# REVIEW ARTICLE

# The journey towards elimination of gambiense human African trypanosomiasis: not far, nor easy

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SUMMARY

Considering the epidemic situation of gambiense human African trypanosomiasis (HAT) at the end of the twentieth century, the World Health Organization (WHO) and partners strengthened disease control and surveillance. Over the last 15 years, the activities implemented through the National Control Programmes have brought gambiense HAT under control and now its elimination is deemed as an achievable goal. In 2012, WHO targeted gambiense HAT for elimination as a public health problem by 2020. The final goal will be the sustainable disease elimination by 2030, defined as the interruption of the transmission of gambiense HAT. The elimination is considered feasible, because of the epidemiological vulnerability of the disease, the current state of control, the availability of strategies and tools and international commitment and political will. Integration of activities in the health system is needed to ensure the sustainability of the elimination. The development of user-friendly diagnostic and treatment tools will facilitate the integration process. Adequate funding is needed to implement activities, but also to support research that will make the elimination sustainable. A long-term commitment by donors is needed and ownership of the process by endemic countries is critical.

Key words: Human African trypanosomiasis, HAT, sleeping sickness, disease elimination, gambiense HAT, *T.b. gambiense*.

## BACKGROUND

Human African trypanosomiasis (HAT), or sleeping sickness, is a disease caused by extracellular protozoa belonging to the genus *Trypanosoma*, which are transmitted by the bite of an infected tsetse fly (genus: *Glossina*). The disease is endemic in 36 countries in sub-Saharan Africa, with about 70 million people living at risk of infection (Simarro *et al*. 2012). HAT is considered as a neglected tropical disease (NTD) (World Health Organization, 2012*a*) and it afflicts mainly neglected populations in rural areas where suitable environmental conditions for the occurrence of the tsetse vector are present.

There exist two human pathogen subspecies (i.e. *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*), which are morphologically indistinguishable. Western and central sub-Saharan Africa are affected by *T. b. gambiense*, which leads to a chronic disease that may last for years (gambiense

HAT) (Checchi *et al*. 2008). This form of HAT currently accounts for more than 95% of the total cases. In eastern and southern Africa *T. b. rhodesiense* causes an acute disease that may be fatal within weeks or months (rhodesiense HAT) (World Health Organization, 1998; Brun *et al*. 2010).

After inoculation, the parasite is initially found in the lymphatic system and bloodstream (haemolymphatic stage) but after a period of variable duration, trypanosomes cross the blood–brain barrier and enter the central nervous system (meningoencephalic stage) causing a progressive neurological breakdown. If untreated, patients progress to coma, severe organ failure, and eventually death (Kennedy, 2008).

## HISTORICAL PROGRESS, SITUATION DURING THE PAST DECADE AND CURRENT EPIDEMIOLOGICAL STATUS OF THE DISEASE

After the epidemics that took place at the beginning of the 20th century, which killed an estimated 300 000 and 500 000 people in the Congo Basin and the Busoga focus, respectively (Hide, 1999; Steverding, 2008), it appeared that HAT had been progressively

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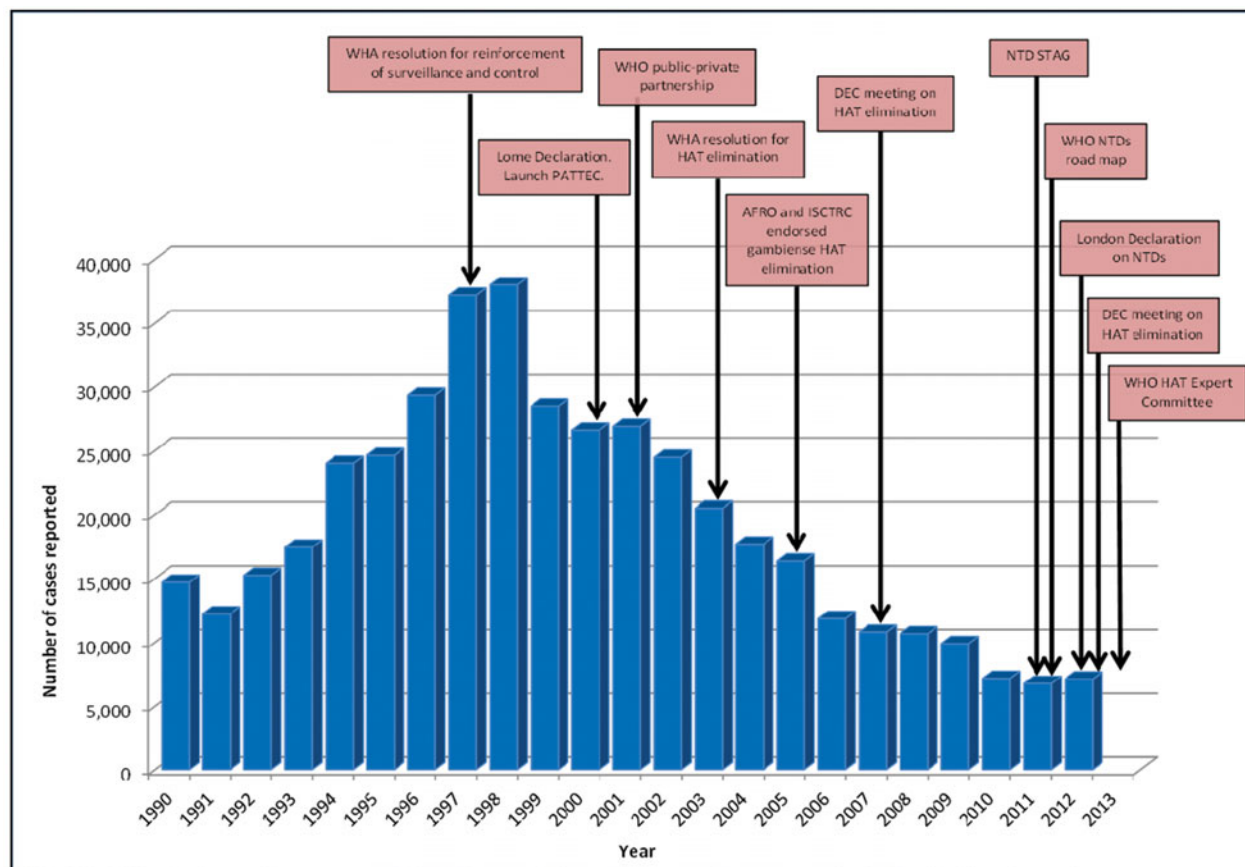
Fig. 1. Number of gambiense HAT new cases reported (1990–2012) and key events on the road to the elimination.

controlled during the mid-50s. The annual number of new declared cases decreased from more than 55 000 (1940) to a minimum of 4435 (1964) (World Health Organization, 2000). In the following decades the rarity of the disease and competition from other health priorities led to neglect of disease control and surveillance. This allowed the number of new cases to rise again to alarming levels at the end of the twentieth century, reaching 37 991 new cases declared in 1998 (World Health Organization, 2006), with an estimation of more than 300 000 people infected (World Health Organization, 1998). In addition, social instability in some endemic countries and the scarcity of funds contributed to hampering disease control.

To face this epidemic situation, the World Health Organization (WHO) and partners implemented a series of initiatives aimed at bringing HAT back under control. In 2001, pharmaceutical companies producing medicines against HAT (Aventis (currently Sanofi) and Bayer) agreed to provide these free of charge to affected countries through the WHO. In addition, resources were made available for strengthening disease control and surveillance through the support of the WHO to Sleeping Sickness National Control Programmes (SSNCP). At the same time, bilateral cooperation (Belgium, France) and non-governmental organizations (NGOs) joined the effort and contributed to reversing the upward trend in the number of HAT cases (Simarro *et al.* 2011). These enhanced control activities resulted in an improved epidemiological knowledge of the disease, as well as in a sustained decrease in the number of reported cases. By 2009, the number of reported new cases had fallen below 10 000, with fewer than 8000 in 2010, 2011 and 2012, and an estimated number of infections at around 20 000 (World Health Organization, 2013*c*).

Recent trends in new HAT cases (Fig. 1) are promising, but figures should be interpreted with care: the disease occurs mainly in remote rural areas where health infrastructures are weak. Cases are not always recognized, which results in significant under-detection and under-reporting. Under-detection and under-reporting are difficult to estimate, but some available data suggest that 50–65% of cases are currently not reported (Mumba *et al.* 2011; Simarro *et al.* 2013*a*). In particular, some of the areas concerned by this problem are hard to reach because of insecurity or difficult terrain.

It has been estimated that 70 million people live at different levels of risk of HAT infection. 57 million (81%) are at risk of gambiense HAT, and this population is distributed over an area of approximately 1·38 million km$^2$ in 14 of the 24 countries listed as endemic for gambiense HAT. More than 2 million people live in areas classified as high to very high risk of gambiense HAT (Simarro *et al*. 2012). The distribution of the disease, the population and areas at risk and the level of control activities are shown in Table 1.

The number of new reported cases of gambiense HAT has been below 10 000 since 2009, with 7106 cases declared in 2012. As of 2008, gambiense HAT cases represent 98% of the total HAT cases and cases of rhodesiense HAT accounting for the remaining 2%. In the last 5 years (2008–2012), 78% of gambiense HAT cases were reported from the Democratic Republic of the Congo (DRC), followed by Central African Republic (8%), South Sudan (4%), Chad (3·5%) and Angola (3%) (Table 1) (World Health Organization, 2012*b*).

Currently, SSNCP are functional in 15 endemic countries (Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, the DRC, Equatorial Guinea, Gabon, Guinea, Mali, Uganda and Togo). All these countries have a functioning surveillance system for gambiense HAT. In Ghana, Nigeria and South Sudan there is not a structured SSNCP but there is a surveillance system run by different structures of the Ministry of Health. In Gambia, Guinea Bissau, Liberia, Niger, Senegal and Sierra Leone, SSNCP do not exist, and no surveillance activities are performed. Field assessments of the epidemiological situation have been carried out in Senegal and Sierra Leone (Table 1).

## EPIDEMIOLOGICAL CHARACTERISTICS OF DIFFERENT FOCI OF GAMBIENSE HAT

HAT has a patchy geographical distribution, which is restricted to circumscribed areas (foci) (Welburn and Maudlin 2012). This distributional pattern is caused by a complex set of factors involving interactions between the environment, the host, the vector and the parasite. These complex relationships are not always fully understood. The foci of the disease have been fairly stable over time. The focus was qualitatively defined by the WHO Expert Committee in 1986 as 'a zone of transmission to which a geographical name is given (locality, region or river)' (World Health Organization, 1986). This definition is useful to allocate resources, to plan control activities, to measure the burden of the disease and to monitor the evolution of the epidemiological situation. Currently, 303 foci of gambiense HAT are identified (Table 1) (World Health Organization, 2012*b*).

Analysing the epidemiological patterns of these foci, it is possible to distinguish three different situations. The three epidemiological settings can be characterized on the basis of the reported intensity of disease transmission (Simarro *et al*. 2012, 2013*a*):

1. Foci at high to very high intensity of transmission. These are defined as those where the average annual number of cases reported is at least 1 per 1000 inhabitants.
2. Foci at moderate intensity of transmission. They are those where at least 1 case per 10 000 inhabitants (but less than 1 per 1000 inhabitants) has been reported yearly.
3. Foci at low to very low intensity of transmission. They are those where at least 1 case per 1 000 000 inhabitants per annum (but less than 1 case per 10 000 inhabitants) has been observed.

The average annual number of reported cases can be calculated for different time periods. In previous studies, a 10-year study period was used. However, a shorter time period (i.e. 5 years) might be more appropriate to follow the evolution of the epidemiological situation.

There are still a few areas where transmission intensity is not well known, and which require further investigation. Among these areas we distinguish two different situations:

1. Foci where disease transmission is known to be taking place (cases are present), but which are characterized by difficult access because of terrain or security constraints. As surveillance in these areas has been hampered, the intensity of transmission needs to be better assessed.
2. Foci which have not reported cases in the last decades but which do not have an effective surveillance system in place. These areas have a history of disease transmission, and for most of them the current ecological characteristics still make it possible. The absence of reported cases over a long period of time makes the absence of transmission probable. Investigations are needed to ascertain the presence or absence of transmission.

## THE CASE OF RHODESIENSE HAT

Rhodesiense HAT has to be considered as a zoonosis with occasional presence in human beings. Its current epidemiology is characterized by a low level of endemicity with sporadic human cases. However, epidemics can occur. They have been linked to environmental changes or major social disruptions (Morris, 1959; Fèvre *et al*. 2001; Jelinek *et al*. 2002; Kaare *et al*. 2007), which have resulted in changes in population distribution and large-scale movements of livestock and people to marginal areas more exposed to infected tsetse flies. As opposed to

Table 1. Gambiense HAT endemic countries (cases reported, area and population at risk, number of foci, surveillance and control activities)

| Country | No. of cases | | Area at risk ($km^2 \times 10^2$) (% of total country area) | Pop. at risk (no. people $\times 10^3$) (% of total country population) | No. of foci described | Activities of surveillance and control | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2003–2007 | 2008–2012 | | | | SSNCP | Active screening | Passive screening | Vector control | Surveillance |
| Angola | 8875 | 1206 | 2253 (18%) | 5864 (46%) | 46 | Yes | Yes | Yes | Sporadic | Yes |
| Benin | 0 | 0 | – | – | 3 | Yes | No | Integrated | No | Yes |
| Burkina Faso | 0 | 0 | – | – | 5 | Yes | Sporadic | Yes | Yes | Yes |
| Cameroon | 75 | 75 | 173 (4%) | 631 (3%) | 12 | Yes | Yes | Yes | Sporadic | Yes |
| Central African Republic | 3057 | 3156 | 658 (10%) | 433 (10%) | 8 | Yes | Yes | Yes | No | Yes |
| Chad | 1268 | 1411 | 142 (1%) | 465 (5%) | 4 | Yes | Yes | Yes | Sporadic | Yes |
| Congo | 2477 | 456 | 1150 (34%) | 2566 (64%) | 19 | Yes | Yes | Yes | No | Yes |
| Côte d'Ivoire | 226 | 49 | 286 (9%) | 2672 (13%) | 15 | Yes | Yes | Yes | Sporadic | Yes |
| Democratic Republic of the Congo | 48 304 | 31 716 | 7894 (34%) | 36 242 (53%) | 118 | Yes | Yes | Yes | Sporadic | Yes |
| Equatorial Guinea | 90 | 29 | 65 (24%) | 43 (7%) | 4 | Yes | Yes | Yes | Sporadic | Yes |
| Gabon | 189 | 86 | 167 (6%) | 803 (53%) | 8 | Yes | Yes | Yes | Sporadic | Yes |
| Gambia | 0 | 0 | – | – | 1 | No | No | No | No | No |
| Ghana | 0 | 0 | – | – | 1 | No | No | Yes | Yes | Yes |
| Guinea | 436 | 364 | 184 (8%) | 2606 (26%) | 13 | Yes | Yes | Yes | Yes | Yes |
| Guinea Bissau | 0 | 0 | – | – | 3 | No | No | No | No | No |
| Liberia | 0 | 0 | – | – | 4 | No | No | No | No | No |
| Mali | 0 | 0 | – | – | 6 | Yes | No | Yes | Yes | Yes |
| Niger | 0 | 0 | – | – | 1 | No | No | No | No | No |
| Nigeria | 65 | 7 | 70 (1%) | 2183 (2%) | 4 | No | Sporadic | No | Sporadic | Yes |
| Senegal | 0 | 0 | – | – | 5 | No | No | No | No | Field assessment |
| Sierra Leone | 0 | 0 | 18 (3%) | 170 (3%) | 5 | No | No | No | No | Field assessment |
| South Sudan | 7914 | 1785 | 1001 (16%) | 1270 (18%) | 9 | No | Sporadic | Yes | No | Yes |
| Uganda | 1616 | 459 | 176 (9%) | 2131 (7%) | 7 | Yes | Yes | Yes | Sporadic | Yes |
| Togo | 0 | 0 | – | – | 2 | Yes | No | Integrated | No | Yes |
| Total | 74 592 | 40 799 | 14 239 (10%) | 58 080 (13%) | 303 | | | | | |

SSNCP: Sleeping Sickness National Control Programme.

gambiense HAT, the possibility of importation of rhodiense HAT into new areas is not negligible (Fèvre *et al*. 2004). The non-human reservoir is a key element in the transmission cycle of rhodesiense HAT (Hide *et al*. 1996), and the control of the disease requires a multisectoral approach where animal health and natural resources management (national parks and game reserves) have an important role to play (Selby *et al*. 2013).

Therefore, being a zoonosis with an important animal reservoir, the elimination of rhodesiense HAT as the total interruption of transmission of the disease is considered not to be feasible and for this reason has not been included in this analysis. However, the possibility of its elimination has been considered as a public health problem (World Health Organization, 2012*a*).

### KEY EVENTS AND DECLARATIONS ON THE ROAD TOWARDS ELIMINATION OF GAMBIENSE HAT

Over the last 15 years, the success in bringing gambiense HAT from an epidemic situation to control has been accompanied by a number of political and technical declarations. The commitment from partners has also contributed to bring about a situation where the elimination of gambiense HAT is now considered as a reachable goal (Fig. 1). Along the way, key milestones have included:

In 1997, concerned by the worrying epidemiological situation of HAT, the 50th World Health Assembly (WHA) urged all member states in endemic areas to reinforce control and surveillance activities and coordinate their actions through the Programme Against African Trypanosomiasis – PAAT (a joint initiative of the Food and Agriculture Organization of the United Nations – FAO, the International Atomic Energy Agency – IAEA, the WHO and the African Union – Interafrican Bureau of Animal Resources – AU/IBAR)) and emphasized the need for resources to expand the control and surveillance of the disease (World Health Organization, 1997).

In 2000, during the summit held in Lomé (Togo), the heads of states and governments of African countries, considering the severe impact of tsetse-transmitted trypanosomiasis on the socio-economic development, expressed their political will to embark on a continental campaign of eradication, and consequently the African Union (AU) established the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC).

In 2001, two manufacturers of medicines against HAT, Aventis and Bayer, committed to ensuring production of the disease-specific drugs and to donating the drugs to the WHO for free distribution. An agreement was signed between Aventis and WHO aimed at providing the WHO with the financial support to face the worrying situation of gambiense HAT.

In 2003, the 56th WHA welcomed and supported the PATTEC initiative and commended the efforts of the WHO to implement a programme for the elimination of African trypanosomiasis as a public health problem (World Health Organization, 2003).

In 2004, the 57th WHA Assembly urged member states 'to continue to give high priority to the control of HAT" and requested the WHO to refine control strategies and to promote an integrated approach with the sectors and agencies concerned (World Health Organization, 2004).

In 2005, the goal of elimination of HAT was endorsed by the 55th WHO Regional Committee for Africa and by the International Scientific Council for Trypanosomiasis Research and Control (ISCTRC).

In 2006 the agreement between WHO and Sanofi-Aventis (previously Aventis) was renewed. The goal was to consolidate the control of the disease, preparing the conditions for elimination and to replace melarsoprol as the first-line treatment for the second stage of gambiense HAT.

In 2007, representatives of countries in which HAT is endemic gathered in Geneva (Switzerland) to discuss the elimination of HAT as a public health problem. They concluded that the elimination of gambiense HAT was feasible (World Health Organization, 2012*b*).

In 2011, the WHO – Sanofi (previously Sanofi-Aventis) agreement was renewed with the goal of implementing strategies to achieve and sustain disease elimination through innovative strategies.

In the same year, the WHO's Strategic and Technical Advisory Group for NTDs (WHO NTD STAG) deemed elimination to be technically feasible and HAT was included in the WHO Roadmap on NTDs, which was launched in early January 2012 with the target date for elimination as a public health problem set by 2020 (World Health Organization, 2012*b*).

In January 2012 a number of stakeholders including pharmaceutical companies, donors and some NGOs committed to the largest coordinated effort against NTDs through the London Declaration (World Health Organization, 2013*a*). The declaration

supports the WHO Roadmap on NTDs to sustain, expand and extend programmes to eliminate, among other NTDs, HAT by 2020.

In December 2012, WHO convened a meeting of SSNCPs focal points, experts from WHO collaborating centres and members of the WHO STAG NTD in Geneva. Elimination of gambiense HAT was endorsed by SSNCPs of disease-endemic countries. Strategies, tools and criteria for the process of eliminating gambiense HAT were laid out.

In April 2013, the WHO Expert Committee on HAT control and surveillance met in Geneva after 18 years, to discuss the current epidemiological patterns of the disease, the new diagnostic approaches and the new therapeutic regimens. Final recommendations to achieve disease elimination were addressed (World Health Organization, 2013*c*).

## CONCEPT OF ELIMINATION OF HAT

The WHO Roadmap on NTDs included HAT with the target date for elimination as a public health problem by 2020, defined as the reduction of HAT incidence to fewer than 1 new case per 10 000 population in at least 90% of foci and to fewer than 2000 cases reported globally (World Health Organization, 2012*a*). The disease-endemic countries and experts from WHO collaborating centres considered this target as an advanced level of control only and as an intermediate objective in the way to reach the final goal of sustainable HAT elimination by 2030. This last goal was defined following the WHO NTD STAG recommendation as the interruption of the transmission of gambiense HAT (zero disease incidence) in a condition where continued actions to prevent re-emergence of the diseases may be required (World Health Organization, 2012*b*).

## FEASIBILITY OF ELIMINATION OF GAMBIENSE HAT

In 1989, the International Task Force for Disease Eradication (ITFDE) set out criteria for assessing potential eradication or elimination of diseases or conditions (Centers for Disease Control and Prevention, 1993), some related to the technical feasibility (epidemiological vulnerability, availability of effective and practical interventions or demonstrated feasibility of elimination) and others related to the political will or popular support as the perceived burden of the disease.

### Epidemiological vulnerability

Gambiense HAT does not spread easily and humans are the only significant reservoir. Animal hosts have been described but more data are needed to elucidate their role as a reservoir in the transmission cycle. Such a role does not seem to be major (Funk *et al.* 2013).

The geographic distribution of the disease is well known and limited to 24 endemic countries. Besides, 97% of the cases are declared in just 5 countries, with approximately 80% of all the cases being reported from the DRC (Simarro *et al.* 2013*a*). In addition, in countries where gambiense HAT is endemic, only 10% of the national area is affected by the transmission of the disease (Simarro *et al.* 2012). A comprehensive database (WHO Atlas of HAT) compiles geo-referenced data which enable mapping at the village level, cases and screening activities reported from 2000 (Simarro *et al.* 2010).

### Effective, practical intervention tools available

There is no vaccine against trypanosomiasis, and one will not become available in the coming years. However, effective tools for screening and treatment are available, although they are not easy to implement. Also, control tools are not appropriate for the involvement of fixed facilities of the health system in control and surveillance. Nevertheless, these tools have proven effective in reducing prevalence. The production and quality of specific medicines is guaranteed and they are affordable as they are generously donated at no cost by manufacturers. Availability is ensured by an effective distribution system managed by the WHO in collaboration with MSF-Logistique.

Integration of treatment and diagnosis in the health system is of the essence to spread the activities in time and space and ensure sustainability. Cheaper and user-friendlier diagnosis and treatment tools will make integration easier. There are currently new promising screening (Buscher *et al.* 2013) and treatment tools (Torreele *et al.* 2010; Jacobs *et al.* 2011) in the pipeline, which could facilitate the involvement of the health system.

Complete elimination of the vector does not seem feasible (World Health Organization, 1998; Molyneux, 2001; Hargrove, 2002). Nevertheless, new tools for vector control are being introduced, which are cheaper and easier to use (Esterhuizen *et al.* 2011). They have a role to play in supporting targeted interventions in particular transmission areas, where vector control will synergize with medical approaches.

### Demonstrated feasibility of elimination

As a proof of principle, elimination has been achieved previously in some foci (Bruto da Costa *et al.* 1916; Simarro *et al.* 2006) and a strong reduction of the disease was reached at the continental level in the past

with tools that have lower performance levels than those available today (Simarro *et al.* 2008; Welburn *et al.* 2009). Technical feasibility was acknowledged by SSNCPs during a meeting held in Geneva in December 2012 (World Health Organization, 2012*b*).

### Political will

Political commitment to fight the disease was expressed by the heads of state and government of African countries through an official declaration issued from the summit of the OAU held in Lomé in 2000 (Organization of African Unity, 2001). In addition, WHO member states committed to HAT elimination by endorsing the WHO Road Map on NTD during the 66th WHA held in Geneva in May 2013 (World Health Organization, 2012*a*, 2013*b*). The international community showed their commitment to HAT elimination through the London Declaration in January 2012 (World Health Organization, 2013*c*).

### Perceived burden of the disease

The disease has a case fatality rate that is close to 100%. In endemic areas, people fear infection because of the suffering, lethality and the risk of stigma it entails. Affecting mainly individuals of productive age, and being a chronic disease, a case of gambiense HAT in a family unit causes important economic losses, as measured in terms of decreased income and increased expenditure (Lutumba *et al.* 2007).

### STRATEGIES FOR ELIMINATION OF GAMBIENSE HAT

In the case of gambiense HAT, three classical control methods have been described and used for almost 100 years:

1. Active case-finding by mobile teams, which perform a serological screening in large populations (villages, neighbourhoods or other population settlements) and subsequently seek parasitological confirmation of serological suspects. Active case detection may determine a substantial reduction in disease prevalence, mainly when applied in successive rounds (Robays *et al.* 2004; Simarro *et al.* 2006; Checchi *et al.* 2012). Low participation rates of at-risk populations have been described under certain circumstances mainly when screenings are periodically repeated, prevalence is lowering, and the impact of the active case finding is decreasing (Robays *et al.* 2004; Welburn *et al.* 2009). Active case finding always has to include adequate treatment of all detected cases.

2. Passive case-finding and adequate treatment by fixed health facilities. This method concerns patients seeking healthcare with signs or symptoms suggestive of HAT infection. Serological tests are used for initial screening, followed by tests for parasitological confirmation in serological suspects. The introduction of individual and simple serological tests (lateral flow formats) (Buscher *et al.* 2013) can facilitate passive screening in sites where staff are not highly skilled in HAT-related techniques. Cases should always be adequately treated after detection.

3. Vector control to reduce the tsetse population, using the different methods available according to the characteristics of the different foci (World Health Organization, 2013*c*).

To combat the disease it is necessary to combine these three methods as appropriate. In the different epidemiological situations, different combinations and 'dosage' of each method has to be deployed, based on:

– Intensity of transmission;
– Precise understanding of the epidemiological setting, including geographic and demographic data;
– Accessibility and capabilities of the existing health facilities; and
– Knowledge of vector ecology, including the patterns of human–vector contact, the sites where vector control must be applied and the methods to be utilized.

Control and elimination strategies defined according to the intensity of transmission and epidemiological settings have to be flexible and dynamic enough to be adapted to the changing disease patterns and capacities of the local health services (Simarro *et al.* 2013*a*).

### IMPLEMENTATION OF CONTROL AND SURVEILLANCE ACTIVITIES ACCORDING TO THE EPIDEMIOLOGICAL STATUS OF EACH VILLAGE

Considering that HAT is a focal disease, the focus and its level of transmission is the epidemiological unit and disease elimination strategies must be planned and monitored at the focus rather than the country level. At the same time, field interventions are to be planned and implemented at the village level, according to its specific epidemiological status.

Villages in each focus can be categorized according to the presence of cases in the previous years:

Villages which have reported cases in the previous 3 years.
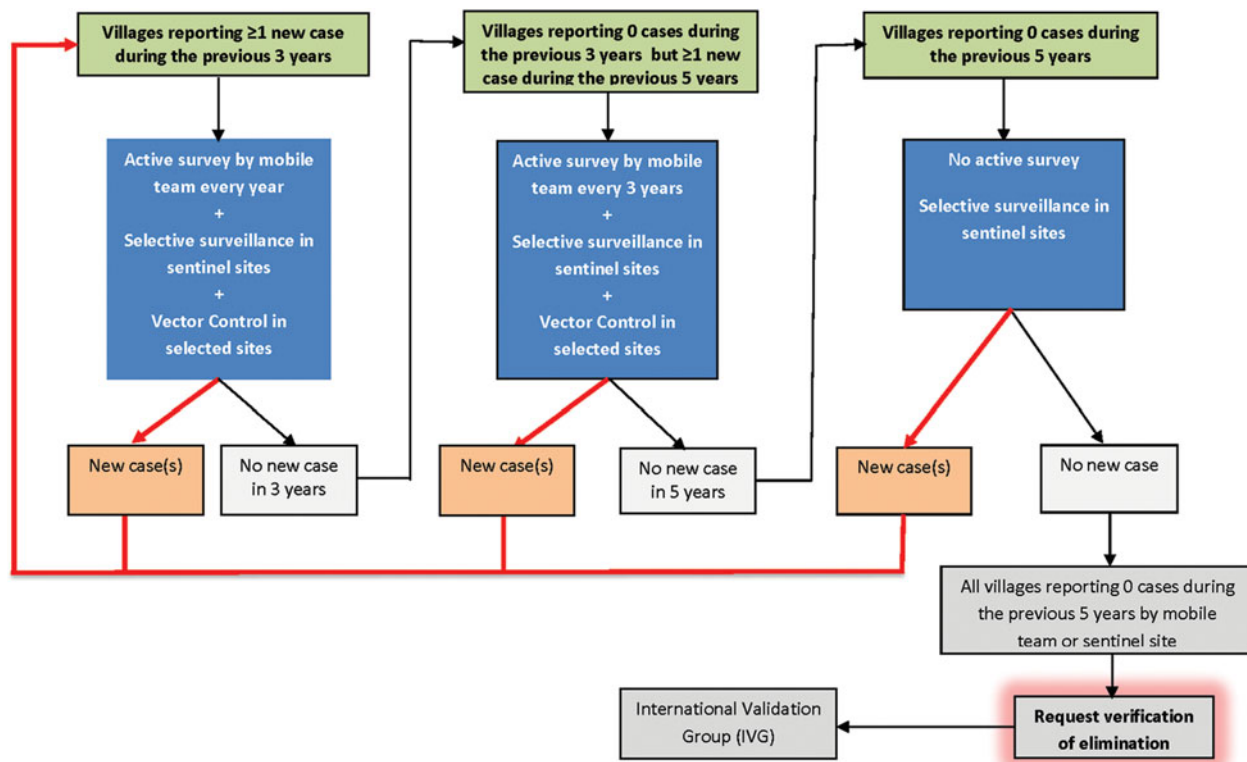Villages which have reported cases in the previous 5 years, but not in the previous three.

Fig. 2. Algorithm of interventions according to the epidemiological status of the villages in each focus.

Villages which have reported no cases in the previous 5 years.

Control and surveillance activities therefore will be planned according to this village-level categorization within a focus (Fig. 2). The classification of villages is updated yearly. To this end, diagnosed cases have to be carefully reported, including the possible village where the transmission took place.

### Active screening

Active screening plays an important role in foci where transmission is high or very high. The active case-finding through mobile teams will be done yearly in all the villages which have presented cases in the previous 3 years. In the villages which have reported cases in the previous 5 years, but not in the previous 3, an active screening will be performed every 3 years. In foci at moderate, low and very low intensity of transmission it is expected that the number of villages presenting cases will be low, and therefore the volume of active screening will be limited. The Card Agglutination Test for Trypanosomiasis (CATT) is the main tool used for active screening.

If a serological suspect detected in a sentinel centre is confirmed by parasitological examinations, a reactive active case-finding survey will be carried out for 3 consecutive years in the area of activity of the newly detected case. In some foci, the skills of the local health staff to perform the parasitological tests and an active screening could have been lost; in those cases, support from national or regional institutions can be requested in order to carry out the active screening and to build the local capacity.

### Passive screening

Passive screening has to be performed in the selected health structures located within the focus (sentinel sites). The sentinel sites will be selected according to their capacities, the population covered and the frequenting by the population at risk. The performance of the passive detection could be increased by healthcare workers in health posts, who could detect the signs and symptoms evoking HAT infection and then refer clinical suspects to the sentinel sites.

Passive screening is the most important component for gambiense HAT control and surveillance in foci with low and very low intensity of transmission, where infection is rare and active case detection has poor cost-effectiveness. Passive screening is also a key element in high, very high and moderate transmission foci, as effectiveness of active screening is limited because of incomplete attendance at screening sessions, inherent limitations of screening tools and the lag between successive surveys.

If serological positive cases are detected by sentinel sites among clinical suspects through individual screening tests (also erroneously called rapid diagnostic tests – RDT), parasitological tests have to be carried out to confirm the diagnosis. If the serological

suspicion is not confirmed, in particular epidemiological settings samples could be sent to a WHO collaborating centre for a more specific test (i.e. immune trypanolysis) for confirming the presence of anti-trypanosomal antibodies (Van Meirvenne *et al*. 1995; Jamonneau *et al*. 2010).

When staff at the peripheral level are not familiar with parasitological tests for confirmation, serological suspects could be referred for parasitological tests to health structures able to perform them or request support from national or regional referral centres.

### Vector control

Vector control is an efficient tool to reduce tsetse flies numbers and therefore to reduce HAT transmission (Solano *et al*. 2013). Vector control is applied according to medical results in selected sites. It could play an important role in high-prevalence foci to help reduce transmission quickly, or in foci where the intensity of transmission does not decrease after repeated active screening rounds. It is not a priority in foci with low or very low intensity transmission, where it is only applicable if the intensity of transmission is not reduced after repeated active screening rounds.

There are a variety of tools for tsetse control and the choice of the most suitable will depend on local conditions (World Health Organization, 2013c).

### MONITORING AND EVALUATING GAMBIENSE HAT ELIMINATION. CERTIFICATION AND VALIDATION OF ELIMINATION

Continuous monitoring and evaluation of the HAT elimination process is needed to adapt the strategies to the epidemiological situation and to assess the results obtained. It will assure the sustainability of the elimination and will prevent the re-emergence of the disease.

The monitoring and evaluation of progress toward elimination has to be based on data collected by mobile teams and sentinel sites. Standard surveys based on sampling approaches are not appropriate for monitoring and evaluating trypanosomiasis elimination as they do not have sufficient statistical power for decision-making due to the low prevalence of the disease. The xenomonitoring of HAT infection in vectors could contribute to monitoring the elimination of sleeping sickness by assessing the presence or absence of parasites circulating in the vector. However it is not currently applicable since tests for molecular detection of *T. b. gambiense* infections in tsetse flies need to improve their sensitivity and specificity if reliable results are to be obtained. In addition, the low prevalence of infection in tsetse flies will require large-scale capture of flies and to develop protocols for pooling samples.

HAT will be considered eliminated in those foci where after adequate surveillance is in place, no cases are detected in all villages during a 5-year period. The country will have to submit to the WHO a technical report about the elimination of the focus and request external evaluation by an international validation group (IVG). The validation system has to be able to ascertain the accessibility, coverage and quality of the surveillance activities to verify the absence of transmission and therefore to validate the elimination. The IVG will submit to the WHO a report with the appropriate recommendations concerning HAT elimination in the assessed focus. If the IVG evaluation is positive, the WHO will endorse elimination in the focus; otherwise, the WHO will recommend corrective measures and the way forward.

Even after a positive evaluation from the IVG, the surveillance system has to be maintained in sentinel sites to continue monitoring and evaluating the focus. Staff working in primary healthcare centres and staff in sentinel sites will receive regular refresher training to recognize the signs and symptoms suggestive of gambiense HAT, and to maintain awareness of the disease. The duration of this surveillance and preparedness for response has yet to be determined (World Health Organization, 2012b).

### INDICATORS AND MILESTONES

In the framework of HAT elimination, the initial aim is the reduction of HAT incidence to fewer than 1 case per 10 000 inhabitants in at least 90% of endemic areas, and to fewer than 2000 new cases reported globally by 2020 (Maurice, 2013). The final aim is elimination as defined by a reduction of HAT incidence to no new cases from any foci by 2030 (World Health Organization, 2012b).

The progress towards elimination will be measured by two primary quantitative indicators that will be updated annually:

1. The number of new cases of HAT reported.
2. The number of foci validated as eliminated.

Two secondary sets of indicators are proposed to assess the quality of the primary indicators and the scope of the elimination activities.

1. Proportion of the population at risk covered by control and surveillance activities (including active and passive screening) (Simarro *et al*. 2013b). This indicator will be updated yearly.
2. Geographical extent of the infection and population at different levels of risk, as measured with a previously described method (Simarro *et al*. 2012). This indicator will be calculated every 2 years.

Table 2. Quantitative indicators for HAT elimination as public health problem, 2012–2020 (World Health Organization, 2012*b*)

|  | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|
| Cases annually reported | 6000 | 5500 | 5000 | 4500 | 4000 | 3500 | 3000 | 2500 | < 2000 |
| Number of foci reporting fewer than 1 case per 10 000 inhabitants |  |  |  | 10% | 30% | 40% | 60% | 80% | > 90% |

The milestones defined for HAT in the WHO Roadmap on NTDs and agreed by the SSNCPs are shown in Table 2.

ROADBLOCKS TO BE OVERCOME AND RESEARCH GAPS AND TOOLS NEEDED

On the road to eliminate HAT there exist important challenges that need to be overcome. These challenges need to be addressed if gambiense HAT elimination is to be achieved. They can be classified in different groups:

*Epidemiological knowledge of the disease*

*Knowledge gaps in geographical distribution.* Grey areas are still present, where epidemiological knowledge is limited. These are found mainly in old foci without appropriate surveillance, and in regions characterized by difficult accessibility, or affected by security constraints. The epidemiological situation in these areas needs to be clarified. Adapted and adequate sensitive tools will help to assess these areas and to fill the mapping gaps.

*Epidemiological role of asymptomatic, seropositive human carriers with undetectable parasitaemia.* The presence of seropositive/aparasitaemic human cases and healthy carriers is well described in gambiense HAT (Bucheton *et al.* 2011; Jamonneau *et al.* 2012). They could play a role in the persistence of disease transmission. Further studies are needed to clarify their epidemiological significance, and to develop appropriate strategies for their management.

*Epidemiological role of animals as reservoir of gambiense HAT.* The presence of *T. b. gambiense* in animals has been widely described (Duke, 1931; Makumyaviri *et al.* 1989; Njiokou *et al.* 2006, 2010; Cordon-Obras *et al.* 2009). The role they can play as reservoirs to maintain the transmission of gambiense HAT needs to be elucidated.

*Underdetection and underreporting.* Gambiense HAT is a rural disease, occurring in remote areas not always fully accessible for the health system. Under-detection and under-reporting are a reality, and they have been estimated in different ways.

Additional indicators and modelling tools for estimating the location and abundance of undetected cases have to be developed.

*Risk of reintroduction of the infection after elimination from a focus.* A risk of reintroduction of HAT after elimination exists, and it requires maintenance of surveillance activities after HAT has been eliminated from a focus. Studies on the risk factors of HAT reintroduction are encouraged, with a view to ensuring sustainability of elimination.

*Integration of control and surveillance into existing health systems.* Health systems in gambiense HAT endemic areas are often characterized by low attendance rates at healthcare facilities, lack of preparedness of staff and sometimes staff overloading. Operational research is needed to improve the integration of control and surveillance of gambiense HAT into the existing health systems.

*Lack of skills of health staff on gambiense HAT control and surveillance.* Experienced and committed staff presently involved in HAT control and surveillance are progressively retiring, and perspectives for appropriate replacement are limited. Approaches to engage a new generation of health staff on gambiense HAT elimination need to be implemented.

*Lack of awareness among people at risk.* When the disease becomes rare, local knowledge of the disease among the affected populations is progressively lost. Campaigns and tools to maintain awareness of gambiense HAT among the populations in endemic areas have to be developed and implemented.

*Xenomonitoring for assessing gambiense HAT elimination.* The feasibility of monitoring *T. b. gambiense* infections in vectors should be further explored as a potential tool for assessing HAT elimination programmes.

*Screening, diagnosis and staging*

*Simpler and ensured serological tests.* The introduction of simple, individual serological tests can help the integration of gambiense HAT control and surveillance into the health system, which will be critical to achieve the elimination goal. Individual

serological tests are already under evaluation for gambiense HAT. The available screening tools (CATT and individual screening tests) are based on the same native antigen which has a ceiling in its production. New screening tools using new recombinant antigens which are easier to produce are needed.

*Accurate and simpler parasitological confirmation tests.* The current diagnostic tools to confirm the disease are complex and tedious, have a limited sensitivity and they need skilled and experienced staff. More user-friendly diagnostic tests for confirmation are needed to spread the diagnostic capabilities to the health services.

*Less-invasive staging tests.* The staging of HAT to establish the appropriate treatment is based on the analysis of CSF obtained from a lumbar puncture. This is a painful and not risk-free procedure. Development of tests on blood or urine for stage determination are encouraged.

### Treatment

*New user-friendly treatments.* The current therapeutic regimens are complex to apply, cumbersome in their logistics for distribution, and characterized by considerable safety concerns. Safe drugs – if possible oral – which are easy to use and active against both forms and both stages of the disease are required.

*Clinical trials.* Clinical trials to develop new drugs for HAT are complex and long lasting. The reduction in the number of patients as elimination progresses will further complicate clinical trials. Efforts to facilitate clinical trials, always ensuring the safety of the patients, have to be considered.

### CONCLUSIONS

The elimination of gambiense HAT is feasible, as a result of the epidemiological vulnerability of the disease, the current state of disease control, the availability of effective strategies and tools, the existence of international commitment and political will. The available strategies and tools have to be adapted to the different epidemiological settings to maximize cost-effectiveness.

Basic and operational research is needed to address knowledge gaps and to improve control tools. The development of new diagnostic and treatment tools will enhance control interventions and will facilitate the integration of a sensitive surveillance into the health systems. The strategies for elimination should be monitored and evaluated to ensure their appropriateness and effectiveness in an elimination

scenario, to identify optimal interventions, and to establish the timing for switching from one strategy to the next.

The successful control activities carried out over the last 15 years have substantially reduced the burden of disease. Donors tend to lose interest when the burden of a disease is decreasing. To eliminate gambiense HAT a long-term commitment by donors is needed. Advocacy is needed to sensitize donors on the importance of switching from a control to an elimination mindset. Adequate funding must be made available not only to implement elimination activities in the field, but also to support research that will make the elimination effort sustainable.

Alongside the commitment of donors, ownership of the objectives and process of elimination by endemic countries is critical. Gambiense HAT elimination has to be included in national health plans to facilitate its prioritization and to maintain its profile against competing health priorities.

The integration of gambiense HAT control and surveillance programmes in health systems is a major challenge. In the rural areas where trypanosomiasis is prevalent, the overall performance of peripheral health systems is often weak and characterized by unskilled staff, low attendance and low coverage. Therefore, the strengthening of health systems to implement the activities included in the elimination strategies is essential.

Political instability and insecurity are inescapable challenges in an elimination programme. The successful elimination of gambiense HAT requires a turmoil-free socio-political context.

Past and current experiences show that HAT elimination is difficult and will require more effort, time, and money than initially anticipated. The inherent risks of failure are offset by the benefits that accrue from a successful elimination campaign. An elimination campaign has the ability to inspire dedication and sacrifice among health workers, and to attract donors, both of which are needed to overcome the hurdles to success (Hopkins, 2013).

Much progress has been made in the fight against gambiense HAT, but the final line of the struggle is not in sight just yet.

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