2020 **Status of validation of elimination at country level** **Report of the WHO HAT elimination network**	WHO
15.45–16.00	Q&A discussion	
16:00–16.05	Break	
HAT advances in new tools		
16:05–16:45	**HAT treatment** State of the art on gambiense HAT treatment. Updated treatment guidelines and implementation of treatment Pharmacovigilance of fexinidazole Status of development of acoziborole Report from WHO HAT elimination network working group: "Integration of new tools into national and global policies"	WHO/ DND*i*/ J. Seixas (chair working group)
16:45–17:30	Q & A. Discussion	

Day 2, 2 June 2021		
14:00–14:40	**HAT diagnostics** Advances and perspectives in HAT screening and diagnosis Report from the WHO DTAG HAT-Subgroup, TPPs	ITM/FIND/IRD E. Matovu (chair HAT subgroup DiTAG
14.40–14.50	Q&A discussion	
14:50–15.30	**Innovation in surveillance and control. Different contexts, different methods** ⊙ Case-finding in the elimination context. ⊙ Integration of control activities in the primary health care system ⊙ Evidence-based planning of activities. HAT Atlas, microplanning	IRD ITM WHO/DRC
15:30–15:40	Q&A discussion	
15:40–15:45	Break	
15:45–16:00	**HAT vector control** Advances in vector control tools Current vector control interventions in g-HAT and r-HAT	LSTMH/IRD
16:00–16.10	Q&A discussion	
16:10–17:30	**Open floor to statement of** **Donors, public and private partners:** Sanofi, Bayer, BMGF, Cytiva, Belgium Government, Vestergaard Frandsen, Standard Diagnostics/ Abbott, Coris, Other **Research institutions and academia:** ITM, IRD, DND*i*, FIND, LSTMH, Institut Pasteur, Swiss Tropical & Public Health Institute, University of Warwick, University of Glasgow, University of Makerere, INRB **International organizations**: PATTEC, PAAT, FAO, IAEA **Nongovernmental organizations:** MSF, PATH	Each institution participant can use up to 5 min to make a statement
Day 3, 3 June 2021		
Targeting elimination as interruption of transmission in 2030		
14:00–14:20	**2030 road map** Interruption of transmission: indicators and targets	WHO
14.20–14.30	Q&A discussion	
14:30–14:45	**Country involvement on HAT elimination. Ownership**	WHO/NSSCP
14:45–15:00	**HAT-e-TAG: Integrating new tools in the way to elimination. Adapting strategies (treatment)** Possible strategies of widened treatment with acoziborole TPP for new HAT treatment	HAT-e-TAG/ WHO
15:00–15:15	Q&A discussion	
15:15 – 15:20	Break	

15:20–15.35	**HAT-e-TAG: Integrating new tools in the way to elimination. Adapting strategies (diagnosis)** Verification of elimination: methods and diagnostic tools Post-elimination surveillance	HAT-e-TAG/ WHO
15:35–15:50	Q&A discussion	
15.50–16:30	**Conclusions and outcomes** Consensus on the main conclusions of the meeting and points to be followed up. Way forward	
16:30–17: 00	**Closing**	

Annex 2. List of participants

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