The effectiveness of active population screening and treatment for sleeping sickness control in the Democratic Republic of Congo

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Summary

BACKGROUND   The human African trypanosomiasis (HAT) control programme of the Democratic Republic of Congo (DRC) uses mass screening with the card agglutination test for trypanosomes (CATT). We looked at the contribution of CATT and improved parasitological confirmation to the effectiveness of screening and treatment.

METHOD   The effectiveness of the screening and treatment process is measured by the percentage of HAT cases that is effectively cured after a single round of screening. The process is analysed in five steps: (i) the attendance at the screening, (ii) the sensitivity of the screening procedure, (iii) the sensitivity of the parasitological confirmation, (iv) the proportion of the confirmed cases that effectively receive treatment and (v) the cure rate of the treatment. We used a simplified model that multiplies proportions of infected persons that go through each step. We estimated these parameters using a combination of routine data collected by the national control programme over the period January 1997 to December 1998 and published data. For varying attendance rates we compared the effectiveness of screening strategies based on CATT or on CATT combined with improved parasitological confirmation by mini anion exchange column technique (mAECT) with the previously used strategy based on palpation of neck glands and microscopy alone.

RESULTS   The model shows that overall effectiveness of the active case detection and treatment strategy is <50% under most scenarios. Attendance rates averaged 74% but showed considerable regional variability and are a major problem in some areas of DRC. The CATT and replacing traditional parasitology by mAECT increases the sensitivity of the screening but a substantial part of the gains are lost at other stages of the screening process.

CONCLUSION   Improvements of the HAT screening process such as introduction of CATT or mAECT only make sense if other parameters and attendance rate in particular are optimized at the same time.

keywords human African trypanosomiasis, effectiveness, Democratic Republic of Congo, card agglutination test for trypanosomes, population screening

Introduction

Human West African trypanosomiasis, mainly affecting poor rural communities, can be considered as one of the neglected diseases (Trouiller et al. 2002). While a considerable amount of fundamental research is carried out on the unique molecular properties of the parasite, in striking contrast only meagre human and financial resources are allocated to research in the field of better diagnosis, treatment or cost-effective control strategies.

Human African trypanosomiasis (HAT) is a slowly progressing fatal disease with no or few specific symptoms in its initial stage (Burri & Brun 2003). Patients usually consult a health professional when the disease is already well advanced and involves the central nervous system. At that point, the patient may have irreversible brain damage, requires more expensive and dangerous treatment and has posed a threat to the community due to his infectiousness to tsetse flies for a prolonged period (WHO 1998). Therefore, active screening of the population at risk has been advocated for two reasons: to reduce mortality and morbidity by finding cases at as early as possible, and to reduce transmission by eliminating the parasite from the human reservoir.

The impact of an active case finding strategy on transmission is still poorly understood and the optimal frequency of screening rounds is debated. There is some empirical evidence that active case finding programmes can reduce transmission. Van Nieuwenhove (1991a,b) recommends three repeated screening rounds at 1-year intervals. Other successful repeated screening programmes (Simarro *et al.* 1991; Bruneel *et al.* 1994; Paquet *et al.* 1995) used intervals of 6 months. In the three latter studies, the screening rounds were repeated at intervals of 6 months. The dynamics of transmission form a complex system in which the density, type and vector capacity of glossinae, environmental factors, proximity, activity and exposure to glossinae of human beings interact (De Muynck 1991; WHO 1998). Attempts have been made to model transmission of *Trypanosoma brucei gambiense* trypanosomiasis (Jusot *et al.* 1995; Artzrouni & Gouteux 1996). These models are not suited to study the effect of screening rounds with intervals of 6 months or 1 year on transmission.

Successful active case finding must have an adequate frequency, cover a high proportion of the infected population, use very sensitive tests and assure sufficient capacity to treat the cases. The reservoir of HAT cases could then be reduced so as to interrupt transmission for some years. Screening intervals can thereafter be spaced once every 5 years. Alternatively, surveillance methods could be used to detect emerging epidemics at an early stage, such as serological surveys or surveillance based on data collection from passive case finding in the primary health structures (WHO 1998). The methods used for active screening vary. For many years, strategies were based on palpation of the neck glands (Winterbottom's sign), with parasitological examination of lymph node aspirates as confirmatory test. The sensitivity of this poorly standardized method is estimated at 30–70% (WHO 1998) and depends on how palpation and confirmation is carried out, staff training and motivation, mix first/second stage in the population and presence of lymph nodes due to other diseases. The sensitivity of population screening can be considerably improved by the use of the card agglutination test for trypanosomes (CATT), which is, according to some authors, up to 98% sensitive (WHO 1998). Improving parasitological confirmation by introducing a better confirmation test, such as the mini anion exchange column technique (mAECT), is also frequently advocated (Miezan *et al.* 1994).

The gain in sensitivity obtained by better serological tests can, however, be partly offset by other factors such as low attendance rates to screening sessions, relatively low sensitivity of parasitological confirmation and the limited proportion of cases effectively treated after diagnosis. We used a combination of routine data and estimates derived from the literature to study the different steps in active case finding from the initial screening to treatment and cure to identify the areas where there is scope for improving effectiveness and to identify gaps in our knowledge.

Methods

Background

After having virtually disappeared in the 1960s, sleeping sickness has re-emerged as a major public health problem in Democratic Republic of Congo (DRC) (Ekwanzala *et al.* 1996). Political turmoil caused an interruption of the control efforts in 1991 but in 1997 active population screening with 29 mobile teams resumed. In 1998, 31 mobile teams were operating in the provinces Bas-Congo, Bandundu, Maniema, Kasai, northern Equator, southern Equator and Kinshasa. In 1997, the CATT test was used in 26% of the screened population. By 1998, CATT screening covered 42% of the examined population. Mobile teams consist of eight to nine members, one head, three to four microscopists, one secretary, one driver (or boatsman), one messenger and one guard. Each mobile team has its own, well-defined action radius, which can include a population up to 800 000. They make excursions of 20 days each month, going from village to village. Each village is visited only once a year. The choice of the target villages to cover is based on a combination of tradition, findings of the previous year, information from the local health structures and sometimes, local political pressure. Two days before the team arrives in a village, a messenger is sent to announce and to discuss the screening with the local village chiefs. On the day of the screening the diagnostic algorithm presented in Figure 1 is used. Each national programme uses its own diagnostic tree and this diagnostic tree is only valid for the DRC.

Sporadic cases presenting with symptoms (often behavioural changes) who are CATT negative and do not have enlarged lymph nodes, undergo parasitological examination as well. Parasitologically confirmed cases undergo lumbar puncture in the village to stage the disease on the same day. Less than five cells per microlitre is considered first stage and prescribed pentamidine, more than five cells per microlitre is considered second stage and prescribed Arsobal. The patient is referred to a health facility for treatment. The mobile team supplies trypanocidal drugs to the health structures and collects data on treatment. The relationships between the mobile teams and health structures of the health district, and the degree of integration of the mobile teams in the health district management tend to vary greatly between and even within provinces.
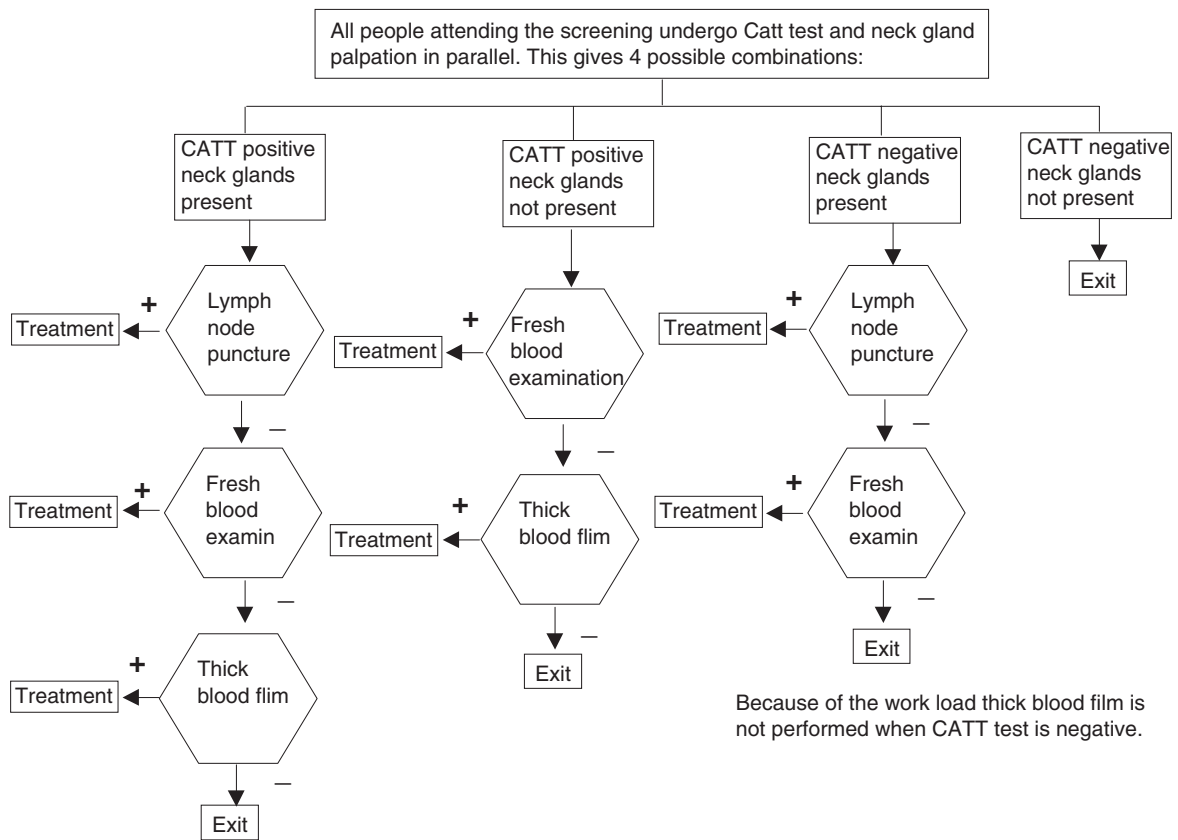
Figure 1 Flowchart for the screening process for human African trypanosomiasis as performed by the mobile teams in Democratic Republic of Congo.

Framework for the estimation of effectiveness using Piot's model

We used a simplified version of a model developed in the 1960s to evaluate case finding and treatment in tuberculosis programmes (Piot 1967). The method is frequently used to evaluate effectiveness of case finding programmes such as primary health care programmes for sexually transmitted diseases (Dallabetta *et al.* 1996; Buvé *et al.* 2001). We defined effectiveness of active HAT case finding and treatment under operational conditions as the overall proportion of all prevalent sleeping sickness cases in the population that are detected by the mobile teams, receive appropriate treatment and eventually get cured. In ideal circumstances, all infected people would attend the screening, be picked up by the first screening test, be confirmed, complete treatment and reach cure. Unfortunately, opportunities are lost at each stage. The proportion of infected people that eventually gets cured depends on all the previous steps. Therefore, in order to estimate the overall effectiveness (*E*) of the process we multiplied the five

parameters (see eqn 1), which assumes that probabilities at each stage are independent of each other (Figure 2).

$$E = \text{Ar} \times \text{Sscr} \times \text{Scon} \times \text{Tr} \times \text{Cu}, \qquad (1)$$

where Ar = attendance rate, Sscr = sensitivity of the screening test, Scon = sensitivity of the confirmation test, Tr = treatment completion rate, and Cu = cure rate.

We tried to obtain reliable estimates and a plausible range for each of the five proportions, based on the available data from the control programme and on data reported in the literature. To deal with the uncertainty surrounding these parameters, three scenarios were considered: a baseline, a worst and a best case scenario. For each, we calculated the effectiveness for different values of the attendance rate, reflecting the local variability in this parameter.

Finally, we examined the potential effectiveness when three screening and confirmation algorithms were used: (i) an algorithm using cervical gland palpation alone as entry point for the screening followed by parasitological confirmation, which was the strategy used before the CATT was introduced; (ii) an algorithm using the CATT
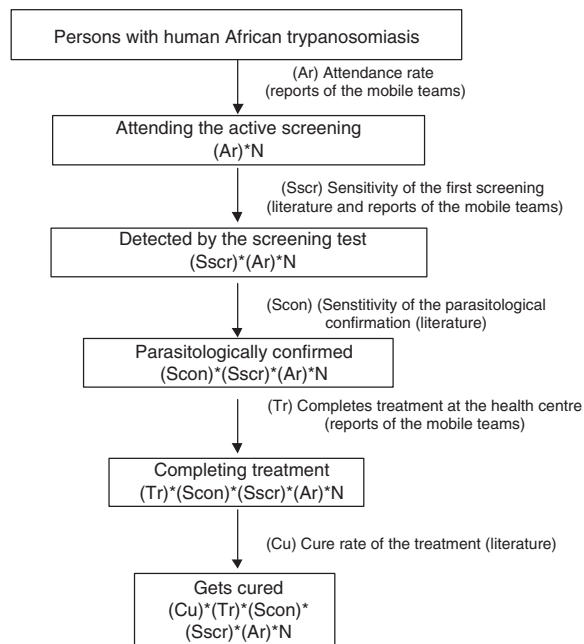
Figure 2 Model used to estimate effectiveness of screening and treatment for human African trypanosomiasis in Democratic Republic of Congo and sources of data.

(Figure 1); and (iii) an algorithm using the CATT test combined with an improved parasitological confirmation by the mAECT. This is a hypothetical algorithm, because mAECT is currently only used for research purposes in DRC.

Source of the data

The data were obtained from the national sleeping sickness control programme of DRC ('Bureau Central de Trypanosomiase' or BCT). Data on number of detected cases, stage, residence and treatment were collected by the mobile teams. We analysed all monthly and annual reports for 1997 and 1998. Quality and limitations of the information provided by these reports are discussed in the section 'Results'. JR observed the functioning of the mobile teams during supervision visits of all teams over the period 1996–97. Cure rates and estimates of the sensitivity of screening and confirmatory tests reported in the literature were used and contrasted with available information from the routine data.

Attendance rate

Attendance rate was assumed equal between infected and non-infected individuals. The mobile teams are instructed

to make a census of the population in each village, considering all persons who have been living in the area for more than 2 years as resident. Other persons presenting at the screening are considered as floating population and are not used in the computation of the attendance rate. The attendance rate is calculated as the proportion of resident people that attended the screening and is reported per village. Mean attendance rates, with range and 95% confidence intervals were computed for each mobile team using these attendance rates as point estimates.

Sensitivity of the screening test

Baseline estimates and a plausible range for the sensitivity of the palpation of neck glands and for the CATT were retrieved from the literature and contrasted to observed data. As CATT test and neck gland palpation are used in parallel, part of infected individuals that are false negatives for CATT are found by neck gland palpation. Joint sensitivity was calculated as

$$
\begin{aligned}
&(1 - \text{Sensitivity screening test}) \\
&= (1 - \text{Sensitivity CATT}) \\
&\quad \times (1 - \text{Sensitivity of neck palpation})
\end{aligned}
$$

assuming independence between CATT and neck palpation.

Sensitivity of the confirmation test

Sensitivity estimates for different combinations of parasitological confirmation tests were retrieved from the literature. We computed a common parameter for the joint effect of the different tests used. Sensitivity of fresh blood examination and thick blood film are both dependent on parasitaemia and positivity of neck gland aspirate might also be associated to parasitaemia.

Proportion of confirmed cases that complete treatment

We derived an estimate and a plausible range from the annual reports of the mobile teams. Monthly, the mobile team collects information on how many treatments are prescribed and completed. This determinant is a combination of different factors: the proportion of patients who are prescribed the correct treatment, the proportion that arrives at the health centre they are referred to, the proportion which actually obtains the treatment and the proportion that completes treatment. As information on each individual factor is not consistently available from the routine reports, we combined them in one parameter.

Cure rate

Estimations of cure rates were retrieved from the literature. The mix first/second stage must be taken into account and limitations are discussed in the following section.

Results

Attendance rate

Table 1 shows the available information on the attendance rates per village. The mean attendance rate per mobile team varied between 50% and 99%. Overall mean was 74%, median 76%. Census data and attendance rates are only available for 30% of the villages. Motivation and time constraints of the mobile team, opposition from population to census and high dispersion of population are cited as reasons for not doing a proper census. There was important variability of the attendance rate between villages, between mobile teams and between provinces. Some of the high attendance rates in the Equatorial Provinces lack credibility and some exceed 100%, probably due to summing resident and non-resident population in the enumerator. Reliable statistics are missing for the province Bas Congo. Discussions with the staff of the mobile teams revealed that attendance rates depended on different factors such as local beliefs, local conflicts, perception of trypanosomiasis as a problem, accessibility, quality of care, acceptability of

lumbar puncture (believed to cause impotence) and opportunity cost.

In the sensitivity analysis of the overall effectiveness estimate, we used the range 0.3–1.0 for the attendance rate.

Sensitivity of the screening test

Sensitivity of palpation of the neck glands alone has never been properly documented, sensitivity of the combination of palpation and parasitological confirmation is assumed to be between 30% and 70% (WHO 1998). Moreover, the figure varies probably with the stage of the epidemic as neck glands are more present in the first stage. As a baseline value for the sensitivity of clinical screening we retained the value of 0.5.

Published estimations of the sensitivity of CATT on whole blood also vary between 98% and 87% (WHO 1998; Magnus *et al.* 1998; Simarro *et al.* 1998; Truc *et al.* 2002). This variability is probably due to different antigenic characteristics of strains but variability in execution or interpretation of the test also plays a role. In our data, the number of parasitologically confirmed cases that were CATT positive ranged from 86% to 98% with an average value of 95.3%.

We estimated the sensitivity of the initial screening as 0.95 in the baseline scenario, with 0.86% in the worst and 0.98% in the best case scenario.

Sensitivity of the confirmation test

The routine data collected by the mobile teams in DRC do not really allow an estimate of the sensitivity of the confirmation procedure. Miezan *et al.* (1994) compared the sensitivities of single and combined parasitological techniques in Ivory Coast with a gold standard, defined as the combination of all the techniques, including the sensitive mAECT. He found that the sensitivity of the combination 'stained thick blood film and lymph node puncture' was 75%, that the combination 'lymph node puncture and fresh blood examination' was 69% sensitive and that the sensitivity of a combination of lymph node aspiration and mAECT was 90%. The sample in the study, however, was small and the situation in Ivory Coast may not be comparable with the situation in DRC Bailey and Smith (1992, 1994) compared capillary tube centrifugation, mAECT and quantitative buffy coat (QBC) and found QBC to be 100% sensitive.

Based on the above we retained the value 0.75 for the performance of the parasitological confirmation in the baseline. The values 0.90 (baseline) and 0.95 (best case) were chosen to simulate the effect of introduction of

Table I Mean attendance rate (%) per village at population screening sessions organized by 15 mobile teams in Democratic Republic of Congo, 1997–1998, for the provinces Bandundu, Kasai and Equateur

Mobile team	Mean	Standard deviation	Range	n	Confidence interval
Bandundu					
Mobile team 1	86	11	33–99	58	84–87
Mobile team 2	72	15	33–97	117	71–74
Mobile team 3	64	25	4–121	112	61–66
Kasai					
Mobile team 1	58	11	42–79	22	54–61
Mobile team 2	50	15	26–82	34	48–53
Mobile team 3	53	19	20–89	31	50–57
Equateur					
Mobile team 1	75	16	44–94	9	70–80
Mobile team 2	86	10	48–100	52	85–87
Mobile team 3	75	22	18–100	13	69–81
Mobile team 4	69	14	35–89	22	66–72
Mobile team 5	93	7	64–100	42	92–94
Mobile team 6	82	13	54–100	39	80–84
Mobile team 7	99	12	74–132	50	97–100
Mobile team 8	52	18	24–83	8	46–58
Mobile team 9	66	11	48–84	8	62–70

Table 2 Frequency (%) of treatment of diagnosed human African trypanosomiasis cases in Democratic Republic of Congo per year and per province

	1997			1998		
	Cases detected	Cases treated	%	Cases detected	Cases treated	%
Bas Congo	1036	988	95.4	857	733	85.5
Bandundu	5624	5568	99.0	8153	8051	98.7
Maniema	371	320	86.3	115	106	92.2
Kasai	2919	2536	86.9	2847	2556	89.8
Equateur	14 913	14 122	94.7	14 339	12 044	84.0
Total	25 089	23 770	94.7	27 044	24 129	89.2

mAECT as a more powerful parasitological confirmation technique.

Proportion of confirmed cases that completes treatment

The annual report of the BCT in 1997 reported that 94.7% of the parasitological confirmed people actually received treatment. The annual report of 1998 reported a rate of 89.2%. The figures per province are presented in Table 2. The routine data do not distinguish between active and passive case finding but usually more than half the cases are found by passive detection in the health care facilities. Cases from passive case finding are already in contact with the health structure and therefore more likely to receive their treatment there. Therefore, we use a baseline value of 0.9 with a worst case scenario of 0.7 and a best case of 0.95.

Cure rate

No reliable statistics on treatment outcomes are available from the routine data, very few follow-up lumbar punctures are carried out. Relapse rates of pentamidine are fairly constant around 7% (Jonchère 1951; Pépin & Milord 1994). Relapse rates for melarsoprol vary from 3% to 11% (Ginoux *et al.* 1984; Pépin *et al.* 1989; Pépin & Milord 1994). Some more recent studies show much higher relapse rates for melarsoprol in Uganda, 30% (Legros *et al.* 1999), and Mbanza Congo, 25% (Stanghellini & Josenando 2001).

The value of this parameter differs according to the mix first/second stage. Overall, 55% of the cases in active case finding was first stage but the figure ranges from 25% to 69% per province. This is function of the stage of the HAT epidemic is and of the effect of past consecutive screening rounds. On the contrary, relapses may be effectively retreated and there is no information on retreatment. In

Table 3 Overall effectiveness of human African trypanosomiasis screening and treatment for the three screening algorithms in a baseline, pessimistic and optimistic scenario

	Baseline scenario			Pessimistic scenario			Optimistic scenario		
	Algorithm 1	Algorithm 2	Algorithm 3	Algorithm 1	Algorithm 2	Algorithm 3	Algorithm 1	Algorithm 2	Algorithm 3
Attendance rate (Ar)	0.75	0.75	0.75	0.50	0.50	0.50	0.95	0.95	0.95
Sensitivity screening (Sscr)	0.50	0.90	0.90	0.50	0.90	0.90	0.50	0.98	0.98
Sensitivity parasitological confirmation (Scon)	0.75	0.75	0.90	0.75	0.75	0.85	0.75	0.75	0.90
Treatment completion rate (Tr)	0.90	0.90	0.90	0.70	0.70	0.70	0.95	0.95	0.95
Cure rate treatment (Cu)	0.90	0.90	0.90	0.80	0.80	0.80	0.95	0.95	0.95
Overall effectiveness (Ar × Sscr × Scon × Tr × Cu)	0.23	0.41	0.49	0.11	0.19	0.21	0.32	0.63	0.76

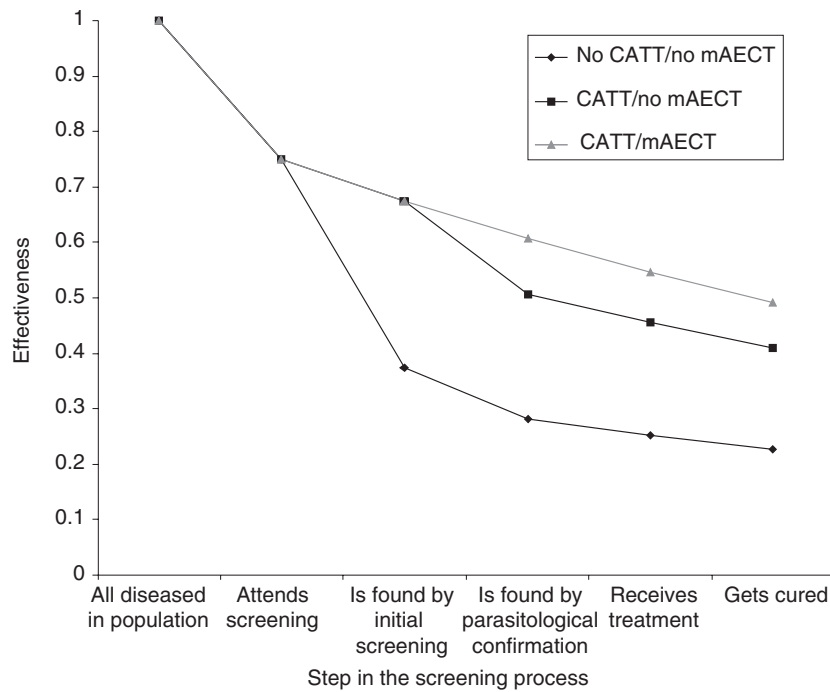J. Robays *et al.* **Sleeping sickness control in DRC**

Figure 3 Decline in the effectiveness per step in the screening treatment process under a baseline scenario using three different screening algorithms: algorithm 1 as it was used before introduction of the card agglutination test for trypanosomes (CATT) test, using neck gland palpation and 'classic' parasitological confirmation based on neck gland puncture, fresh blood examination and thick blood examination, the screening algorithm 2 with CATT as it is currently used (Figure 1) and the (theoretical) screening algorithm 3 that uses CATT and parasitological confirmation improved with mini anion exchange column technique.

order to take into account, this variability we took 0.9 as baseline value for this parameter worst case value of 0.8 and a best case value of 0.95.

Overall effectiveness

Table 3 shows the estimates of the overall effectiveness of active HAT screening under the scenarios defined above: pessimistic, baseline and optimistic. Figure 3 shows how opportunities to cure patients are lost at each step in the process under the three scenarios. Fixed values for the attendance rate were used as illustration. Figure 4 shows the increase in effectiveness by introduction of CATT and by the introduction of CATT and mAECT. The overall effectiveness varies with the attendance rate in a linear way (Figure 5).

Marginal improvement brought by introduction of the CATT is considerable under the three scenarios compared with clinical screening. However, most of the estimates of the effectiveness are below 50%. An important part of the improvement of the effectiveness is lost during other steps in the screening process. Even in the third optimistic scenario effectiveness does not exceed 76%. An improvement of the parasitological confirmation could enhance the effectiveness of the screening process but the active screening only leads to reasonable effectiveness if the attendance rate is sufficiently high, even if other parameters are optimized.
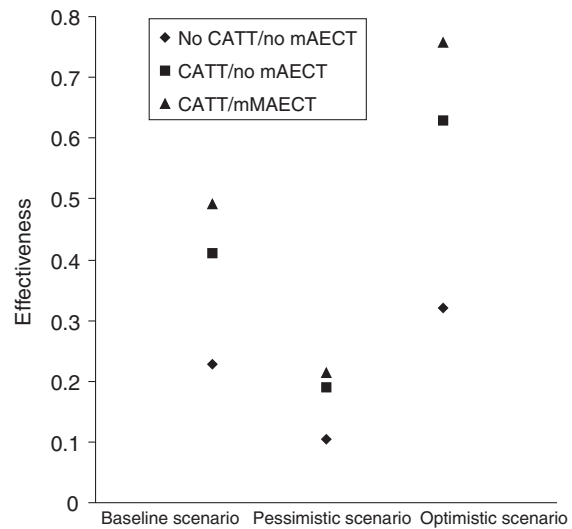

Figure 4 Increase in effectiveness by introduction of card agglutination test for trypanosomes (CATT) alone and by adding CATT plus mini anion exchange column technique (mAECT).

Discussion

The model is a simple multiplication of the five parameters that quantify the steps determining the effectiveness of screening programmes for HAT. One of the basic assumptions of the model is that these can be considered as
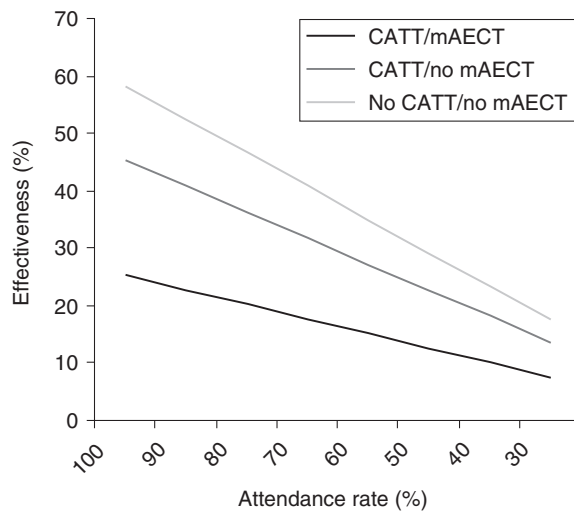
Figure 5 Decline in effectiveness with declining attendance rates in the baseline scenario for the three different screening algorithms.

more or less independent. This is a simplification because at different stages there may be interactions between them.

The attendance rate can be different in infected and non-infected people because part of the infected people may experience symptoms or feel sick and may therefore be more motivated to attend the screening. Certain subgroups in the population that are more at risk may have lower attendance rates, such as fishermen, hunters or women working in remote fields as they may be not in the village on the day of screening. The stage of the disease may influence the health seeking behaviour, sensitivity of the screening and confirmation test, and cure rates. The presence of enlarged cervical glands influences both the sensitivity of the screening tests and more importantly, the chance of a parasitological confirmation. Hence, the sensitivity gains of the CATT test may be partially offset by problems in parasitological confirmation in patients without palpable neck glands.

During the study period, only 5% of all the confirmed cases were CATT negative and lymph node positive. This implies that the loss of effectiveness by using only CATT as a screening test would be limited and that this strategy may be more cost-effective. Overall operational effectiveness is relatively low, even in the optimistic range of estimations for the parameters. Low attendance rates were a major problem and, in many places, the factor that crippled the screening efforts the most. Improving attendance rates deserves major attention, but because the causes are multiple and differ according to circumstances, there is no single uniform solution for this problem. Social research is needed to clarify causes and develop solutions. If

attendance rates remain low then the considerable means spent on active case finding are pointless.

Part of the gains in effectiveness due to the CATT test are lost in the parasitological confirmation. With the currently used techniques this loss amounts to 20–30%.

Simulations in the section 'Results' show that improving parasitological confirmation with mAECT combined with the use of CATT can lift the overall effectiveness. The screening strategy without CATT, however, seems to be ineffective in all circumstances. There is no information on the time between diagnosis and treatment, and this simplified model does not take this factor into account.

No attempt is made to model the effect on transmission of this or other control measures such as vector control. Therefore, we cannot make statements on the needed effectiveness of screening to cut transmission or on the optimal frequency of screening rounds. Notwithstanding, our results show that overall effectiveness of HAT screening was relatively low, even under a best case scenario, as a result of losses at each step. So it is unlikely that one screening round sufficiently reduces the circulation of trypanosomiasis in the population. Only intervention trials or the possible construction of a dynamic model of *T. gambiense* transmission could answer the question of the best mix of strategies.

In the meanwhile, we can conclude that CATT plays a major role in making HAT screening effective. Further research is needed to better understand the factors that determine the attendance rate and other major determinants of screening effectiveness. Finally, improving parasitological confirmation is only meaningful if attendance rates are high, CATT test is used and if there is sufficient access to effective treatment.

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